INSIDE STANFORD MEDICINE

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A new emergency protocol at Stanford Hospital drastically cuts the time it takes to give stroke patients a lifesaving treatment.

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‘Wow, beautiful’: Public glimpses new hospital

By Ruthann Richter

STEVE FISCH

Visitors take in a view of the atrium at the new Stanford Hospital during its community open house, which was held Sept. 14-15.

More than 10,000 people of all ages streamed through the new Stanford Hospital during a Sept. 14-15 open house that gave the community its first glimpse of the pristine new medical facility.

Visitors touring the hospital said they were thrilled to see it when they were healthy and grateful to know that it would be there should they need it.

“One of the things that’s been amazing is that as people come through, they are saying, ‘Wow.’ I think people feel they’re part of it — that it’s their hospital. That’s what we hoped to accomplish,” David Entwistle, president and CEO of Stanford Health Care, said as he greeted guests in the soaring, light-filled atrium.

The event featured tours of the 824,000-square-foot hospital, which is next to the current hospital on the Stanford campus. It also included a street fair that was particularly popular with children, who stuffed 1,500 teddy bears and dressed them in little hospital T-shirts. Some youngsters had their faces painted, played an oversized game of Operation, took part in a treasure hunt or petted Moogie, a serene black Labrador retriever who provides comfort to hospital patients.

Aidan Sharp, 12, of Menlo Park, said the seven-floor hospital was much bigger than he had expected. “It doesn’t seem like an emergency place. It’s so nice,” said Aidan, who came with his father, Christopher Sharp, MD, clinical professor of medicine at Stanford.

Lloyd Minor, MD, dean of the Stanford School of Medicine, said the new hospital will help fulfill the vision of Stanford Medicine, which is to predict, prevent and cure disease with precision.

“With access to Stanford School of Medicine’s breakthrough research and facilities, this hospital will set a new global standard, offering patients the most advanced care in a healing environment created to meet the needs of the whole person — socially, emotionally, spiritually and physically,” Minor said.

How Peter was cared for

During the tour, visitors walked down ivory-colored hallways, past hundreds of donated artworks, to follow the path of a fictitious patient, “Peter,” who was injured in a bicycle accident in Napa Valley. He was flown via helicopter to the hospital’s new, rooftop helistop. Caregivers shown on a video narrated Peter’s progress as he was rushed directly to the new emergency department.

That stop on the tour particularly impressed Brendalyn Ucol-Co, who is a patient care manager in emergency services. “We’re so happy that it’s finally happening,” said Ucol-Co, who brought her 11-year-old daughter, Clarissa, to the open house.

With the new 45,000-square-foot emergency department, the hospital will have 2 ½ times more space to treat trauma patients and those with urgent needs. Patients will receive care in 66 individual treatment bays, where they can recover in privacy and quiet. The adjoining parking garage can be engineered to be an extension of the emergency department in the event of a disaster, Andra Blomkalns, MD, professor and chair of emergency medicine, noted in a videotaped interview at the entrance to the unit.

Onscreen, caregivers stabilized Peter in the emergency department, then wheeled him into one of the 20 new operating rooms, where he underwent surgery for a punctured lung. There, tour participants viewed the overhead imaging system, where CT and X-ray images will be displayed and magnified up to five times for detail not visible to the naked eye. These digital images can be shared in real time with clinicians elsewhere in the hospital. That will enable See HOSPITAL, page 6

Brain tumors form synapses with healthy neurons, study finds

By Erin Digitale

Scientists at the School of Medicine have shown for the first time that severe brain cancers integrate into the brain’s wiring.

The tumors, called high-grade gliomas, form synapses that hijack electrical signals from healthy nerve cells to drive their own growth. Experiments demonstrated that interrupting these signals with an existing anti-epilepsy drug greatly reduced the cancers’ growth in human tumors in mice, providing the first evidence for a possible new way to treat gliomas.

SEBASTIAN KAULITZKI/SHUTTERSTOCK.COM

A new study found that high-grade gliomas form synapses with healthy neurons, which transmit electrical signals to the cancerous tissue.

A paper describing the findings was published online Sept. 18 in *Nature*.

“One of the most lethal aspects of high-grade gliomas is that the cancer cells diffusely invade normal brain tissue so that the tumor and the healthy brain tissue are knitted together,” said senior author Michelle Monje, MD, PhD, associate professor of neurology and neurological sciences. The discovery helps explain why gliomas are so intractable, she added. “This is such an insidious group of tumors. They’re actually integrating into the brain.”

The study’s lead author is postdoctoral scholar Humsa Venkatesh, PhD.

Discovering that tumors wire themselves into the brain was “unsettling,” Monje said. Still, she said she is optimistic about what the knowledge means for glioma patients. Several drugs already exist for treating electrical-signaling disorders such as epilepsy, and these may prove useful for See GLIOMA, page 7

A cure for the common cold in sight?

By Bruce Goldman

PAUL SAKUMA

Jan Carette is a senior author of a paper describing how he and his colleagues found a way to stop a broad range of enteroviruses from replicating inside human cells in culture, as well as in mice.

Temporarily disabling a single protein inside our cells might be able to protect us from the common cold and other viral diseases, according to a study led by researchers at Stanford University and University of California-San Francisco.

The findings were made in human cell cultures and in mice.

“Our grandmas have always been asking us, ‘If you’re so smart, why haven’t you come up with a cure for the common cold?’” said Jan Carette, PhD, associate professor of microbiology and immunology. “Now we have a new way to do that.”

The approach of targeting proteins in our own cells also worked to stop viruses associated with asthma, encephalitis and polio.

Colds, or noninfluenza-related upper respiratory infections, are for the most part a weeklong nuisance. They’re also the world’s most common infectious illness, costing the U.S. economy an estimated $40 billion a year. At least half of all colds are the result of rhinovirus infections. There are roughly 160 known types of rhinovirus, which helps to explain why getting a cold doesn’t stop you from getting another one a month later. Making matters worse, rhinoviruses are highly mutation-prone and, as a result, quick to develop drug resistance, as well as to evade the im- See COLD, page 7

New incubator to fuel life science innovation in Stanford Research Park

By Amy Adams

To bolster the long-term vision of a thriving bioscience community near its campus, Stanford University is working to shape part of Stanford Research Park into a leading life science district focused on fast-growing sectors such as bioengineering, gene therapies, diagnostics, medical technology and devices, surgical robotics and digital health. As a key component of this effort, Stanford is collaborating with Alexandria Real Estate Equities, Inc. to convert an existing 92,000-square-foot facility at 3160 Porter Drive into a life science incubator — Alexandria LaunchLabs at Stanford Research Park — and small lab suites.

When the building was recently vacated, Stanford saw an opportunity to create a flexible and vibrant space that would enhance the connections between the existing life science ecosystem of medical facilities, researchers and companies in the surrounding area, while also encouraging progress toward an even more diverse life science community. The university held a competition for firms that specialize in this work and chose Alexandria, an experienced developer and operator of successful life science communities near academic campuses.

VANTAGE POINT PHOTOGRAPHY INC.

The 92,000-square-foot building at 3160 Porter Drive in Palo Alto will be developed into a life science incubator and small lab suites.

"Stanford has a legacy of translating life science research discoveries into cures, but the opportunities in this field are greater than ever before. We want to take advantage of this current momentum and further accelerate solutions," said Stanford President Marc Tessier-Lavigne, PhD. "This new incubator will support entrepreneurs in the development of new therapies and cures for critical diseases and create a community for life sciences entrepreneurship and innovation. We were delighted to enlist Alexandria, which has a strong history of not only building lab space but stimulating discovery and collaboration through their unique approach to creating life science ecosystems."

The university envisions the incubator as the anchor of an 85-acre life science district, within the existing Stanford Research Park, that will become a new center of gravity for life science innovation in the Bay Area — a community for scientists and entrepreneurs who desire to collaborate, discover and invent pioneering medicines, therapies, devices and technologies to help humankind.

Accelerating therapies

Positioned roughly a mile from campus and in close proximity to Stanford's adult and children's hospitals, the VA hospital, and Stanford University School of Medicine, as well as Jazz Pharmaceuticals, Varian Medical Systems, Kodiak Sciences, the Canary Foundation and other biotech firms, Alexandria LaunchLabs at Stanford Research Park will catalyze emerging life science research. It also aligns with the goals of the Innovative Medicines Accelerator — an initiative that arose out of Stanford's long-range planning process, which aims to help basic and applied researchers from across the schools of Medicine, Engineering and Humanities & Sciences translate their research discoveries into new therapies and diagnostics.

