STANFORD MEDICINE

Fall 2019

special report

THE NEW STANFORD HOSPITAL
The future is here

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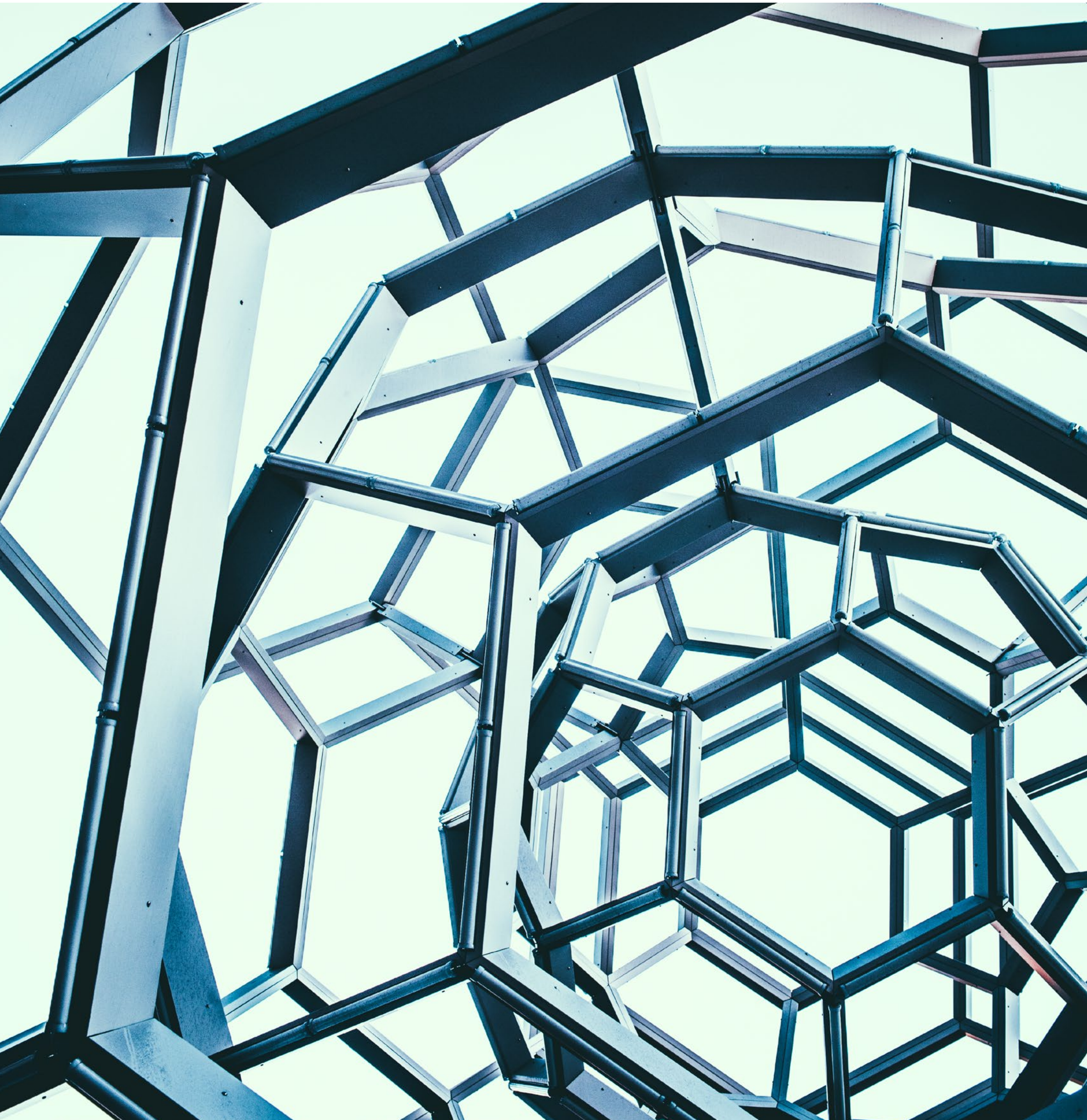

SCHOOL'S IN SESSION AT THE HOSPITAL

ENGLISH, MATH AND EVEN SCIENCE EXPERIMENTS HELP SCHOOL-AGED PATIENTS KEEP UP

High school science experiments often have elements of danger: Students heat chemicals over Bunsen burners, wrangle fragile glassware, wield scalpels during dissections and try to "always add acid" to water (instead of the other way around) to avoid hazardous splashes. But the hands-on part of the science curriculum is hard to teach in a hospital, where many dangerous materials, such as open flames and lab animals, are not allowed.

As a result, Kathy Ho, a longtime high school teacher at the hospital school at Lucile Packard Children's Hospital Stanford, used to struggle to offer experiments to her students. Ho is part of the hospital's team of four teachers who run the K-12 hospital school, a part of the Palo Alto Unified School District, and work with several hundred hospitalized children a year. At Packard, some patients stay for just a few days, but the majority stay for a month or more. Ho and her colleagues help all of these pupils keep up with their studies.

"Providing the opportunity for our students to stay on par with their peers at home means giving them hope that things are going to be normal again," Ho said.

In 2008, to address the science-lab challenge, Ho tapped a local resource: Stanford scientist Andrew Spakowitz, PhD, associate professor of chemical engineering and of materials science and engineering. Ever since, Spakowitz has recruited Stanford undergraduate and graduate students to design biology, chemistry, physics and engineering experiments that fit California curriculum standards.

Kathy Ho, left, teaches math to high school student Travis Weston at the Lucile Packard Children's Hospital Stanford school.

"The Stanford students come up with clever ways to develop new labs suitable for the hospital environment," Spakowitz said, noting they've created more than 30 lab activities using cheap, safe, easily available materials.

To get around the restriction on bringing lab animals into the hospital, one biology lab employs Stanford students as guinea pigs: While the Stanford students jog in place, the hospital students measure such variables as heart rate and breath volume. In an engineering assignment, kids evaluate the good and bad features of hospital gowns. In an optics lab, students point inexpensive hand-held lasers through Jell-O to see how the material bends light.

The labs get rave reviews from the pupils. "Science gets kids excited and engaged," Ho said. "They can forget for a while that they're in the hospital."

MEETING KIDS' NEEDS

When school-aged patients arrive at the hospital, the teachers assess their needs. As long as they're well enough to do some schoolwork, pupils in kindergarten through fifth grade receive instruction in English, language arts and math. For older students, the teachers coordinate with a counselor at their usual school to determine if the student can work on assignments while they are away.

The hospital school also provides extracurricular activities, including in art and drama. And any student who has attended classes at the hospital during the school year is invited to the spring prom, an evening of fun, games, food and dancing.

Besides working together on school activities, students also bond over their medical experiences.

"They may not have the same diagnoses, but they help each other talk through things," Ho said. "A kid who has had a heart transplant maybe empathizes with a kid with cancer."

Older students also mentor the younger ones, with high schoolers sometimes befriending kindergarteners. "It's so fun to watch," Ho said. "We're lucky that we can provide all of these children with a dynamic, really vibrant school environment." — ERIN DIGITALE

TIMOTHY ARCHIBALD

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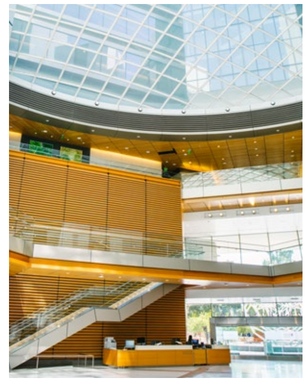


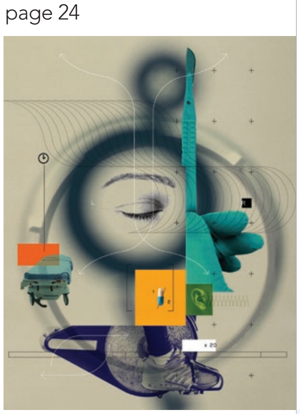
Let the sunshine in
page 6

SPECIAL REPORT

The new Stanford Hospital

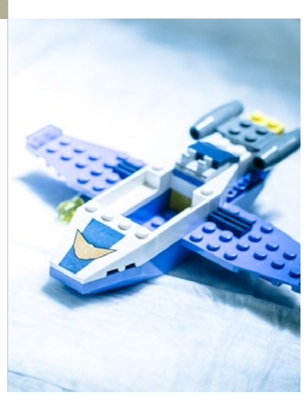
The future is here

Better surgery recovery
page 24



PLUS

Outside-the-box solutions for improving collaboration
page 28



DEPARTMENTS

COVER: TIMOTHY ARCHIBALD

letter from the dean

Though the new Stanford Hospital was built with steel and concrete, its foundation is precision health.