"This space will be key to our shared vision of ensuring Stanford discoveries continue to benefit the world," said Sanjiv Sam Gambhir, MD, PhD, Virginia and D.K. Ludwig Professor of Cancer Research and chair of the Department of Radiology. "Together with the Innovative Medicines Accelerator, the hope is the incubator can do even more to initiate commercialization of novel therapies for the greater good of humanity."

Having an expanded life science-focused community close to campus will also complement existing efforts within the School of Medicine to translate basic science discoveries into new therapies.

"The breadth and depth of innovative research emerging from Stanford Medicine is astonishing," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "The incubator will provide our researchers with resources and access to experts to streamline and speed the translation of groundbreaking discoveries. Additionally, its close proximity to Stanford's School of Medicine, two world-class hospitals, and the VA will help to realize the promise of bench-to-bedside research."

As new technologies, devices, treatments and therapies move from ideas to labs to applications in the real world, it is important to have spaces that can adapt to support this development — and early-stage life science solutions have diverse needs. Such flexible spaces can be challenging to find in the Bay Area and companies often end up renting space that is longer-term than what they require. Spots close to the Stanford campus, and the venture capital groups nearby, are especially rare.

"Biotech entrepreneurs often need to commit to multiyear leases, large footprints and expensive lab build-outs when they aren't even sure they have a viable product yet," said Jennifer Cochran, PhD, Shriram chair of bioengineering at Stanford. "This flexibility and proximity to campus will greatly benefit Stanford faculty and other entrepreneurs, and provide them with a supportive community and shared resources to facilitate their new ventures."

Bridging academia and industry

Since its origin in the 1950s, Stanford Research Park has drawn pioneering researchers and industry leaders, in part, due to the potential for collaboration with the university nearby. The 700-acre research park is home to about 150 diverse companies focused on scientific discovery, technological innovation and commercialization of groundbreaking research. It also includes existing biotechnology companies and School of Medicine lab space focused on precision medicine.

Under this new agreement, Stanford has sold a 51-year ground lease for 3160 Porter Drive to Alexandria. Building upon the success of Alexandria's unique space offerings for life science companies near academic campuses, the company will bring its Alexandria LaunchLabs platform to Stanford Research Park to create an environment that stimulates discovery. Alexandria LaunchLabs at Stanford Research Park will provide flexible, move-in-ready lab and office space, as well as strategic programming and access to seed capital. The facility will also offer lab suites for maturing companies.

"As a university-affiliated research park, we recognize we have a unique mission — to bridge academia and industry in an effort to launch solutions that will have an enduring positive impact in our community and world," said Tiffany Griego, managing director of asset management for Stanford Research Park. "Stanford Research Park and Palo Alto have always been at the forefront of new technological and scientific discoveries and inventions. With a renewed focus on drawing life science entrepreneurs to Stanford Research Park, we will support them in their pursuits to deliver therapies and solutions to the public health challenges of the 21st century."

Griego said Alexandria LaunchLabs at Stanford Research Park is expected to open in spring of 2021. ISM

Achilles' heel identified in several neurodegenerative diseases

By Bruce Goldman

Many neurodegenerative diseases have a common feature that may make them amenable to the same treatment, investigators at the Stanford University School of Medicine have found.

"We've identified a potential new way to reduce nerve-cell death in a number of diseases characterized by such losses," said Daria Mochly-Rosen, PhD, professor of chemical and systems biology at Stanford.

A paper describing the researchers' findings was published today in *Nature Neuroscience*. Mochly-Rosen is the senior author. The lead author is postdoctoral scholar Amit Joshi, PhD.

Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis, or Lou Gehrig's disease, share a common mode of damaging brain cells, the scientists learned in studying both human cells in culture and mouse models of the diseases. This damage can be blocked by administering a substance that inhibits a critical step in that process.

The new study implicates two types of normally protective brain cells called glial cells in tripping off neuronal destruction: Microglia monitor the brain for potential trouble — say, signs of tissue injury or the presence of invading microbial pathogens — and scavenge debris left behind by dying cells or protein aggregates. Astrocytes, which outnumber the brain's neurons nearly 5 to 1, release growth factors, provide essential metabolites and determine the number and placement of the connections neurons make with one another.

Neuronal bits and fragments are perceived as foreign and targeted for clearance by microglia. But a vicious cycle of glial-cell activation and inflammation can occur in the absence of neuronal debris.

Mochly-Rosen, the George D. Smith Professor in Translational Medicine, and her colleagues discovered that mitochondria, essential components of cells, were conveying deleterious signals from microglia to astrocytes and from astrocytes to neurons. Mitochondria are tiny power packs: They furnish cells with energy. A typical nerve cell contains thousands of them. Their ability to communicate death signals from one cell to another was

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STANFORD MEDICINE

Study: Mild head trauma can damage brain's protective barrier

By Jonathan Wosen

Mild head trauma in adolescents and adults who participate in contact sports damages the barrier that protects the brain from pathogens and toxins, according to researchers at the Stanford School of Medicine and Trinity College in Dublin.

If the results of their small pilot study hold up, the brain imaging technique employed by the researchers could be used to monitor athletes who've taken a blow to the head and determine when they're safe to resume contact sports.

In the study, which was published online Sept. 5 in the *Journal of Neurotrauma*, scientists scanned the brains of adolescent and adult rugby players with a special type of magnetic resonance imaging. They found damage to the protective barrier that separates the brain from bloodborne pathogens and toxins in roughly half of adolescent rugby players after a full season — even those who did not report a concussion. Professional mixed martial arts fighters showed similar damage after a fight.

The link between repeated head trauma and neurodegenerative disease continues to fuel public interest and debate. And though the new study draws no definitive conclusions, it shows that mild blows to the head may at least temporarily weaken an important brain barrier.

"This is some of the first evidence, certainly in kids, to show disruption of the blood-brain barrier even in the absence of concussion," said David Camarillo, PhD, assistant professor of bioengineering at Stanford and co-senior author of the study.

Barrier breakdown

Most traumatic brain injuries are mild. That may sound like an oxymoron, but mild traumatic brain injuries only temporarily affect normal brain function.

The current diagnosis for mild head trauma is based on a temporary change in awareness and responsiveness, short-term amnesia, headache or general difficulty thinking clearly. But it can be difficult to reliably spot these symptoms during contact sports.

Researchers at Stanford and Trinity College teamed up to find a more objective way to pinpoint mild head trauma. The Dublin contingent had previously studied brains from patients afflicted with chronic traumatic encephalopathy, a neurodegenerative disease. Brains from these patients had a defunct blood-brain barrier — a border that allows oxygen and nutrients to pass into the brain while blocking larger molecules. This barrier operates a lot like a tea bag, which lets water through but holds leaves in place.

The researchers wondered if mild head trauma damaged the blood-brain barrier. So they recruited a group of rugby players and scanned their brains with magnetic resonance imaging, or MRI, after a season or single match. To see if the blood-brain barrier was intact, Dublin researchers injected participants with a commonly used MRI contrast agent. Little to no contrast agent will show up in the brain of a person with an intact barrier.

Ten of 19 adolescent rugby players showed signs of blood-brain barrier disruption by the end of the season. The barrier breakdown appeared on the scans as red blips concentrated throughout the inner regions of the brain. The researchers also scanned eight college rugby players after a match and saw disruptions of the barrier in two of them. Notably, the injuries most study participants experienced were below the current bar for mild head trauma since they did not suffer a concussion.

"We've always been interested in studying rugby," said co-author Gerald Grant, MD, professor of neurosurgery and a concussion expert at Stanford's Children's Health, whose lab studies the blood-brain barrier. "People have this sense that rugby must be safer because you're usually avoiding head contact much more than in football since you're not as protected."

Based on these initial findings, the researchers hypothesized that impact forces were damaging the blood-brain barrier. But they needed a way to precisely measure those forces. And they wanted to test other contact sports, as well.

A productive partnership

Enter Camarillo, whose lab has developed a mouth guard that tracks speed, acceleration and force at nearly 10,000 measurements per second. That level of speed and precision was vital for the next contact sport the researchers studied: mixed martial arts. The scientists recruited five professional mixed martial arts fighters, who wore the mouth guards during fights and had their brains scanned before and after fights.