This 824,000-square-foot facility, which opened Nov. 17, is advancing research, education and patient care, and helping us to usher in our vision of predictive, holistic health care.

For decades, Stanford Medicine has been synonymous with innovation, and the new Stanford Hospital continues this pioneering legacy. Though many contributed to this extraordinary achievement, I am especially grateful to Stanford Health Care President and CEO David Entwistle. His vision and leadership have been critical to overcoming the many challenges that accompany a project of this magnitude.

In conjunction with our state-of-the-art multidisciplinary research buildings and the recently renovated Lucile Packard Children's Hospital Stanford, we have some of the most advanced infrastructure and technology anywhere. Through an increased capacity for translational medicine, we are expanding our ability to rapidly move breakthroughs from researcher bench to patient bedside.

Students, trainees and experienced clinicians alike are practicing their skills in an immersive, digitally rich environment. Consider the hospital's 28 new operating rooms.

They bring together imaging and other technologies that give surgeons critical real-time access to the information they need, whether it's through video conferencing with specialists on the other side of the world or using an interventional MRI to scan patients while in surgery.

The new hospital offers the same unparalleled patient care for which Stanford is known, but on a greater scale. It features 368 patient beds, bringing our total to 600. The Marc Andreessen & Laura Arrillaga-Andreessen Emergency Department enables us to treat 30,000 more patients each year. By expanding access, we will better serve our community today and for years to come.

Though it is one of the most technologically sophisticated in the world, our hospital prioritizes the real and powerful impact of high-touch care and emotional and spiritual wellness. Our patients can walk acres of beautiful gardens, take in the original paintings and sculptures that fill the halls and grounds, and be revitalized in rooms filled with natural light. All of these contribute to their healing and demonstrate our deep commitment to providing compassionate care.

Beyond its physical characteristics and capabilities, the hospital is second to none because of our dedicated and talented physicians, nurses, researchers, students and staff. It is only through the coordinated efforts of our entire Stanford Medicine team that we will realize the full potential of this beautiful space.

After a decade of designing, planning and building, we have created a hospital that will profoundly change health care. The new Stanford Hospital combines the best possible resources with the best possible environment to bring about a precision health future where we no longer just treat disease but predict, prevent and cure it — precisely.

I look forward to continuing to work closely with David and Stanford Children's Health President and CEO Paul King as we welcome this bright future of health care.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery

LEFT: GLENN MATSUMURA; TOP: PAUL KEITZ PHOTOGRAPHY

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

Small but mighty

TENS OF THOUSANDS of previously overlooked tiny proteins are now being hailed as instrumental in advancing scientific understanding of how the microorganisms that dwell in and on our bodies affect our health, researchers have found. What's more, if their shapes and functions can be recreated in the lab, the knowledge could lead to new drug discovery, they said.

There's mounting evidence that many aspects of our health are closely intertwined with the composition and hardiness of these microscopic hitchhikers, collectively known as the human microbiome.

The proteins, which belong to more than 4,000 new biological families, are predicted to be involved in the warfare waged among different bacterial strains as they vie for primacy in coveted biological niches.

They are so small — fewer than 50 amino acids in length — they likely fold into unique shapes that represent previously unidentified biological building blocks. A paper describing the research was published Aug. 8 in *Cell*.

"It's critically important to understand the interface between human cells and the microbiome," said senior author, Ami Bhatt, MD, PhD, assistant professor of medicine and of genetics. "How do they communicate? How do strains of bacteria protect themselves from other strains? These functions are likely to be found in very small proteins, which may be more likely than larger proteins to be secreted outside the cell."

But the proteins' miniscule size makes them difficult to identify and study. "We've been more likely to make an error than to guess correctly when trying to predict which bacterial DNA sequences contain these very small genes," Bhatt said. "So until now, we've systematically ignored their existence. It's been a clear blind spot."

ELVIS SWIFT

'It's critically important to understand the interface between human cells and the microbiome.'

Pain blocker

THE EXPERIMENTAL DRUG filgotinib provides relief from rheumatoid arthritis by blocking a set of enzymes that cause inflammation, a Stanford-led trial shows.

About 75 million people suffer joint pain, stiffness, inflammation and deterioration from rheumatoid arthritis. But three-quarters of patients surveyed reported being dissatisfied with treatment.

"For patients who haven't done well on other therapies, these findings are cause for optimism, enthusiasm and hope," said author Mark Genovese, MD, professor of immunology and rheumatology and the lead author of a paper describing the trial published July 23 in *JAMA*.

Better leukemia treatment

A NEW DRUG combination for chronic lymphocytic leukemia appears to be better tolerated by patients and helps them live longer than traditional chemotherapy, a clinical trial Stanford and multiple other institutions showed.

"This represents a paradigm shift in how these patients should be treated," said Tait Shanafelt, MD, the Jeanie and Stew Ritchie Professor of medicine and lead author of a paper on the research, which was published Aug. 1 in *The New England Journal of Medicine*. "We can now relegate chemotherapy to a fallback plan rather than a first-line course of action."

Researchers recruited 529 patients newly diagnosed with the common blood cancer who were randomly assigned in a 2:1 ratio to receive a treatment that combines ibrutinib and rituximab — which target the B cells that run amok in the disease — or traditional chemotherapy of the drugs fludarabine, cyclophosphamide and rituximab.

Participant Dan Rosenbaum, 57, said he saw "marked" improvements with the new treatment, with few side effects. "It's so unbelievable it is almost hard to talk about."

Three years after the trial, 98.8% of the people who received the new drug combination were alive, versus 91.5% of those who received the traditional treatment, the study showed.

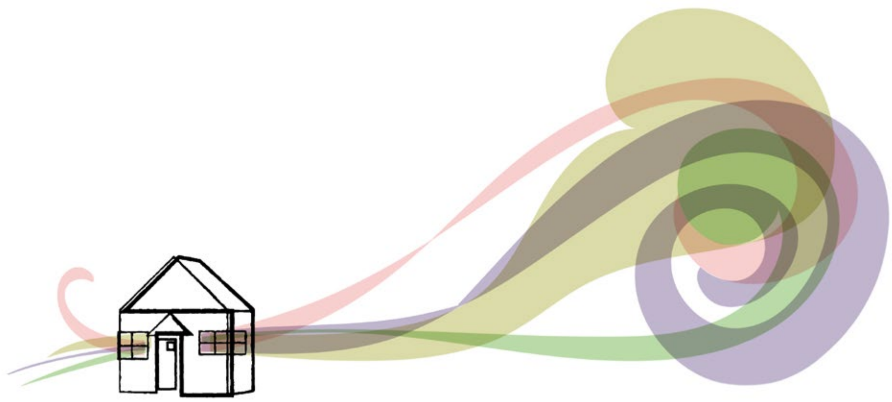
SILENT KILLER

INFLAMMATION FROM A SIMPLE INFECTION can awaken a silent genetic defect in rats that carry it, resulting in a deadly form of pulmonary hypertension, a Stanford study shows.

Pulmonary hypertension is a type of high blood pressure that damages arteries in the lungs and heart. About 200,000 Americans are hospitalized each year with difficulty breathing, fatigue and chest pain from the disease, the cause of which has been unknown.

"It's a kind of one-two punch," said Amy Tian, PhD, senior research scientist in pulmonary and critical care, and lead author of the study published Aug. 29 in *Circulation*.

"Basically, the first hit is the mutation, and the second hit is inflammation in the arteries of the lungs. You can be healthy and carrying this mutation, and all of the sudden you get a bacterial or viral infection, and it leads to this terrible disease."



Pesticides and kids

BRAIN SCANS OF A GROUP OF ADOLESCENTS in California's Salinas Valley show a direct link between reductions in certain brain functions and the level of pesticides their mothers were exposed to during pregnancy.

This research, by scientists at Stanford and UC-Berkeley, adds to existing data about the health effects of insecticides used on the abundance of lettuce, strawberries, broccoli, spinach and other produce grown in the Salinas area.

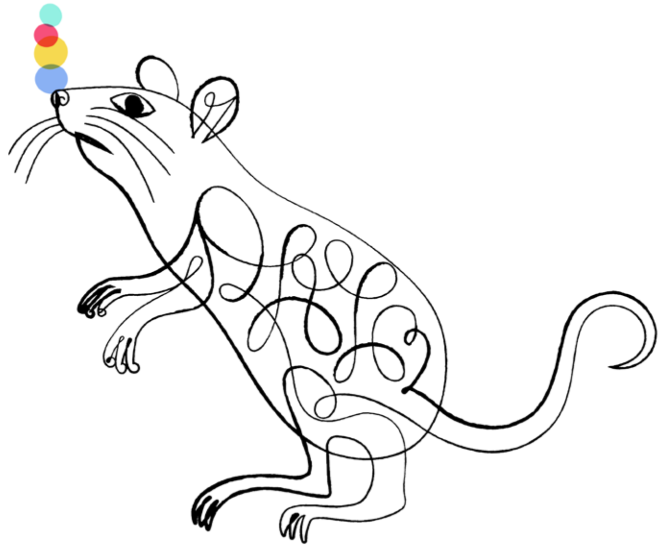
Though the federal Environmental Protection Agency has banned some organophosphate pesticides and the California EPA recently expanded prohibitions, many are still used in farming. Most people ingest pesticides through food, while farming community residents are exposed through field dust.

Stanford researchers scanned the brains of 95 adolescents who grew up in Salinas and whose mothers lived there during pregnancy. The Berkeley team began following the children in 1999, using data about where the mothers lived to estimate levels of pesticide exposure in utero.

Scans were taken as children completed tasks that measured brain function. When tasks required such skills as strategic planning or modulating impulses, scans revealed lower brain activation in children with more prenatal pesticide exposure.

"It's really quite amazing that we see a long-term association between these exposures and brain function," said neuroscientist Allan Reiss, MD, who co-authored the study with experimental psychologist Joseph Baker, PhD. They hope their findings, published Sept. 10 in *Proceedings of the National Academy of Sciences*, spark further research and more conversation about pesticide use trade-offs.

Balancing act



RESEARCHERS INVESTIGATING how different cells respond when our immune systems mistakenly attack healthy tissues have found a particular cell that jumps in to reduce the friendly fire.

The discovery during research on mice with a multiple-sclerosis-like disease suggests that inflammatory and suppressive immune cells can balance each other out. Stimulating the protective cells, called CD8 T cells, could lead to new therapies for autoimmune diseases, said Mark Davis, PhD, professor of microbiology and immunology and senior author of a study published Aug. 7 in *Nature*.

"We absolutely think that something like this is happening in human autoimmune diseases. It represents a mechanism that nobody's really appreciated. There's this whole subset of CD8 T cells that has a suppressive function," said Davis, who holds the Burt and Marion Avery Family Professorship. "If we could mobilize those cells to function more effectively in patients with autoimmunity, then we'd have a novel treatment for diseases like multiple sclerosis."

For the study, researchers tracked immune cells in the blood of mice with a disease akin to multiple sclerosis and discovered a rise in CD8 T cells, typically known for killing infected or cancerous cells. To their surprise, injecting mice with peptides that activated these CD8 T cells reduced disease severity and killed disease-causing immune cells.

Autoimmune diseases such as multiple sclerosis and celiac disease affect 23.5 million Americans, according to the National Institutes of Health.

TRANSFORMER CELLS

ATHEROSCLEROSIS OCCURS when plaque — a buildup of fat, cholesterol and other substances within artery walls — causes a blockage or clot that can lead to a heart attack.

Now, researchers have identified a group of cells that transform into tissue that caps off plaque, preventing it from bursting into the arteries of someone with the condition.

They also believe they found the gene behind the transition of healthy smooth muscle cells — which form the wall of arteries and regulate blood flow and blood pressure — into fibrous cells that block the plaque from tearing open artery tissue.

"We know that things like poor diet and lack of exercise contribute to atherosclerosis," said Thomas Quertermous, MD, the William G. Irwin Professor in Cardiovascular Medicine at Stanford. "But molecularly speaking, researchers still don't know how the disease progresses or, conversely, is hindered."

A paper describing the study, which showed that people who had more activity of the identified gene had a lower risk for heart attack, was published July 29 in *Nature Medicine*. Quertermous and Juyong Kim, MD, instructor of medicine, are the senior authors; Robert Wirka, MD, instructor of cardiovascular medicine, is the lead author.

Cost of reformatting the 2.3 million scientific articles published annually: over

$1 billion.

More at stan.md/reformat.

Taking to talking

AN AUTISM THERAPY CALLED pivotal response treatment, which taps into children's interests, works better than existing therapies at motivating the children to talk, according to a large study by Stanford School of Medicine researchers.

In the treatment, parents and therapists encourage children who have speech delays to name something they want, such as a toy or a drink, before giving it to them.

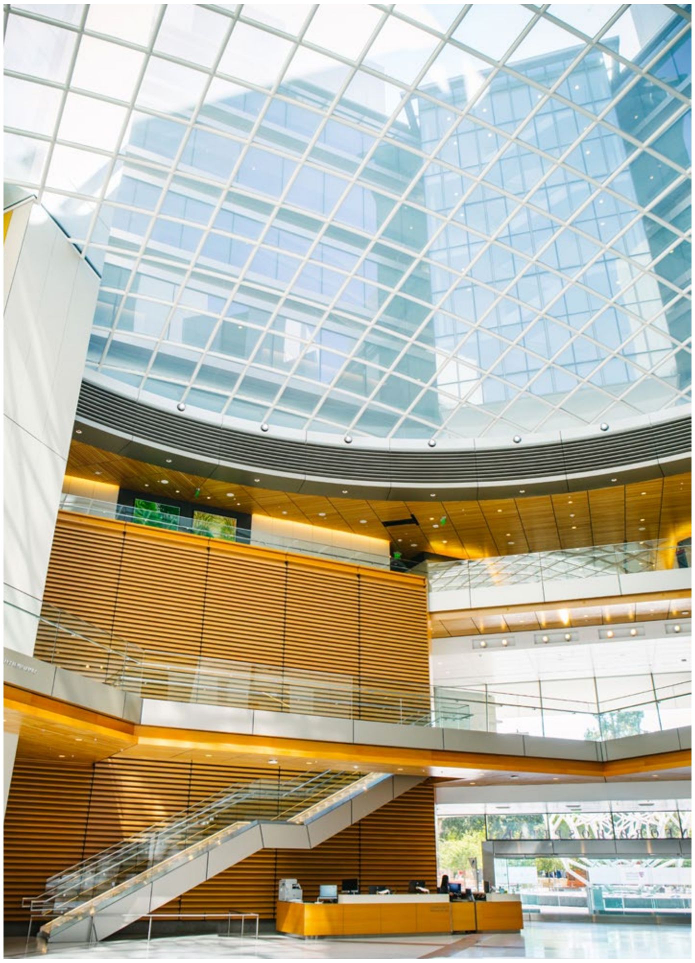
"The results of our study are exciting because we found that children in the pivotal response treatment group improved not just in their communication skills, but also in their broader social abilities," said Grace Gengoux, PhD, clinical associate professor of psychiatry and behavioral sciences and the lead author of the study published Aug. 5 in *Pediatrics*.

ELVIS SWIFT

TOMORROW'S HOSPITAL TODAY

Advanced technology and a design that puts well-being first come together in the new Stanford Hospital

BY JULIE GREICIUS
PHOTOGRAPHY BY TIMOTHY ARCHIBALD



There's a line that David Entwistle, president and CEO of Stanford Health Care, recalls hearing his colleague George Tingwald, MD, say on more than one occasion: "The future is not what it used to be."

Tingwald's quip refers to the potentially mind-warping challenge of planning a hospital meant to serve for at least 100 years. That building, the new Stanford Hospital, opened its doors Nov. 17.

"You future-proof a building by trying to understand how to create the most flexible framework to allow for change, even though you may not know what that change is," said Tingwald, who is Stanford's administrative director of medical planning, as well as an architect and a surgeon.

The result of all this planning, which called on the expertise of hundreds of

Letting the light shine in

An essential element of the design of the new Stanford Hospital is to take advantage of natural light throughout the building to promote healing and tranquility. Patients, visitors and employees pass through the front entrance into a large, open atrium filled with light streaming in through the glass-domed ceiling.

clinicians, staff and community members, is the seven-story, light-filled building designed to promote healing and facilitate teamwork among staffers and clinicians. The building — the largest on the Stanford campus at 824,000 square feet — was built to withstand an 8.0-magnitude earthquake and can double or even triple its patient capacity in the event of a disaster or mass casualty event. It has its own sewer tank, water tank and generators that can produce 2.5 megawatts of power.