SAUL BROMBERGER AND SANDRA HOOVER

David Camarillo is a senior author of a study that found damage to the protective barrier that separates the brain from bloodborne pathogens and toxins in about half of youth rugby players after a full season.

Post-fight MRI scans showed increased blood-brain barrier breakdown, just as the researchers observed in rugby players. And the researchers found that certain measurements from the mouth guards correlated with the level of blood-brain barrier disruption seen by MRI.

"This suggests there might be some combination of number of blows and severity of blows that might explain blood-brain barrier injury," Camarillo said.

Not every hit that looked bad — such as when a fighter was knocked out during the first two minutes — damaged the blood-brain barrier, emphasizing the value of the mouth guard measurements to record the forces of injury.

The findings, Camarillo said, are further evidence that the longstanding model of concussion is likely too simplistic. The current paradigm is that the brain slams into the skull, recoils and slams again on the opposite side. According to this model, most brain damage should occur along the outer surface of the brain. But recent evidence — including the present study — suggests that head trauma's effects are felt much deeper in the brain.

The researchers plan to conduct a similar study in a larger cohort. They're also interested in determining whether the blood-brain barrier disruptions they observed heal on their own and, if so, how long that takes.

While the findings are still at an early stage, the imaging technique used in this study — perhaps in conjunction with blood biomarkers — could one day be used to figure out how much damage an athlete has sustained, and when he or she can return to play, according to Grant.

"I think we're ignoring many of these kids who are experiencing these injuries throughout the season but aren't aware of them, or they have no symptoms," Grant said. "Maybe this study can help us figure out how to better classify some of these kids and figure out if they are truly safe to go back and play."

Camarillo and Grant are members of Stanford Bio-X, the Stanford Maternal & Child Health Research Institute and the Wu Tsai Neurosciences Institute at Stanford.

Other Stanford co-authors of the study are postdoctoral scholar Yuzhe Liu, PhD, and former postdoctoral scholar Chiara Giordano, PhD.

Researchers at the Ben-Gurion University of the Negev in Israel also contributed to the study.

This study was supported by Science Foundation Ireland, the St James's Hospital Foundation, the National Institute of Neurological Disorders and Stroke and the Ellen Mayston Bates bequest to the Trinity Foundation.

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

Neuro

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unexpected.

Viewed close up, mitochondria are convoluted tubular networks that are perpetually being right-sized in a dynamic dance of fusion and fission, performed by opposing assemblies of enzymes. Mitochondria frequently get shuffled around from one part of a cell to another and must shift their shapes accordingly to accommodate their environments: Too much fusion, and they become too tubby to get around or work well. Too much fission, and they break up into dysfunctional fragments.

An enzyme called Drp1 that facilitates mitochondrial fission can be catapulted into hyperactivity by neurotoxic protein aggregates such as those linked to Alzheimer's, Parkinson's or Huntington's diseases or to amyotrophic lateral sclerosis. About seven years ago, Mochly-Rosen's team designed a tiny protein snippet, or peptide, called P110, that specifically blocks Drp1-induced mitochondrial fission when it's proceeding at an excessive pace, as happens when a cell is damaged.

The study showed that sustained P110 treatment via a subcutaneous pump over periods of several months lowered the microglial and astrocytic activation and inflammation in the brains of mice.

Then, experimenting with microglia in culture, the researchers introduced toxic proteins that cause different neurodegenerative diseases. Each of these manipulations kicked the microglia into an inflamed state, and they released, into the broth they were bathed in, something that could trip off inflammatory responses in astrocytes. But adding P110 to the microglial culture dishes substantially dialed down this subsequent transfer of microglial inflammation to the astrocytes. Something the microglia had expelled was providing the signal.

Likewise, something in the culture broth in which inflamed astrocytes had been immersed killed neurons. But P110 blunted that destruction, as well. Additional experiments showed that both types of glial cells were expelling damaged mitochondria into the broth.

"Most people have thought that mitochondria situated outside of cells must be ghosts of dead or dying cells," Mochly-Rosen said. "But we found plenty of high-functioning mitochondria in the culture broth, along with damaged ones. And the glial cells releasing them appear very much alive."

As has been recently reported, even healthy cells routinely release mitochondria into their surrounding environment. This can be beneficial if those mitochondria are healthy, too. However, the mitochondria released by inflamed microglia and astrocytes were more apt to be damaged. When expelled mitochondria are in bad shape, it's lethal for nearby neurons.

Blocking this mitochondrial fragmentation with P110 in the microglia or in the astrocytes was enough to significantly reduce neuronal death.

How do expelled mitochondria that are damaged produce inflammation and neuronal cell death? "We're working hard to find that out," she said.

Joshi and Mochly-Rosen have filed for a patent on P110 and its utility in Huntington's disease, ALS and other neurodegenerative diseases.

Mochly-Rosen is a member of Stanford Bio-X, the Stanford Cardiovascular Institute, the Stanford Maternal and Child Health Research Institute, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford, a faculty fellow of Stanford ChEM-H, and founder and co-director of SPARK at Stanford and the founder and president of SPARK Global.

Other Stanford co-authors of the study are medical student Paras Minhas; former postdoctoral scholar Shane Liddelow, PhD; Bereketeab Haileselassie, MD, instructor in pediatric clinical care medicine; and Katrin Andreasson, MD, professor of neurology and neurological sciences. Researchers from the Washington University School of Medicine also contributed to the study.

The study is dedicated to the memory of the late Stanford neuroscientist Ben Barres, MD, PhD, who first identified many of the crucial roles of glial cells.

The work was funded by the National Institutes of Health, a Stanford Discovery Innovation Award, the Paul & Daisy Soros Foundation and the Glenn Foundation.

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

Treating blood clots in brain: Going from fast to faster to fastest

By Mandy Erickson

By the time the man arrives at Stanford Hospital's emergency bay doors, paramedics have already called in vital information: He is unable to move his right arm and his speech is garbled, suggesting a stroke. His blood glucose is normal, ruling out hypoglycemia as the culprit.

BRIAN SMALE

BRIAN SMALE

After taking on stroke care oversight in the hospital's emergency department, Nirali Vora, left, closely observed emergency department stroke protocol to find ways to speed treatment further. As quality director for Stanford Health Care, Eric Bernier, right, says he's "the grumpy guy in the basement" asking why door-to-needle treatment for stroke patients in the ED took so long.

As soon as the ambulance rear doors open, at 3:47 p.m., a clerk leans inside to record the man's name, then runs back to the registration desk to enter his information into the system. A few yards beyond the ambulance bay a crowd of physicians, nurses and a pharmacist are waiting.

The paramedics lift the man (a composite Stanford stroke patient created for the scenario described here) onto a hospital gurney. With the press of a button, the gurney records the patient's weight (let's call him David Williams), and the crowd wheels him into the computed tomography room.

They quickly transfer him onto the CT bed, positioning his head inside the doughnut-shaped scanner. One of the paramedics, meanwhile, calls out his medical information: "Right-side facial droop, aphasia. Age 82. Last OK was 2:30."

While the scanner takes detailed X-ray images, the medical team stands behind a glass partition, eyes on computer screens. They are watching for telltale signs of bleeding in the brain, which would appear in the form of white, shapeless masses.

Once the scan is complete, as cross-sectioned images of Williams' head flow onto the screens, nurses insert an intravenous line into his arm and draw his blood. Out in the hall, a pharmacist searches for Williams' medical information in Stanford's records.

The physicians need to decide, quickly, if tissue plasminogen activator would help. The medication will dissolve a stroke-causing blood clot, but it will worsen and may provoke cerebral bleeding. If tPA is warranted, they must give it immediately, in the scanner room: Minutes saved in stroke treatment can make the difference between walking and not walking, living alone and relying on caregivers.

The pharmacist finds that Williams is not taking any medication and does not have a medical condition that could lead to bleeding. The neurologist orders tPA, the pharmacist hands a nurse the correct dose in an IV bag and the nurse sets the pump to deliver the medication. A quality assurance nurse checks his watch: 4:02 p.m. Fifteen minutes have passed from the moment the ambulance bay doors opened until the tPA entered Williams' vein.

"During a stroke, 1.9 million neurons die every minute," said Nirali Vora, MD, an associate professor of neurology and a stroke specialist. "When we are able to administer tPA quickly, that translates into saved neurons, saved independence and saved health care costs."