Within its walls, advanced technology; highly skilled, compassionate staff; and patient rooms with picture-window views of nature come together to make an outstanding setting for medical care, research and education.

"The new Stanford Hospital presents unprecedented opportunities to transform care," said Lloyd Minor, MD, dean of the Stanford University School of Medicine.

"It's a beautiful, serene setting for healing that is also an advanced incubator where we can cultivate our vision of precision health — predicting and preventing disease in the healthy and precisely diagnosing and curing disease in the ill. For patients and families as well as medical students, trainees and scientists, the new Stanford Hospital promises to raise the bar for all we do in care, research and education."

FUTURE DESIGN TO HELP PATIENTS FLOURISH

The motivation to build a new hospital came from stringent seismic safety requirements set by California in 1994, and from the need to increase capacity to serve a ballooning San Francisco Bay Area population.

Into its operations are woven about 180 applications that make the hospital a working laboratory for health care technology — including patient-comfort controls at every bedside to adjust lighting, room temperature, window shades and entertainment, and two units equipped with artificial intelligence-enabled cameras to study how monitoring can improve quality and patient safety.

Wheeled robots will transport linen and refuse, so people won't have to. Heart-rate monitors, oxygen saturation monitors, infusion pumps, automated prescription-filling machines and hand-held devices used by nurses and doctors are connected to patients' electronic health records that are updated in real time.

Artwork and nature's beauty are visible throughout the hospital — 4 acres of gardens, views from every patient room, wall-to-wall windows in common areas and dramatic artworks that delight and inspire. The emphasis on art and nature reflects the growing recognition that they contribute to healing and well-being.

"From the patient rooms, the views are spectacular," said local resident Michael Moore, a member of the hospital's Patient and Family Advisory Council who toured the new building before it opened. "You've got the mountains to the west, the skyline of Palo Alto to the east and campus — one of the greatest views of Hoover Tower. It's absolutely beautiful. And then at night, when the sun goes down, in that pure light, it's absolutely breathtaking."

With the new hospital open, the older hospital next door houses the pediatric emergency department and the inpatient psychiatry unit, and a section is being renovated to become a cancer hospital. The two hospitals, which together hold 600 adult beds, are joined by a bridge spanning an outdoor pedestrian promenade.

The new hospital, designed by a team led by Rafael Viñoly Architects, is built on base isolators — a structural foundation decoupled from the building it supports — to allow the structure above to remain steadier during an earthquake, versus making the entire building fixed and rigid. That early decision opened the door to the building's architectural potential. The $2 billion project is the result of more than a decade of work, including six years of construction.

Coming through the new hospital's front doors, patients and visitors find themselves in a wide-open, circular atrium topped with a soaring glass ceiling. Incorporating natural light and large windows with views guided the planning process from the beginning, said Tingwald. "There is daylight and a view within 50 feet of any point in the building. Every corridor ends in a window."

Patient rooms are on the top four levels of the hospital, where four towers extend out from the center of the building. Each of the 368 rooms has a single bed and wall-to-wall picture window showcasing views of the Stanford campus and foothills. And each has a bathroom and a daybed for visitors.

BRINGING THE BUILDING TO LIFE

THE FOCUS FOR ALPA VYAS, vice president of patient experience for Stanford Health Care, is not so much on the building, but on the people within it.

"The real task for our team, as we were getting closer to opening day, was how do you kind of breathe life into this beautiful, amazing building?" she said. "It's really the people within the building who bring it to life. The experience is not only the physical facility and the environment, it's also the culture and service."

Beyond the floors dedicated to patient care and procedures, the new hospital's third floor is devoted to cultivating wellness. The floor features lounges for patients and their families, a lounge for staff, a dining area, a meditation/chapel space, and access to outdoor gardens and a walking trail. It also has a health library and caregiver resource center.

The goal is to build a knowledgeable network of people to

A design for the future, today

David Entwistle, president and CEO of Stanford Health Care (opposite page, top) and George Tingwald, Stanford's administrative director of medical planning (bottom), were two key leaders of the effort to build a hospital that can serve the community for 100 years. The resulting hospital includes larger operating rooms to accommodate technological innovations as yet to be imagined (right).

Building a culture of wellness

Alpa Vyas, vice president of patient experience for Stanford Health Care, said that as her team prepared to move into the new hospital, their focus was on bringing the 'beautiful, amazing building' to life with a culture of service. 'There's a balance between future innovation, technology and the human touch.'

support patients and their families long after they leave the hospital, Vyas said.

"How do we care for these individuals as well, not only their health, but also their knowledge and understanding about the future of the disease or diagnosis that their loved one is dealing with?" she asked. "How do we empower them to be the extension of Stanford when it comes to helping their loved one?"

The patient navigation team members are available to explain resources that add to the ability of family or friends to support the patient's successful care, even from a distance. One of those resources, MyHealth, an app that Stanford patients have used for several years to manage their care and medical information, has been updated with new features. A "hospital view" feature activates as soon as patients are admitted, guiding them through their stay using navigation tools and content elements that keep them, and others they designate, informed about their care.

"Family members may be in a chair right next to the patient, or they may be 3,000 miles away," Vyas said. "A daughter who lives in Washington, D.C., can keep tabs on what's happening with a parent who may be hospitalized." The daughter could also learn about the parent's transportation needs upon discharge from the hospital.

Interactions with patient navigation experts add an important layer of personal care to continuing advances in medicine. "There's a balance between future innovation, technology and the human touch," Vyas said.

THE FUTURE WE KNOW

Building a hundred-year hospital means understanding the future in two ways, said Tingwald. "There's one category, the future you know, and then there's this whole category of the future you don't know. And we tried to respond to both of those."

Emergency department planners learned from events like 9/11 that they need to be able to rapidly scale up to accommodate more patients after a disaster or mass casualty event.

‘THERE’S ONE CATEGORY, THE FUTURE YOU KNOW, AND THEN THERE’S THIS WHOLE CATEGORY OF THE FUTURE YOU DON’T KNOW. AND WE TRIED TO RESPOND TO BOTH OF THOSE’

“You have to plan for today, but also for this enormous contingency,” said Tingwald, while noting that it wouldn’t be cost-effective to design a disaster-ready hospital that on an average day would be relatively empty. The difference in scale between the single patient and multiple patients — doubling or tripling the hospital’s capacity — is the critical ingredient of smart, future-ready design.

As the only hospital on the San Francisco Peninsula verified as a Level 1 trauma center by the American College of Surgeons — and one of only five in California — Stanford’s Marc Andreessen & Laura Arrillaga-Andreessen Emergency Department is equipped to handle worst-case scenarios.

“We are not the emergency room of sniffles,” said Alison Kerr, RN, chief administrative officer of clinical operations. “We see the transplant patients, the cardiac surgery patients, the trauma patients. These are our patients.”

The new emergency area is 2½ times the size of the older department. The length of a football field, it has 66 large, private bays — each with the equipment necessary to accommodate at least one extra patient.

Four full, private triage rooms are equipped with exam lights, oxygen and full-size gurneys so patients can be treated in those spaces if necessary. New features include a dental emergency room and 55-inch, two-way video monitors near the foot of every patient’s bed for services that include both remote consultation services and medical translation for the hospital’s many non-English-speaking patients.

BY THE NUMBERS

How the new **$2 billion** Stanford Hospital is poised to serve the community for **100** years

The new complex is the largest building on campus at **824,000** square feet. • It can withstand an **8.0** magnitude earthquake. • More than **5,500** Stanford Health Care employees work in the new space. A medical helicopter stop atop one wing is **160** feet above ground. • The hospital can produce **2.5** megawatts of power. • About **180** tech applications are being used, including a MyHealth app that helps patients, families and staff access patient health records.

A daylight view is visible within **50** feet of any spot inside the building. • Wall-to-wall windows provide sweeping views from the **368** new patient rooms; the new hospital connects to the older hospital, which is being renovated — bringing the bed total to **600**. • More than **400** pieces of art and **4** acres of gardens grace the new public spaces. • In the kitchen’s **7,000** extra square feet of space, staff serve **1,300** meals a day, accommodating more than **100** different diets.

The **42,692**-square-foot emergency department has **66** private bays and is **1 of 5** Level 1 trauma centers in California. • Staff is expected to handle up to **90,000** emergency patients by the end of 2020. • **Nine of 28** operating rooms are outfitted with in-room equipment for advanced image-guided surgeries in real time.

Twenty-three robots will carry linens, refuse and food trays; Lucile Packard Children’s Hospital Stanford has **five** of these devices, for a total of **28**. • They are **4** feet tall, can haul **a ton** and travel at **2** mph. • A **4-mile** pneumatic tube system in the new building connects to the tubes in the older building to transport tissue, blood samples and other medical materials; the system total is now **8** miles.

Three large-cabinet-sized machines load single doses of medications into packets for delivery to **115** dispensing stations. • One machine can package **1,000** doses an hour — a task that would take **10** hours for a pharmacy technician.

SOURCE: STANFORD HEALTH CARE

The adjacent 900-space parking structure can, in the event of a mass-casualty event, double as a triage center, with emergency showers and eye wash stations. Patients who arrive by helicopter at the touch-down space on the roof are quickly taken to a nearby elevator that whisks them straight down to the emergency room.

"The point A to point B is much quicker — a direct line," said Kerr. For time-sensitive conditions like stroke or trauma, the moments saved can make a life-saving difference.

"It's not just curing or caring for someone's incision. It's caring for the whole well-being, the spiritual, the emotional, the family," Kerr said. "That's reflected not only in the architecture, but the nature, the natural elements of light and greenery, that to me, as a nurse, are part of a holistic healing framework, peace and tranquility, not just for our patients and their families, but also for our teams."

THE FUTURE WE DON'T KNOW

THE PLAN FOR THE intensive care and acute care units allows the possibility of one to be converted to the other over time. And an "interventional platform" has been built on the second floor, dedicated to diagnostics, procedures and surgeries of all kinds. The 3½ acres of space includes 28 operating rooms — among them nine hybrid surgery suites equipped with fluoroscopy units, which use X-rays to obtain real-time moving images during operations. Two of the ORs connect directly to an intraoperative MRI.

To understand what makes the interventional platform so advanced, it's important to understand how things worked in the past, said Sam Wald, MD, associate chief medical officer for perioperative and interventional services.

At the older hospital, operating rooms and catheterization labs, where providers do image-guided heart or gastrointestinal tract procedures, for example, were all in separate areas. Patients who needed a combination of services received them independently of each other.

"We have both inpatients and outpatients who need extremely complex procedures, performed by multiple doctors from different services," said Wald, who is also vice president of inpatient perioperative services. In the new Stanford Hospital, he said, "doctors from different specialties can work together at the same time on the patient, with a single anesthetic. Our new interventional platform allows all of those things that are usually housed in separate spaces to be all in one place."

"Our faculty gave up their own personal silos to come together because they understood the value of working together," Tingwald said. "It was really, really important, both operationally and from a design standpoint. Now that it's done,

'OUR FACULTY GAVE UP THEIR OWN PERSONAL SILOS TO COME TOGETHER BECAUSE THEY UNDERSTOOD THE VALUE OF WORKING TOGETHER. IT'S REALLY, REALLY IMPORTANT, BOTH OPERATIONALLY AND FROM A DESIGN STANDPOINT.'

it seems so intuitive. Like, how could people work any other way? Well, a lot of the world is still working any other way.

"In traditional hospital planning, you'd say, 'Well, I know that an ophthalmology room needs to be this big. And that a gynecology room needs to be this big and a trauma room needs to be bigger and an open-heart operating room needs to be bigger than that,'" Tingwald said. "And you'd end up with five or six or seven different size rooms, responding to the traditional square footage for each of those procedure types."

Procedures change dramatically over time, Tingwald explained, and many that once required fully opening a patient's chest, such as heart valve replacement, can now be done through a small opening in the skin, where a catheter tube, laparoscope, endoscope or robotic device can be inserted.

Still, that doesn't mean the space needed to perform such surgeries is smaller: Advanced equipment often takes up more space, and it's hard for surgical teams to work — and teach — in tight spaces. Small rooms, therefore, become obsolete quickly.

The demand for bigger rooms is only growing, Tingwald said, so he planned for that: "We have all big rooms," he said, "and they're all the same size."

The decision has a surprising advantage, he said, because surgeons will usually choose to operate in a larger room over a smaller one. Plus, space is needed for new equipment and technology.

"So when they're all large, everybody has access to the same size rooms," Tingwald said. "Some might say, 'Why are we building all big rooms? Doesn't that cost more money?' At the end of the day, it is a savings because of the flexibility it provides."

SUPPORTING THE PATIENT

In many cases, the futuristic technology of the new hospital also makes way for more meaningful human interactions, offloading tasks that can be automated so caregivers have more time and patients are interrupted only when necessary.

"Imagine maybe concentric rings, where the first ring is technology that the patient experiences directly," said Gary Fritz, vice president and chief of applications. "Then one ring out is technology that's used by clinicians to take care of the patient. And in the next ring further out, there's technology that supports the hospital, which supports the people who are taking care of the patients."

It's easy to imagine those rings separate from each other, but in fact most of the technology they illustrate is deeply interconnected. The system that's wired through the walls, ceilings and a multitude of medical devices in the new hospital is wirelessly connected, for example, to secure hand-held devices for the care team and for patients.

The same MyHealth app technology that prepares and

Putting technology to work

Gary Fritz, vice president and chief of applications for Stanford Health Care (opposite page), next to a prescription-filling machine, said the hospital's technology is meant to improve care and support the people providing it. Twenty-three wheeled robots (right), for instance, will transport linens and other materials.

guides patients throughout their stay also gives care teams seamless access to patients' electronic health records.

"Our care team members check in and check out for their shifts in our electronic health record system," said Fritz. "So we actually know who's taking care of patients at any given moment in time. What we're doing is exposing this to the patient, demystifying the experience for patients who may wonder who they're talking to or who is taking care of them."

Technology also gives patients more control over their environment: They can use a bedside tablet — or their own device — to control the lighting, temperature and window shades, and to order food. They can also request such services as music, a massage or a visit with a therapy dog. The video monitor at the foot of every bed can display educational programming and entertainment.

And, in a major technological leap, their electronic health records are automatically updated with each new medical activity, relieving providers of the burdensome task of manually updating the records. In addition, telemetry systems record data from any device linked to the patient, such as a heart-rate monitor, an oxygen saturation monitor or an infusion pump, which delivers controlled amounts of fluid medication or nutrition.

SUPPORTING THOSE WHO SUPPORT THE PATIENT

Traditionally, many hospital devices have audible alarms that alert a nurse to check the patient or the device. But alarms disturb a patient's rest and sometimes go off when there's nothing of concern. "There are published reports showing that about 72% to 90% of these alarms are false," Fritz said. "So we're changing the way alarms are presented to make them easier to identify and address."

The alarms and alerts will also no longer be audible in patient rooms. Instead, providers will get immediate notifications on a hand-held device, called a Voalte or Connect

phone, that they carry with them. Providers can review and respond to the alerts accordingly, and in some cases handle the issue through the devices, without disturbing the patient.

Besides providing alerts and allowing for phone calls and text messaging between colleagues, the devices have a staff directory, provider availability information and access to patient health records. At Stanford Hospital and Lucile Packard Children's Hospital Stanford, 2,200 of the devices have been distributed.

"We're using technology to deliver better services in ways that won't upset patients or interrupt their recovery process," Fritz said.

Fritz described the integrated electronic system used at the new hospital as an example of the "internet of things" — known in tech as simply IoT — in which devices are interconnected and able to automate the transfer of data. "This is an IoT hospital of the first order," Fritz said.

Sensors in every biomedical device and most of the laptops and other equipment are also connected to a real-time

'WE'RE USING TECHNOLOGY TO DELIVER BETTER SERVICES IN WAYS THAT WON'T UPSET PATIENTS OR INTERRUPT THEIR RECOVERY PROCESS.'

A healing atmosphere

Lloyd Minor, dean of the Stanford University School of Medicine (opposite page, left), and David Entwistle, Stanford Health Care president and CEO, stand by one of the new hospital's five gardens. The lounges (right) are designed to be airy, open and restful.

location system throughout the hospital, allowing for more accurate inventory and servicing, and, ultimately, the need for fewer devices because they'll be better managed, Fritz explained. The system is also linked to employee badges, so when doctors or nurses call for assistance, they need only press a button on their badge to alert other staff or security of their location.

SUPPORTING THE HOSPITAL

GETTING THINGS FROM ONE place to another in the new hospital has also stepped into the future. Twenty-three wheeled robots with mapping sensors are on deck to deliver linen and other materials.