Seven years ago at Stanford Hospital, the average door-to-needle time — starting when a stroke patient arrives at the emergency department and ending when they receive tPA — was 66 minutes, typical for a U.S. hospital. Today, at Stanford, it's 26 minutes, with an all-time record of nine. Shaving so much time from a process, in a department already primed for quick action, required months of research, years of changing work habits and a good dose of diplomacy.

Developing new stroke protocols

The rapid stroke protocol at the bustling emergency department got its start at Stanford's Clinical Excellence Research Center. CERC's office lies in the oak-studded hills about a mile south of the center of campus, reached by a winding, single-lane road.

CERC is the brainchild of Arnold Milstein, MD, an economics major who entered medical school and specialized in psychiatry and care quality before turning his attention to the rising cost of U.S. health care. Funded by grants and private foundation gifts, CERC generates research on lowering health care costs while preserving or improving quality.

Every year, CERC accepts and funds four to seven fellows, early career professionals with an interest in health care value. Most fellows work in the medical field, though some come from the business and engineering worlds. Split into two groups, they spend 11 months tackling two challenges that Milstein chooses. "I work backward," Milstein said. "I ask, 'Where is America spending the most on health care?' Then I pick a plausible target." CERC fellows have developed recommendations for such aspects of health care as outpatient surgery, prescription medication, spine pain treatment and ICU care.

During the second year of the program, 2012 to 2013, one of the teams took on stroke care, the leading cause of disability in the United States. The fellows started out "in a sort of innovation camp," according to Waimei Amy Tai, MD, who was one of the stroke fellows and is now a neurologist at Christiana Care Health System in Delaware.

They learned about the economics of medicine as well as lean process management, a manufacturing approach that maximizes customer value by minimizing waste. They pored over the scientific literature on stroke care innovation and visited health care facilities to observe treatment protocols. They took a field trip to Hillsboro, Oregon, to learn how Intel reduces waste in its microchip fabrication plant.

Their research completed, the fellows devised three proposals to lower spending by improving stroke care: coaching patients to better manage their blood pressure, avoiding long hospitalizations for stroke patients whose symptoms disappear before or during emergency department visits, and sharply reducing door-to-needle times.

In the next step of CERC fellowships, the fellows pitch their proposals to health care organizations and share them at medical conferences, hoping to find buyers for their ideas. Virginia Mason Medical Center in Seattle and Allina Health in Minneapolis took on the second proposal, avoiding long hospitalizations. Kaiser Permanente's Northern California hospitals adopted the third proposal, reducing door-to-needle times, as did Stanford Health Care.

Shaving off the minutes

Stanford's new door-to-needle protocol was inspired by a stroke treatment innovation at Helsinki University Central Hospital; the CERC fellows uncovered it in a Scandinavian medical journal. In the Helsinki hospital, staff reduced their average time from nearly two hours to less than 20 minutes, largely by eliminating unnecessary steps and starting evaluations while stroke patients were traveling to the hospital.

But simply telling the staff at Stanford Hospital's emergency department to follow the Finns wouldn't bring lasting changes. "You have to understand how attached people are to their sense of mastery," Milstein said. "They are grounded firmly in how they currently do their work."

The task of reducing door-to-needle times fell, in part, to Tai, who stayed at Stanford for two years after the fellowship ended. Like Milstein, Tai was an economics major. "I've always had an interest in quality improvement," she said. "I applied to CERC because I wanted to take a look at health care from a value perspective."

Tai, Vora and other physicians, as well as nurses and CT technicians, began their project by observing. Whenever the charge nurse issued a stroke code — a text message alerting on-call nurses, pharmacists, registration clerks and physicians that a stroke patient is on the way — they watched.

They identified a few steps that were unnecessary, such as running an electrocardiogram and assigning a room, and eliminated them. They also realized that some steps, such as inserting an intravenous line and running lab work, could take place after the scan. They saved time by ensuring everyone on the stroke code team knew in advance the role they'd play in getting the patient to the CT scanner and, ultimately, treatment.

Like actors rehearsing for a play, they ran mock stroke codes with one staff member playing patient and everyone else acting out their assigned roles. When they found snags, they fixed them and ran more mock stroke codes, shaving off minute after minute.

"There was a lot of resistance initially because we were changing people's habits," Tai said. She employed a host of management tactics, but perhaps her most effective tool was humility.

"At a meeting, I would suggest inserting the IV while we were waiting for CT scans, and no one would say anything," she said. "Then I would email reference papers around, and someone at the next meeting would say, 'Why can't we insert the IV in the CT scanner?' and I'd say, 'That's an awesome idea!'"

When Tai left Stanford in 2015, Vora took on the job of overseeing stroke care in the emergency department. At that time, stroke patients arriving by ambulance received speedy treatment, but those who showed up on their own were put through the old, slower process.

Like Tai, Vora spent a lot of **See STROKE, page 5**

Stanford Medicine recognized by Vizient as a top performer in quality and safety for 2019

Stanford Medicine has been ranked in the top 10% among peer academic medical centers for both inpatient and outpatient care by Vizient Inc., the nation's leading health care performance improvement company that measures overall safety and quality in patient care.

In recognition of these achievements in care quality and safety, Vizient presented Stanford Medicine with two awards that were jointly accepted by David Entwistle, president and CEO of Stanford Health Care and Lloyd Minor, MD, dean of the Stanford School of Medicine, on Sept. 19 during the 2019 Vizient Connections Education Summit.

"This tremendous achievement is a tribute to the hard work and dedication of our staff and faculty at Stanford Health Care and the School of Medicine," said Entwistle. "I want to thank each and every one of our colleagues who have prioritized our commitment to continuously improving patient care. We could not have done this without them. I look forward to continuing our important work to further enhance safety and quality as we move into our new, state-of-the-art hospital where we will be able to bring the latest biomedical advances to patients."

"Our rankings in the top 10% for both inpatient and ambulatory care are a direct result of the collaboration between staff and faculty at Stanford Health Care and the School of Medicine that began years ago when we aligned our priorities and focused on strengthening the safety and quality of care," said Minor. "Working together, we have been able to improve faster than we ever imagined possible."

As a top performer in the 2019 Bernard A. Birnbaum, MD, Quality Leadership Award category, Stanford Medicine was one of 11 Vizient members in the academic medical center cohort that was recognized for demonstrating excellence in delivering high-quality care based on the Vizient Quality and Accountability Ranking. Stanford Medicine also received the 2019 Ambulatory Care Quality and Accountability Award, which recognized Stanford Medicine as a faculty practice that demonstrates excellence in delivering high-quality outpatient care.

"As a world-class hospital and research center, Stanford Medicine uniquely understands the science of safety and quality as well as the importance of culture," said Karen Frush, chief quality officer at Stanford Health Care. "The recognition by Vizient is additional proof that the systems we use to continually assess and improve the care we provide actually work."

The Bernard A. Birnbaum, MD, Quality Leadership Award recognizes Stanford Medicine's performance-driven culture for achieving the highest quality and patient-centered outcomes. This year, 349 participating hospitals were segmented into four cohorts for the Vizient Quality and Accountability Ranking. The ranking measured performance based on safety, mortality, clinical effectiveness, efficiency and patient centeredness. The ranking's composite scoring system uses patient-level performance data from a variety of sources including the Vizient Clinical Data Base, core measures data, the Hospital Consumer Assessment of Healthcare Providers and Systems survey and the Centers for Disease Control and Prevention's National Healthcare Safety Network.

The Vizient Quality and Accountability Ranking helps participating hospitals and health systems understand their performance against their peers, and identifies structures and processes associated with high performance in quality and safety across a broad spectrum of patient care activity. The recognition period is for work spanning July 2018 through June 2019.

Ambulatory Care Quality and Accountability Award recipients are determined through the Vizient Ambulatory Care Quality and Accountability Study, which assesses data from participating academic faculty practices to measure performance in five domains: access to care, quality, efficiency, continuum of care and equity. The composite scoring system utilizes practice and patient-level data across several databases including the Vizient-AAMC Clinical Practice Solutions Center. The recognition period is for work spanning July 2018 through June 2019. **ISM**

Maternal & Child Health Research Institute symposium registration is now open

Registration is now open for the second annual Stanford Maternal & Child Health Research Institute Symposium, which will highlight the latest research from across campus in maternal and child health. The event, scheduled for Nov. 15 at the Li Ka Shing Center for Learning and Knowledge, is free and open to the public.