And in a first-in-the-world integration, the new Stanford Hospital pharmacy will have a secure system using three robotic machines that select medications and prepare them into single doses to be delivered to one of 115 medication-dispensing stations throughout the new hospital. Best of all, the order can be placed directly in the patient's electronic health record, which monitors returned medication, too.

"It's an integrated pharmacy supply chain system with a single inventory," Fritz said. "So we know if a medication dispensing station is getting low on drugs; it actually communicates with the robot that automatically replenishes it. And if the robot's supply is getting low, it automatically sends an electronic message to the people who manage our supply chain, who then communicate electronically with the distributor or manufacturer. And we get it replenished automatically."

Being able to return unused medication is a great leap forward, Fritz explained, because throwing away medications is costly and potentially hazardous to the environment. "We've taken our medication waste — our throwaway — down to lower amounts," he said.

The new hospital still employs a 120-year-old, tried-and-true delivery system — pneumatic tubes — to deliver tissue and blood samples and other medical materials more quickly and efficiently than any other way. In the system, foot-long cylinders shoot through tubes to stations throughout the hospital, powered by vacuum pressure. The new hospital adds 4 miles of tubing to the 4 miles in the older hospital building.

"We've designed the new Stanford Hospital to be a great place for patient care," Fritz said. "But it's also a platform for the next generation of medical innovation, and for teaching the next generation of physicians."

Minor agrees. "Through transformative discoveries, the education and training of future health care leaders, and innovations in predicting, preventing and curing disease, the new Stanford Hospital's future-focused environment will surely have an impact that reaches far beyond our campus."

CONTINUES ON PAGE 43

WEB EXTRA: LEARN MORE ABOUT THE NEW HOSPITAL FROM OUR VIDEO AND AUDIO INTERVIEWS AT http://stan.md/newhospital

ART PLAYS A PART

WORKS OF ART AND VIEWS OF NATURE PROMOTE HEALING AT THE NEW HOSPITAL

BY GRACE HAMMERSTROM

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

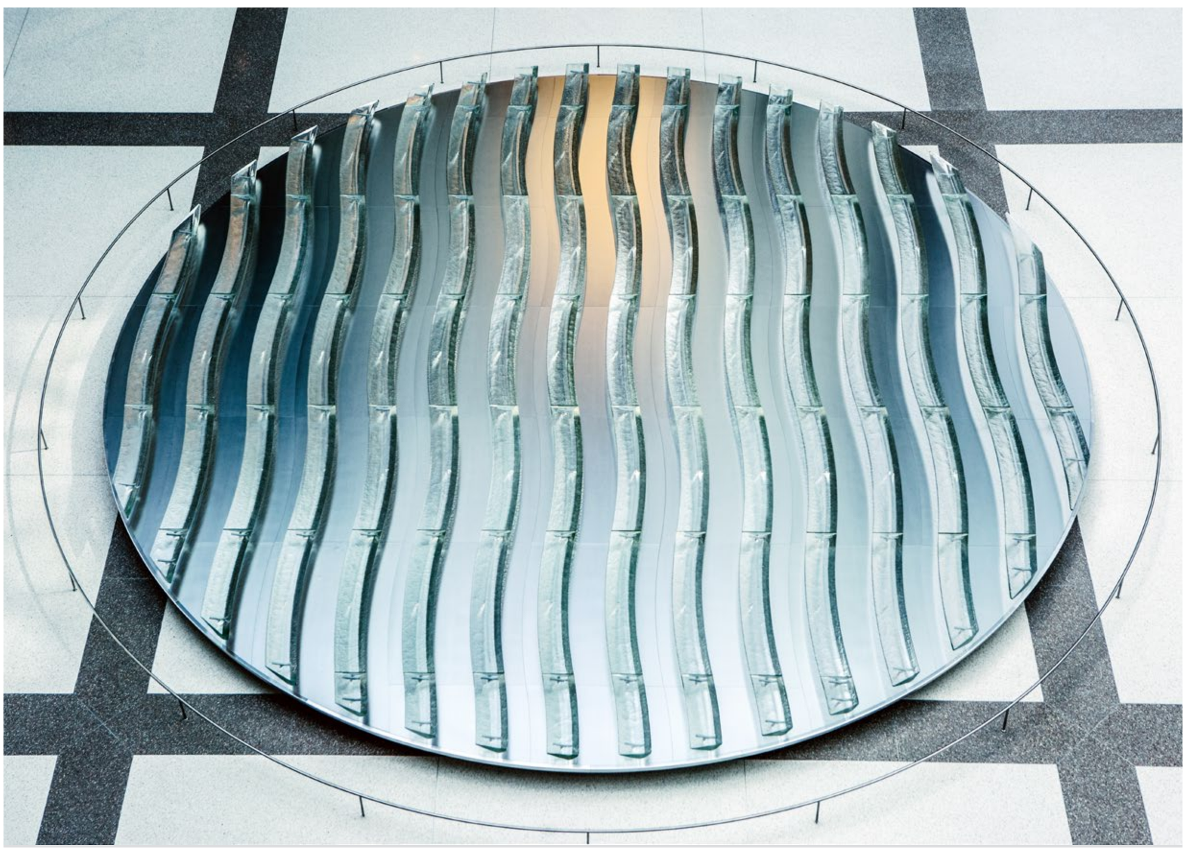
"IN THE WARMTH OF MORNING SUN, WE SEEK SOLACE THAT BRINGS THE PROMISE,
A NEW BEGINNING.
RAYS OF SUN HAVE THE POWER TO HEAL OUR FRAIL BODIES,
FRAGILE MINDS AND LIFT OUR FORSAKEN SOULS.
IN THE LIGHT OF DIVINE WISDOM, WE FIND REFUGE AND WELCOME
THE COMING OF A BRAND NEW DAY."
— *Jinnie Seo*

When artist Jinnie Seo arrived at the new Stanford Hospital this May to begin painting a mural for the interfaith chapel, the project reflected a culmination of five years of ruminating on a theme she calls Rays of Hope.

Seo was so moved by the commission, her first for a chapel and a place of healing, she wrote a poem about the power of light to heal "our frail bodies, fragile minds and lift our forsaken souls."

For two months, Seo and her studio assistant, Jihyun Lee, spent six days a week in residence creating the mural — also called *Rays of Hope*. It is one of hundreds of works of art displayed throughout the hospital, echoing a strong belief by planners in the benefits of art and nature in healing.

During the project, Seo and Lee rose at sunrise, starting each day with a prayer — a moment of reflection



Tumbled glass, woven into waves, reflects light in the hospital's atrium day and night. (above)

LIQUID LIGHT
james carpenter

Metal flaps on the 1,000-pound structure in the third-floor garden move with the wind in ever-changing patterns. (opposite)

AIR CUBE
ned kahn

that guided them as they worked. Immersed in their craft, they stayed on-site for 12 hours a day, sometimes napping in their car, not wanting to interrupt their devotion or concentration.

Using a rendering she had designed as a template, Seo painted each brushstroke free form, allowing the art to evolve spontaneously as she drew inspiration from the space to create the mural, which is one of seven site-specific commissioned artistic works in the hospital.

Fourteen layers of cerulean blue paint formed the mural's backdrop. A series of fine, straight lines in gold and silver metallic paint followed, each at a slightly different angle to convey the impression of curves and movement. For some, the image is reminiscent of butterflies in flight, Seo said. The wall, finished in high-gloss varnish, shimmers in the natural light that emanates from the chapel's large windows.

The mural inside the chapel is reminiscent of butterflies in flight.

RAYS OF HOPE
jinnie seo

"I wanted to give a person a space to pause and be still, even for one moment," Seo said. "That moment can last an eternity and be a life-changing experience."

For Seo, conceptualizing and painting *Rays of Hope* was a personal and spiritual journey. "It is a very intimate chapel. It is a space of healing — spiritual healing and physical healing. I hope that the people who enter here will find their own space, their own light within."

The same philosophy was inherent in the planning and design of the hospital, which opened Nov. 17. Equal value was placed on the restorative qualities of art and nature as was placed on other design elements in and around the hospital, including multiple outdoor gardens and expansive windows that provide sweeping views of the surrounding bay and landscapes.

"We think about patients, their loved ones and families and the staff. Those three groups of people are all important to nurture," said Connie Wolf, consulting director of the art program for the new hospital. They wondered, "How can we create an environment that supports the patients' healing and well-being, provides comfort to their families, and offers relief to the complex and challenging work of the staff?"