"The symposium aims to catalyze long-lasting research collaborations and share new insights for improving the health of mothers and children around the world," said Anthony Oro, MD, PhD, professor of dermatology and co-director of the MCHRI.

This year's keynote speaker is Diana Bianchi, MD, director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and head of the prenatal genomics and therapy section of the medical genetics branch at the National Human Genome Research Institute. Bianchi earned her medical degree at Stanford and is an expert in neonatal and perinatal medicine.

The event will also feature Stanford investigators who have been funded through MCHRI programs, as well as poster sessions and networking opportunities. Conference registration is available online at http://med.stanford.edu/mchri/events/symposium.html.

The conference is currently accepting abstracts focused on maternal and child health research for presentation during its poster sessions. Abstracts are due by 5 p.m. Oct. 1 and can be submitted online at http://med.stanford.edu/mchri/events/symposium/poster-session.html. **ISM**

Stroke

continued from page 4

time hanging out in the emergency department, waiting for potential stroke patients to walk in. When they did, she tried to blend into the background, timer in hand. Suspected stroke patients now have a bed reserved for them near the CT rooms — it signals that they need immediate testing — and triage nurses are empowered to call a stroke code. So are the security guards, who Vora ensured were trained to recognize a possible stroke. "Patients often tell the security staff their symptoms," she noted.

A little competition also helped drive the numbers lower: The stroke team started issuing buttons that display the minutes it took from a patient's arrival to the administration of tPA. If the door-to-needle time is impressive, under 30 minutes or so, stroke code team members pin them to their white coats and badge lanyards.

Continuing to improve

Eric Bernier, RN, was typing an email early this year when his cell phone flashed: "Stroke code adult: Emergency room ambulance bay ETA-10." He put on his white coat and walked upstairs to the emergency department. As a quality director for Stanford Health Care, his job is to keep the door-to-CT and door-to-needle times low and to ensure that all the steps in the stroke protocol are followed. "I'm the grumpy guy in the basement who asks why things are taking so long," he said.

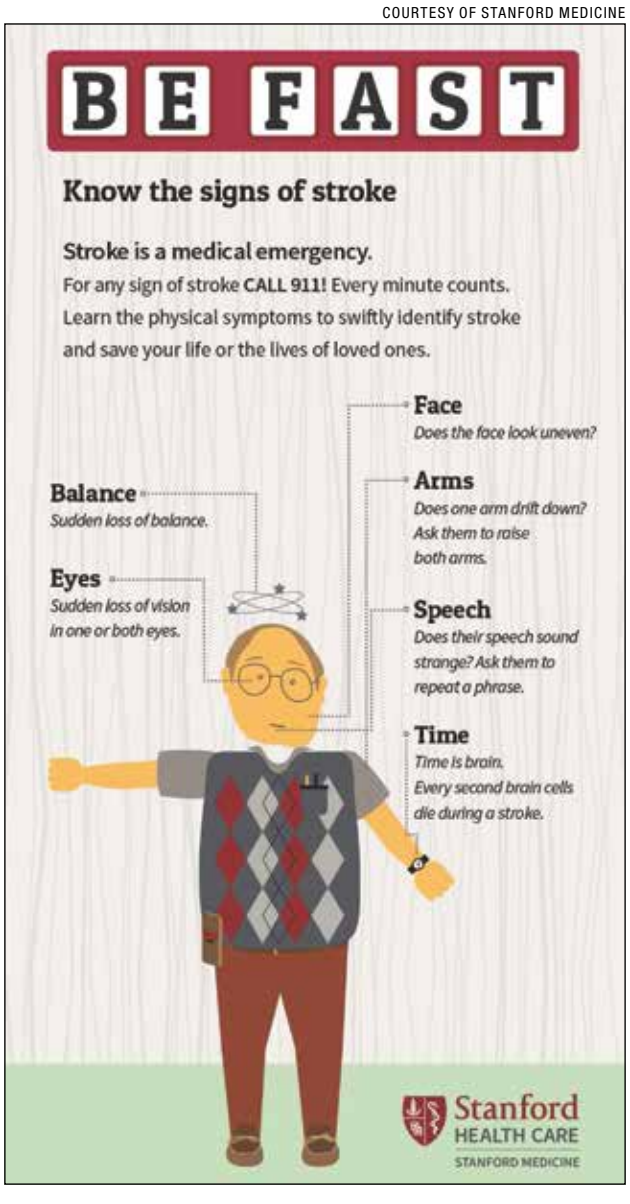
On this day, he observed as the emergency crew ran through its well-practiced choreography and started the CT: It took just five minutes, one less than average. The process played out as it should, except, he noticed, an emergency technician failed to record the patient's weight. He made a note to speak with her supervisor. "Every stroke code is an opportunity to find something to improve on," he said.

Soon after the CT, the patient answered questions and was able to move her leg, so the neurology fellow on duty, Adam MacLellan, MD, decided against giving her tPA. "I'm more suspicious it's a seizure," he said. The lanyard holding MacLellan's Stanford Hospital badge is covered in buttons with his door-to-needle minutes: 21, 25, 17.

Only about a third of stroke codes result in a stroke diagnosis — a migraine, low blood sodium, fainting, even reactions to Novocain from a dental procedure can look like a stroke. But because a stroke can be so devastating, Bernier said, "We'd rather activate way over. We say call often and call early" whenever a stroke is suspected.

And only about one-eighth of stroke codes end with tPA being administered. But the speedy system also helps patients with a stroke that tPA can't treat: Quick diagnosis leads to rapid treatment — such as removing a clot with a device or repairing a damaged vessel — which means more brain tissue is protected.

COURTESY OF STANFORD MEDICINE



If a door-to-tPA time is overly long, Bernier said, it's usually because it took time to confirm information about the patient. Stroke patients often can't speak, and family members or caregivers frequently don't know what medications they're taking. It can also take a while to determine when the stroke occurred; after 4½ hours, tPA is likely to cause more harm than good. In one case, the physicians determined the last time a patient was OK by reading a post on the patient's Facebook page.

But if a patient's record is readily available, the door-to-needle time can drop significantly: "When we had that nine-minute code, we had all the information on hand," Bernier said. "Everything was in perfect alignment."

A patient's perspective

Malinda Mitchell, retired CEO of Stanford Health Care, was speaking with her mother, Rosina Might, in her kitchen when Might's face started to droop. Mitchell, a former nurse, suspected a stroke and called 911. While she was on the phone, her mother collapsed, wouldn't answer questions, and was unable to move one of her arms and one of her legs. An ambulance arrived in minutes.

By the time Mitchell and her sister, who was visiting along with their mother from Atlanta, made it to Stanford's emergency department, Might was undergoing a CT scan. Seventeen minutes after her arrival, she received tPA — a record at the time, 2015.

"The coordination and how synchronized they all were," Mitchell said, "was really an amazing thing to experience from the patient side."

Might, then 92, spent two days in the hospital and flew home two days later. "It was clearly a fairly massive stroke," Mitchell said. "But the next morning she was talking in full sentences and moving her arm and leg."

Might died last year at 95. Without effective stroke treatment, Mitchell said, her mother could have spent the last years of her life unable to speak, possibly paralyzed, relying on round-the-clock care.

Instead, Mitchell said, "She lived a very productive, active three years. It was as if nothing had happened." **ISM**

Camera captures molecular detail to detect prostate cancer

By Hanae Armitage

Getting a close look at the prostate is critical for detecting cancer, but its rather intimate positioning (just in front of the rectum) makes it difficult to image.

Now, Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology, thinks he has a solution: a newly devised hybrid camera.

Traditionally, prostate cancer is detected via prostate cancer-associated blood biomarkers, such as prostate-specific antigen. Doctors often also use ultrasound or MRI to look for physical changes in prostate tissue. Newer techniques that harness positron emission tomography scans can even capture molecular detail, but those tactics are relatively more expensive and use radiation, Gambhir said.

"But the problem is that cancer within the prostate quite often doesn't lead to any anatomical changes until it's quite large or has spread beyond the capsule of the prostate into the lymph nodes around it," he said. "So for decades, we've been looking for ways to analyze and image the prostate with greater detail to detect changes earlier on, safely and at relatively low cost."

Gambhir's new technology, dubbed the transrectal ultrasound and photoacoustic device, or TRUSPA, marries ultrasound and photoacoustic imaging techniques to simultaneously produce a picture showing the anatomy of the prostate, functional details about the gland and molecular information that can help flag cancerous tissue.

In a proof of principle study, Gambhir and a team of scientists across Stanford, including biologists, engineers and doctors, have demonstrated the value of the instrument in about 20 patients. A paper describing the technology and results was published Aug. 28 in *Science Translational Medicine*. Gambhir is the senior author of the study, and Sri-Rajasekhar Kothapalli, PhD, is the lead author.

To improve on poke-and-hope

Since ultrasound is already used widely by urologists and generally in human imaging, Gambhir opted to start with that as the foundation of TRUSPA. Typically, if a biomarker such as prostate-specific antigen is elevated in a patient's blood, doctors then turn to a combination of ultrasound and biopsy, during which they use a needle to take about 20 samples from different regions of the prostate. The technique is rooted in a poke-and-hope theory — as in hopefully you're sampling the part of the prostate that contains the cancer tissue. But it's not guaranteed.

TRUSPA takes a different approach, which incorporates an imaging agent that cancer cells readily take up — more so than regular tissue. Then, through photoacoustic molecular imaging (which monitors the absorption of light waves to help characterize tissue type), doctors can see where the cancer cells are located

COURTESY OF SRI-RAJASEKHAR KOTHAPALLI AND SAM GAMBHIR

A new device employs ultrasound and photoacoustic imaging techniques to detect prostate cancer.

in the prostate. The presence of the imaging agent in tumor tissue changes the way that the light gets absorbed and ultrasound waves are sent back to the device, making it into a sort of flag for cancerous tissue.

"We opted for an imaging agent that was not specific to prostate cancer, but rather to cancerous tissues for our proof of principle," Gambhir said. That imaging agent was already approved by the Food and Drug Administration, making it an easy starting point. "But the idea moving forward is to heighten precision using a molecularly targeted photoacoustic molecular imaging agent that binds specifically to prostate cancer cells."

In the pilot study, the scientists used the device in 20 individuals who had been diagnosed with prostate cancer, looking to see whether it could likewise detect the disease.

"Not only were we able to better understand TRUSPA imaging limitations in the patients, we also were likely seeing tumors that would have otherwise been invisible to conventional prostate ultrasound," Gambhir said.

In one patient, they were even able to differentiate between malignant and nonmalignant cancer tissue, which was confirmed upon further molecular analysis after the diseased prostate was removed from the patient. Gambhir cautions that this is still a pilot, and that the team needs to test the imaging system much more before concluding that TRUSPA can make these sorts of differentiations broadly. But it is a promising start, he said.

With clear evidence that the concept and technology work in humans, Gambhir and his team are continuing to improve the device, including its spatial resolution and the molecular photoacoustic imaging agents specific for prostate cancer, to enhance the accuracy and sensitivity of tumor detection.

"We're now starting to explore TRUSPA for detecting ovarian cancer, thyroid cancer and skin cancer too," he said.

Other Stanford co-authors are Butrus (Pierre) Khuri-Yakub, PhD, professor of electrical engineering; Geoffrey Sonn, MD, assistant professor of urology; Joseph Liao, MD, associate professor of urology; and James Brooks, MD, professor of urology. **ISM**

Hospital

continued from page 1

surgeons to consult immediately with colleagues while patients are still under anesthesia, making surgeries faster, more efficient and safer for patients, said one of the video narrators.

After surgery, Peter moved into the intensive care unit, where a critical care nurse assured his wife at the bedside that he was doing well. Like all clinicians in the hospital, the nurse entered the room using an electronic badge check-in system, which tracks personnel throughout the building. Staff also will be equipped with a phone app enabling them to communicate and virtually monitor patients at all times.

During the ICU stop, hospital visitors were introduced to TUG, an autonomous, laser-guided robot, part of a fleet of 28 robots that will transport supplies throughout the medical center. Caregivers can request a piece of equipment online and ask TUG to retrieve it and deliver it to a specific location.

Peter got the care he needed in the ICU and was transferred to one of the hospital's 368 private rooms to recover.

Seeing a patient room

"Wow, beautiful," came a chorus of voices, as visitors entered one of the patient rooms and began snapping photos of the view of a tree-lined Welch Road, with the Santa Cruz Mountains in the background. Every room in the hospital comes with full-length windows with views, either of the hills or the bay. And family members are welcome to stay at all times, with a couch that opens out into a bed.

On the third floor, which is completely dedicated to wellness, visitors toured the hospital gardens, four acres of meandering pathways and green space with benches and tables for a quiet respite. "It's amazing how they take care of people in pain. They provide for their spirit," said Marie El Khoury of San Mateo as she walked through the gardens on one of the tours. "They give people an opportunity to heal quickly. God bless the hands that provide that."

The tour concluded in the hospital's expansive, circular atrium, with a curved wood and glass ceiling that soars upward, revealing views of the sky and the hospital's upper floors.

STEVE FISCH

(Clockwise from top left) During the new Stanford Hospital community open house, visitors could follow the path of a fictitious patient, "Peter," who was injured in a bicycle accident. More than 10,000 people attended the open house, held Sept. 14-15. A street fair at the event featured interactive activities, including a teddy bear "triage" area and an oversize game of Operation.

Outside, guests lined up at food trucks, where they filled up on sliders, Korean chicken, Vietnamese spring rolls and Indian curries, provided free by Stanford Health Care. Some stopped at a photo booth to have their pictures taken against a backdrop of the new hospital, while others checked in with the "VOICES" mural project, in which 4,000 community members, patients and staff created art to represent their vision of health and wellness. The pictures were molded into a digital mosaic commemorating the hospital's opening. It was unveiled at the open house at a booth where visitors could use a computer to locate their artwork in the final mural.

The hospital is scheduled to welcome its first patients in the fall, when it will be officially dedicated. For more on the new hospital, visit StanfordHealthCares.org. **ISM**

Glioma

continued from page 1

gliomas, she said. "There is real hopefulness to this discovery," she said. "We've been missing this entire aspect of the disease. Now we have a whole new avenue to explore, one that could complement existing therapeutic approaches."

How the tumors grow

High-grade gliomas form synapses with healthy neurons that transmit electrical signals to the cancerous tissue, the study found. The tumors also contain cell-to-cell electrical connections known as gap junctions. Together, the two types of connections allow electrical signals from healthy nerve cells to be conducted into and amplified within the tumors.

High-grade gliomas include glioblastoma, a brain tumor seen in adults that has a five-year survival rate of 5%; diffuse intrinsic pontine glioma, a pediatric brain tumor with a five-year survival rate below 1%; and other diagnoses such as pediatric glioblastoma and diffuse midline gliomas occurring in the spinal cord and thalamus. Studies published by Monje's team in 2015 and 2017 indicated that high-grade gliomas use normal brain activity to drive their growth.

To learn how this worked, the scientists first analyzed the gene expression of thousands of individual cancer cells biopsied from newly diagnosed glioma patients. The cancer cells strongly increased the expression of genes involved in forming synapses.

The researchers then used electron microscopy, a technique that can reveal tiny details of cell anatomy, to show that structures that look like synapses exist between neurons and glioma cells. To confirm that these synapses indeed connect healthy neurons and malignant glioma cells, the scientists studied mice with cells from human gliomas implanted in their brains. After the glioma tumors had become established, the researchers used antibodies that bound to fluorescent markers expressed by the cancer cells to confirm that synapses go into malignant cells. "We saw very clear neuron-to-glioma synaptic structures," Monje said.

Using brain tissue from mice with human gliomas, the researchers measured the transmission of electrical signals into and through the tumors. They recorded two types of electrical signals: brief signals lasting four to five milliseconds, which are transmitted across a synaptic junction from a healthy neuron to a cancer cell by way of neurotransmitter molecules; and sustained electrical signals lasting one to two seconds that reflect electrical current propagated by a flux of potassium ions across the tumor cells' membranes. The potassium currents are caused by signals from neurons and are amplified by gap junctions that connect the cancer cells in an electrically coupled network.

The scientists also conducted experiments using a dye to visualize the gap-junction-connected cells, and used drugs capable of blocking gap junctions to confirm that this type of junction existed between the tumor cells and mediated their electrical coupling. Further experiments measuring changes in calcium levels confirmed that the tumor cells are electrically coupled via gap junctions.

"The live calcium imaging made it strikingly clear that this cancer is an electrically active tissue," said Venkatesh, the lead author. "It was startling to see that in cancer tissue."