In the early 1980s, a group of volunteers formed to acquire and hang art on the then-empty walls of Stanford Hospital. What this group sensed about the power of art — that it could promote healing — was proven later that decade in multiple studies by environmental psychologist Roger Ulrich, PhD, and others.

Research indicated that having access to art can substantially decrease a patient's blood pressure, stress, the amount of pain medication needed and the time it takes to recover. Ulrich's study, released in 1984, of post-surgical patients showed similar outcomes when they were able to see images of nature or had windows that allowed them to view natural settings.

"Integrating art into the hospital environment allows us to think holistically about the healing of the mind, the soul and the spirit," said Wolf. The new hospital is graced by 400-plus works of art, all of which were either donated or paid for through private donations.

Two master painters and two students painted this mural based on a diagram by the artist.

WALL DRAWING #911

sol lewitt

Stanford Health Care has a dedicated art commission, made up of 14 volunteers led by Linda Meier, who also serves on the Stanford Health Care board of directors. Their work for the new hospital began more than five years ago with commissions for the pieces that were planned for specific locations. Acquisition of the hundreds of other works of art that embellish the hallways was a methodical, 2½-year process of finding pieces they believe are not only uplifting, beautiful and inspiring, but also have depth, complexity and layers of meaning.

Patients and families sometimes spend long periods of time at the hospital, Meier said: "We want them to be able to come back to the work and experience something different every time."

The art is on display throughout the hospital, including in patient corridors and other open spaces. The third floor, for example, is distinguished by an acrylic mural based on a diagram by the late conceptual artist Sol LeWitt, who is known for his earlier serial pencil wall drawings and later for his bold, colorful, geometric works composed of straight lines, arcs and curves.

In the 1970s, LeWitt began to have others execute his works based on his directions, which consisted of brief instructions, diagrams or both.

The estate of Sol LeWitt provided the hospital's art commission with a diagram for *Wall Drawing #911* that was based indicated each color should be painted. LeWitt's acrylic wall drawings always use the same primary and secondary colors (along with black, white and gray), which were determined by the artist and are applied in many layers by brush.

In addition to acquired works like the LeWitt, the hospital's public spaces and grounds — the entrance plaza, the atrium, the interfaith chapel and the third-floor galleria and gardens — feature the commissioned pieces.

A grouping of paintings inspired by traditional Japanese Noh theater fill the walls outside the family resource center.

NOH VIEWS: BRIDGE, ECHO AND NOH VISTA
brian isobe

on measurements — side-to-side and top-to-bottom — of the wall where it would be installed.

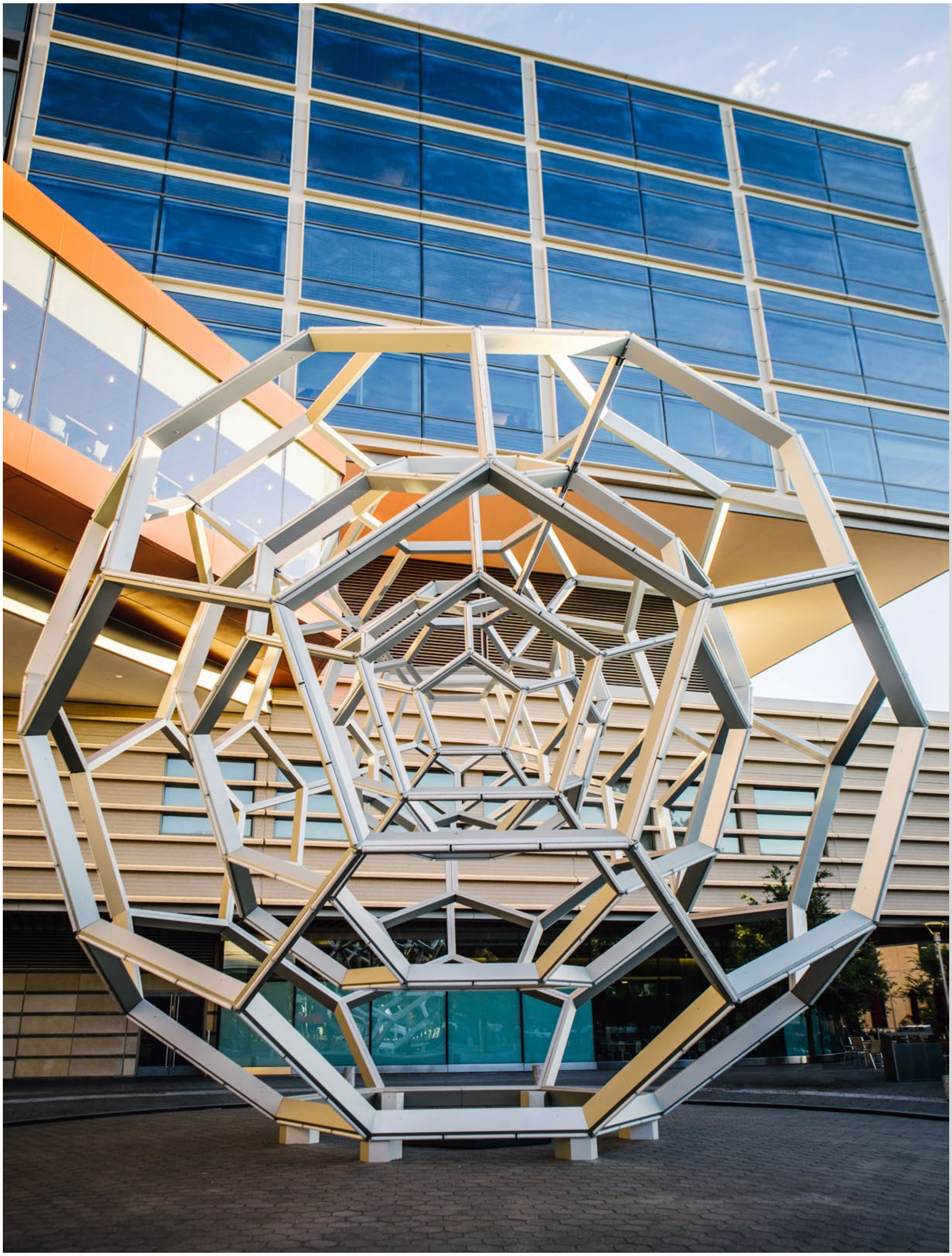
In July, painters Gabriel Hurier and Lexie Bouwsma, who are experienced in following LeWitt's instructions and diagrams, spent 24 days painting the mural, assisted by Stanford undergraduate students Noah DeWald and Savannah Mohacsi.

Their work required sizing the diagram to precisely fit within its 18-by-10-foot wall space, drawing with pencil, and using nearly 75 rolls of masking tape to delineate each line before they began painting, then following where the diagram

Coupled with the new garden areas, all of the art helps evoke a tranquil mood, Wolf said. "We want people to walk in, feel welcome and know they are in a place where their health and spirit matter."

BUCKYBALL

For one of the commissioned pieces, Leo Villareal brought his passion for form and geometry to his larger-than-life sculpture Buckyball, a 30-foot metal structure featuring three nested spheres. As the centerpiece of the hospital's entrance plaza, LED lights illuminate Buckyball at night in a



This sculpture of nested spheres greets visitors at the hospital's entrance.

BUCKYBALL
leo villareal

never-repeating sequence of colors and patterns. Villareal was inspired by the geodesic dome popularized by architect and inventor Buckminster Fuller.

"I've always been interested in underlying structures and rules and geometry," Villareal said. This same geodesic structure was discovered in a carbon molecule by nanotechnologists, he added. "I thought it would be interesting to take something that you could never see with a naked eye and expand it on this monumental scale."

Villareal is best known in the Bay Area for transforming the western side of the San Francisco-Oakland Bay Bridge with his *Bay Lights* installation. As he did with the bridge, Villareal lined Buckyball with light strips and programmed them to twinkle, blink and slowly shift to create a mesmerizing pattern every evening.

This digital installation, featuring wildflowers found on the Stanford campus, links the natural and human worlds.

DIASPORA
jennifer steinkamp

REFLECTING, SPACE, LIGHT AND NATURE

In the hospital's atrium, artist Zadok Ben-David presents two of his Endless Column sculpture works, which intertwine human figures and butterflies that soar in the space. And artist James Carpenter used large waves of tumbled glass woven together to create Liquid Light, a piece that resembles a reflecting pond, directly under the glass dome in the hospital's atrium. Shining in light throughout the day, the sculpture provides changing experiences when you walk around it or look down on it from the upper levels.