The researchers showed that about 5%-10% of glioma cells receive synaptic signals, and about 40% exhibit prolonged potassium currents that are amplified by gap junction interconnections such that half of all tumor cells have some type of electrical response to signals from healthy neurons.

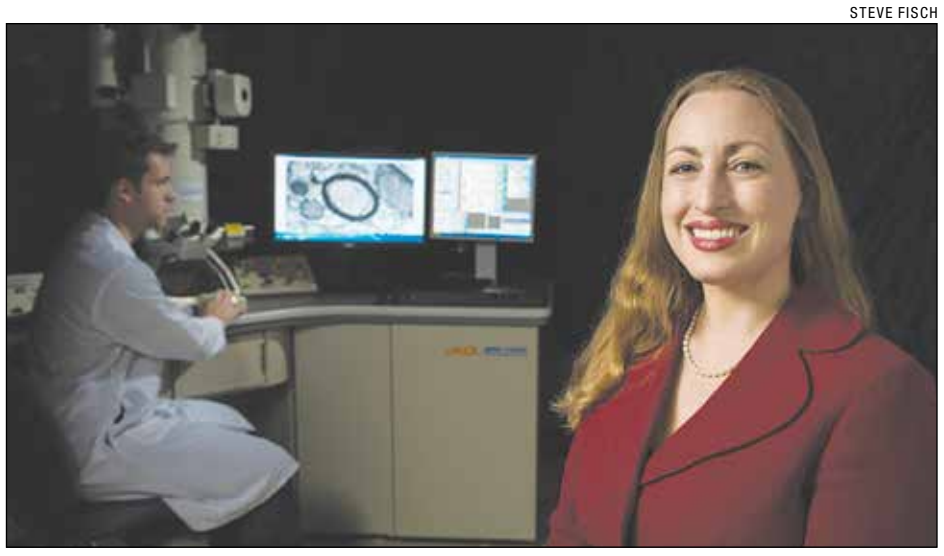
Possible drug therapies

In humans who were having the electrical activity in their brains measured before surgery to remove glioblastoma tumors, and in mice with human gliomas, the researchers saw hyper-excitability of healthy neurons near the tumors, a finding that could help explain why human glioma patients are prone to seizures.

Using optogenetic techniques, which relied on laser light to activate the cancer cells in mice implanted with human gliomas, the researchers demonstrated that increasing electrical signals into the tumors caused more tumor growth. Proliferation of the tumors was largely prevented when glioma cells expressed a gene that blocked transmission of the electrical signals.

Existing drugs that block electrical currents also reduced growth of high-grade gliomas, the research found. A seizure medication called perampanel, which blocks activity of neurotransmitter receptors on the receiving end of a synapse, reduced proliferation of pediatric gliomas implanted into mice by 50%. Meclofenamate, a drug that blocks the action of gap junctions, resulted in a similar decrease in tumor proliferation.

STEVE FISCH



Discovering that tumors wire themselves into the brain was "unsettling," researcher Michelle Monje said.

Monje's team plans to continue investigating whether blocking electrical signaling within tumors could help people with high-grade gliomas. "It's a really hopeful new direction, and as a clinician I'm quite excited about it," she said.

Other Stanford co-authors of the paper are staff scientist Wade Morishita, PhD; postdoctoral scholars Anna Geraghty, PhD, Marlene Arzt, MD, and Kathryn Taylor, PhD; graduate student Shawn Gillespie; medical student Lydia Tam; staff scientist Cedric Espenel, PhD; research assistants Anitha Ponnuswami, Lijun Ni and Pamelyn Woo; Hannes Vogel, MD, professor of pathology and of pediatrics; and Robert Malenka, MD, PhD, professor of psychiatry and behavioral sciences.

Monje is a member of Stanford Bio-X, the Stanford Institute for Stem Cell Biology and Regenerative Medicine, the Stanford Maternal & Child Health Research Institute, the Stanford Cancer Institute and the Wu Tsai Neurosciences Institute at Stanford.

Scientists from Massachusetts General Hospital, Harvard Medical School, the Massachusetts Institute of Technology, Johns Hopkins University, the University of Michigan and the University of California-San Francisco also contributed to the research.

The research was funded by the National Institutes of Health, the National Institute of Neurological Disorders and Stroke, the National Cancer Institute, the Michael Mosier Defeat DIPG Foundation, the Chad-Tough Foundation, the V Foundation, Ian's Friends Foundation, the Department of Defense, the Mckenna Claire Foundation, Alex's Lemonade Stand Foundation, The Cure Starts Now Foundation and DIPG Collaborative, the Lyla Nsouli Foundation, Unravel Pediatric Cancer, the California Institute for Regenerative Medicine, the Joey Fabus Childhood Cancer Foundation, the N8 Foundation, the Sam Jeffers Foundation, Cancer Research UK, the Virginia and D.K. Ludwig Fund for Cancer Research, and the Stanford Maternal & Child Health Research Institute's Anne T. and Robert M. Bass Endowed Faculty Scholarship in Pediatric Cancer and Blood Diseases. **ISM**

Cold

continued from page 1

mune surveillance brought about by previous exposure or a vaccine.

In a study published online Sept. 16 in *Nature Microbiology*, Carette and his associates found a way to stop a broad range of enteroviruses, including rhinoviruses, from replicating inside human cells in culture, as well as in mice. They accomplished this feat by disabling a protein in mammalian cells that all enteroviruses appear to need in order to replicate.

Carette shares senior authorship with Or Gozani, MD, PhD, professor of biology at Stanford and the Dr. Morris Herzstein Professor of Biology; Raul Andino, PhD, professor of microbiology and immunology at UCSF; and Nevan Krogan, PhD, professor of cellular and molecular pharmacology at UCSF. The lead authors are former Stanford graduate student Jonathan Diep, PhD, and Stanford postdoctoral scholars Yaw Shin Ooi, PhD, and Alex Wilkinson, PhD.

Well-known and feared

One of the most well-known and feared enteroviruses is poliovirus. Until the advent of an effective vaccine in the 1950s, the virus spelled paralysis and death for many thousands of children each year in the United States alone. Since 2014, another type of enterovirus, EV-D68, has been implicated in puzzling biennial bursts of a poliolike disease, acute flaccid myelitis, in the United States and Europe. Other enteroviruses can cause encephalitis and myocarditis — inflammation of the brain and the heart, respectively.

Like all viruses, enteroviruses travel lightly. To replicate, they take advantage of proteins in the cells they infect.

Colds cost the U.S. economy an estimated $40 billion a year.

To see what proteins in human cells are crucial to enteroviral fecundity, the investigators used a genome-wide screen developed in Carette's lab. They generated a cultured line of human cells that enteroviruses could infect. The researchers then used gene editing to randomly disable a single gene in each of the cells. The resulting culture contained, in the aggregate, cells lacking one or another of every gene in our genome.

The scientists infected the culture with RV-C15, a rhinovirus known to exacerbate asthma in children, and then with EV-C68, implicated in acute flaccid myelitis. In each case, some cells managed to survive infection and spawn colonies. The scientists were able to determine which gene in each surviving colony had been knocked out of commission. While both RV-C15 and EV-D68 are both enteroviruses, they're taxonomically distinct and require different host-cell proteins to execute their replication strategies. So, most of the human genes encoding the proteins each viral type needed to thrive were different, too.

But there were a handful of individual genes whose absence stifled both types' ability to get inside cells, replicate, bust out of their cellular hotel rooms and invade new cells. One of these genes in particular stood out. This gene encodes an enzyme called SETD3. "It was clearly essential to viral success, but not much was known about it," Carette said.

Impervious mice

The scientists generated a culture of human cells lacking SETD3 and tried infecting them with several different kinds of enterovirus — EV-D68, poliovirus, three different types of rhinovirus and two varieties of coxsackievirus, which can cause myocarditis. None of these viruses could replicate in the SETD3-deficient cells, although all proved capable of pillaging cells whose SETD3-producing capability was restored.

The researchers observed a 1,000-fold reduction in a measure of viral replication inside human cells lacking SETD3, compared with controls. Knocking out SETD3 function in human bronchial epithelial cells infected with various rhinoviruses or with EV-D68 cut replication about 100-fold.

Mice bioengineered to completely lack SETD3 grew to apparently healthy adulthood and were fertile, yet they were impervious to infection by two distinct enteroviruses that can cause paralytic and fatal encephalitis, even when these viruses were injected directly into the mice's brains soon after they were born.

"In contrast to normal mice, the SETD3-deficient mice were completely unaffected by the virus," Carette said. "It was the virus that was dead in the water, not the mouse."

Enteroviruses, the scientists learned, have no use for the section of SETD3 that cells employ for routine enzymatic activity. Instead, enteroviruses cart around a protein whose interaction with a different part of the SETD3 molecule, in some as yet unknown way, is necessary for their replication.

"This gives us hope that we can develop a drug with broad antiviral activity against not only the common cold but maybe all enteroviruses, without even disturbing SETD3's regular function in our cells," Carette said.

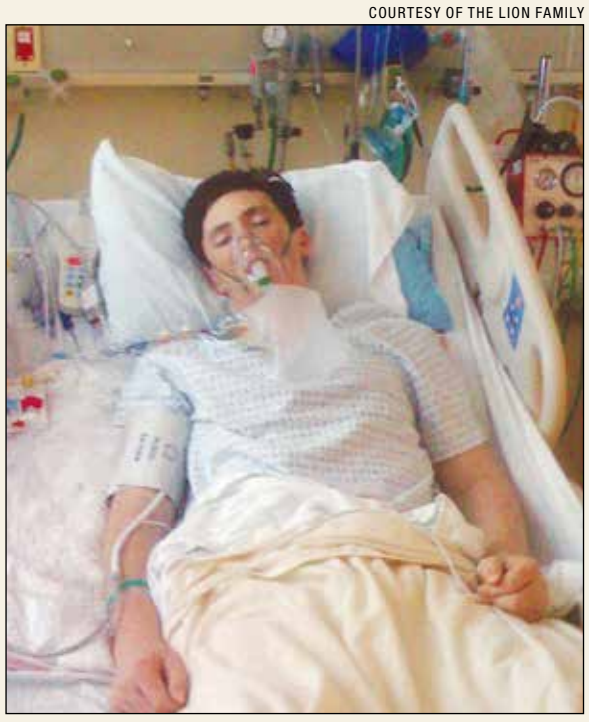
Carette and Gozani are members of Stanford Bio-X and the Stanford Maternal & Child Health Research Institute, as well as faculty fellows of Stanford ChEM-H. Gozani is a member of the Stanford Cancer Institute. **ISM**

Full circle: Former Packard Children's patient returns as resident

By Kate DeTrempe

LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD

COURTESY OF THE LION FAMILY



Left, David Cornfield and Ryan Lion during Lion's residency at Lucile Packard Children's Hospital Stanford. Right, Lion as a patient at the hospital.

When Ryan Lion, MD, began his pediatrics residency at Lucile Packard Children's Hospital Stanford earlier this summer, he already knew some of the doctors and nurses he would be working with. Ten years before, they had saved his life.

In 2009, during the final semester of Lion's senior year at Saint Francis High School in Mountain View, California, he suddenly fell very ill.

"I had felt totally normal, and then in one specific moment everything changed," Lion recalled. "I felt feverish, had chills. The next morning, I woke up with a rash on my arm and had weakness and pain in my joints. I could barely walk."

Ryan's local emergency department completed a series of blood tests that were sent to Packard Children's for further evaluation.

'Hanging on by a thread'

David Cornfield, MD, chief of the Stanford Children's Health Pulmonary, Asthma and Sleep Medicine Center and former chief of critical care medicine, was on service in the pediatric intensive care unit, or PICU, that afternoon. He reviewed Lion's lab results and recognized evidence of disseminated intravascular coagulation, a dangerous condition affecting the blood's ability to clot and stop bleeding. He called for Lion's immediate transfer to the PICU at Packard Children's.

"My impression of Ryan upon arrival was profound septic shock. He was extremely ill," said Cornfield, the Anne T. and Robert M. Bass Professor in Pediatric Pulmonary Medicine. "At that moment, I felt he was hanging on by a thread."

Cornfield and his team worked quickly to place intravenous catheters, deliver fluids and administer antibiotics and a medication to strengthen Lion's blood vessels. Lion spent the next week in the hospital being treated for organ damage caused by the infection.

Ultimately, he went on to graduate from high school a few months after his illness. He attended college, graduate school and medical school before matching for his pediatrics residency program in March 2019 at Stanford.

10 years later: Delivering care

"I was always interested in medicine, and being hospitalized reaffirmed my plans to pursue it," Lion said. "But never did I imagine in that moment that I would be a physician at the very same institution that cared for me, part of the same care team, now on the other side of delivering care."

In the second month of Lion's residency this summer, he spent a week working alongside Cornfield in the PICU.

"It was an awesome, full-circle moment knowing he was the one who cared for me in that very unit," Lion said.

"Walking into Ryan's room and making the observations I did when we could still intervene is a moment I remember well. And even through the lens of now 10 years later, that memory really underscores the importance of the sorts of things we do every day," Cornfield said. "Seeing Ryan today is a profound reminder of the deep trust people place in us as providers, and of the power of healing that has very significant long-term impact in the lives of very real people that lasts well beyond our interactions at the bedside."

> **"Seeing Ryan where he is today is extremely rewarding."**

Lion also feels supported by the nurses he has worked with as a resident, some of whom helped care for him when he was a patient.

Agnes Dado, RN, has been a critical care nurse at Packard Children's for nearly two decades and worked in the PICU during Ryan's hospitalization. "We see our children come and go throughout the years. It can be difficult and yet rewarding at the same time," Dado said. "Seeing Ryan where he is today is extremely rewarding."

A unique perspective

For Lion, the experience of being hospitalized not only solidified his decision to pursue medicine when he entered college later that year, but it inspired an interest in global health and a desire to care for underserved communities.

"Here I was at this premier institution receiving this incredible care," Lion said of his time as a patient at Packard Children's. "I felt a need to go forward and ensure all people, both here and abroad, have access to the health care they require in their time of need."

Ryan said that having been a patient in the same hospital where he is now providing care gives him a unique perspective.

"Knowing firsthand the stress than an ICU admission puts on patients and their families, it has been very humbling for me to be on this side of patient care," Lion said. "I carry that experience with me during all of my patient encounters." ISM

OF NOTE

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

Neal Amin

Jessica Bentzley

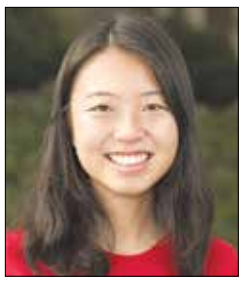
Ira Glick

Steven Goodman

Heather Wakelee

Marius Wernig

Nolan Williams



Serena Yeung

NEAL AMIN, MD, PhD, resident in psychiatry and behavioral sciences, received the National Institute of Mental Health's outstanding resident award, which recognizes psychiatry residents who show great potential for succeeding in research and academia.

JESSICA BENTZLEY, MD, received the Association for Academic Psychiatry's resident psychiatric educator award, which honors residents who show promise as educators and scholars in academic psychiatry.

IRA GLICK, MD, professor emeritus of psychiatry and behavioral sciences, received the Payne Whitney Clinic Award for Extraordinary Public Service from the Weill Medical College at Cornell University. He also received the Jackson E. Spears Community Service Award from New York Medical College.

STEVEN GOODMAN, MD, PhD, professor of medicine, received the 2019 Abraham Lilienfeld Award from the American College of Epidemiology in recognition of his work in expanding knowledge of scientific and statistical inference and his contributions to epidemiology.

HEATHER WAKELEE, MD, professor of oncology, was named president-elect of the International Association for the Study of Lung Cancer and assumed the role in September. Her two-year term as president will begin in 2021.

MARIUS WERNIG, MD, PhD, was promoted to professor of pathology, effective July 1. His research focuses on investigating cellular reprogramming and advancing stem cell-based therapies for genetic diseases.

NOLAN WILLIAMS, MD, assistant professor of psychiatry and behavioral sciences, received the Klerman Prize for Exceptional Clinical Research from the Brain & Behavior Research Foundation in recognition of his work in neurostimulation techniques, mechanistic understanding of rapid-acting antidepressants and the identification of biomarkers in treatment-resistant conditions.

SERENA YEUNG, PhD, was appointed assistant professor of biomedical data science, effective July 1. Her research interests include computer vision, machine learning and deep learning, with a focus on human-activity and video understanding in applications related to health care. ISM