Ned Kahn's Air Cube, a 1,000-pound metal sculpture that changes form with the wind, is installed in one of the rooftop gardens. Kahn strives to create art that interacts with natural processes, with the aim of symbolically replicating the forms and forces of nature. Air Cube is lined with rows of metal flaps that move freely and reflect light in ever-shifting ways.

Jennifer Steinkamp's digital video installation, *Diaspora*, is in the third floor seating area leading to the gardens. Like its location, the piece serves as a link between the natural and the human worlds. Her work features wildflowers found on the Stanford University campus, drawing a connection between the dissemination of people and culture around the world and a plant's ability to spread its seeds.

Nearby, a circular galleria that leads into the chapel and a family resource center is home to a series of paintings by Brian Isobe. These stylized interpretations of water, called *Noh Views: Bridge*, *Echo and Noh Vista*, are calming and renewing, inspired by traditional Japanese Noh theater in which metaphors and allusions are used to tell the essence of a story.

HEALING GARDENS

Besides featuring art, planners also considered the natural environment — on the grounds and in the nearby geography — to be essential for patient recovery and health.

Four acres of gardens surround the hospital, including a newly planted orchard of 85 trees. Grounds crews planted six varieties of fruit, nut or flowering trees — ginkgo, loquat, apricot, olive, buckeye and live oak — each selected for its medicinal or food-bearing properties in Eastern, Western and Native American cultures.

The orchard also includes shrubs, rushes, grasses, ash trees and paths to create a shady, serene retreat for patients, families, visitors and staff. The gardens on the street level also include a dog park, complete with a water fountain and fire hydrant.

There are five interconnected rooftop gardens on the third level of the building that include walking paths and many places to sit and gaze out at the skyline. A vertical garden outside the interfaith chapel creates an additional private space for reflection.

The patient rooms present a different kind of visual beauty from the many works of art in the new hospital: By design, every room has a wall-to-wall window to let in natural light and allow patients to take in the beauty of the surrounding foothills.

"There's such a commitment at Stanford to recognizing that art and nature are part of the healing process," Wolf said. "They help create an environment where people can think about improving their health, their ability to heal." **SM**

— Contact Grace Hammerstrom at medmag@stanford.edu

HEALING GARDENS

Four acres of gardens grace the grounds of the new Stanford Hospital, including an orchard of trees selected for their medicinal or food-bearing properties and five interconnected rooftop gardens.

FROM PREHAB TO REHAB

How Stanford physicians and researchers prepare patients to thrive after surgery

Toni Notar wasn't used to anything slowing her down. She worked over 40 hours a week as a literacy specialist in Hollister, California, teaching adults to read and write. In her off hours, she volunteered for an animal rescue organization and went to the gym three times a week with her husband.

That all changed in 2005, when the pain started. It felt like a punch to the gut, but a punch that somehow kept burrowing into her. Sometimes it was so bad she'd double over, unable to walk or even stand.

"It was literally destroying my life because it was all I could focus on. It was affecting my performance at work, my relationship with my husband and my children," Notar said. "When you don't feel good, it's very hard to interact with other people."

Her doctors diagnosed her with diverticulitis, a condition in which part of the intestine becomes infected or inflamed. She was prescribed antibiotics that she estimates she took for two to three weeks every month. But the pain kept coming back, which meant multiple diagnostic colonoscopies but no new treatment strategies.

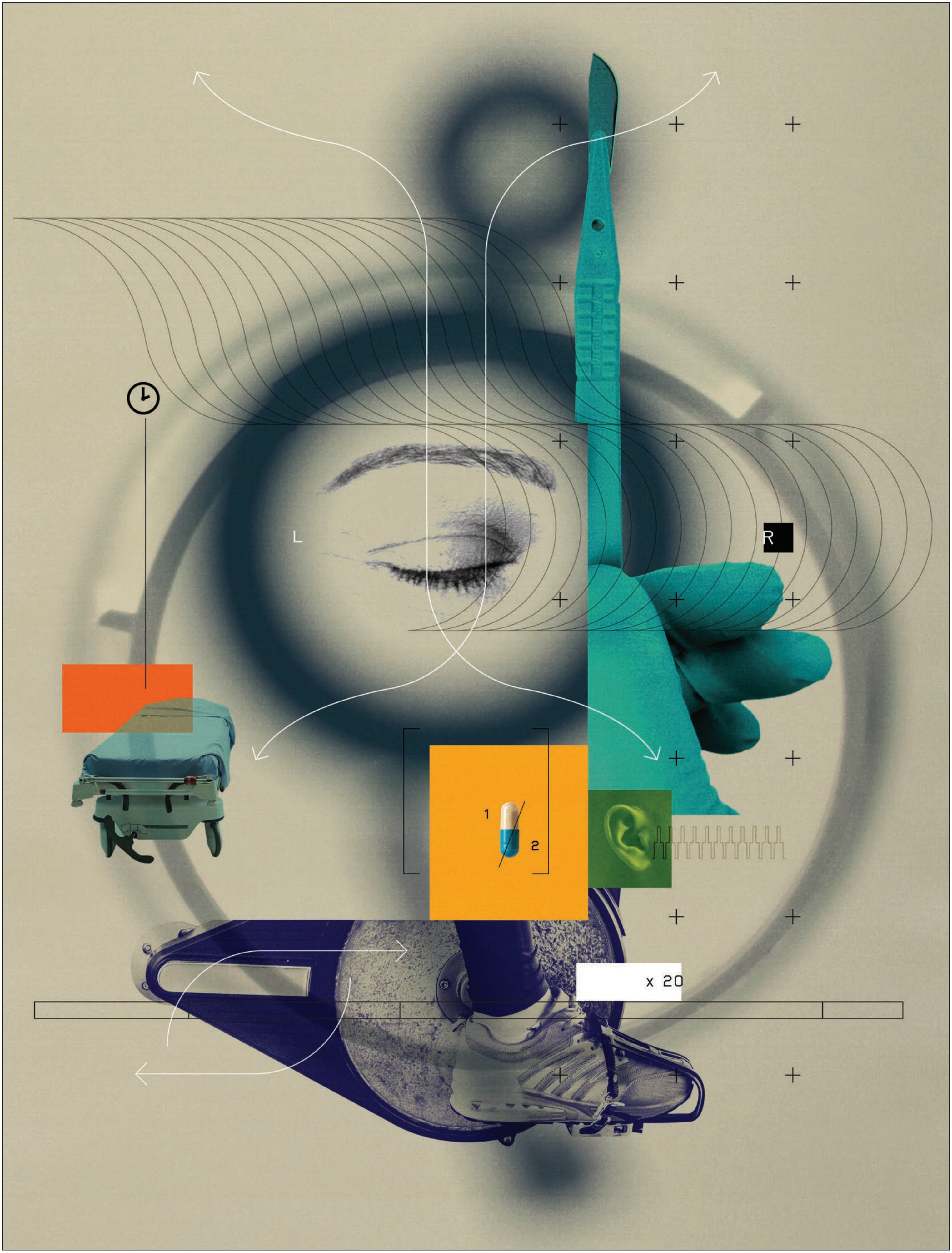
By 2018, the pain worsened, making Notar desperate for other options. She turned to Stanford, where a surgeon offered to remove the inflamed section of her colon to relieve the pain.

"I was ecstatic that she could do something to help me," Notar said, but she also felt a bit worried about undergoing such a procedure at age 62.

On average, nearly 23,000 surgeries are performed at Stanford Health Care each year, and Notar is far from the only patient to feel a mix of relief and concern about a pending procedure.

BY JONATHAN WOSEN

ILLUSTRATION BY STUART BRADFORD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To alleviate some of those patients' concerns, Stanford physicians and researchers have developed programs designed to better prepare patients for surgery and encourage them to play more active roles in their recovery. The efforts include adding training to improve how doctors communicate with patients about surgery. Also, a surgical intensive care unit at the new Stanford Hospital will enhance the care doctors can give patients immediately after an operation.

Here, we highlight some of the programs that help surgeries and recovery go more smoothly so patients can live healthier, happier lives in the long run.

TRAINING FOR THE BIG RACE

Many doctors, including Cindy Kin, MD, assistant professor of surgery, compare the stress surgery places on the body to running a marathon. Running for hours and lying on an operating table might seem like polar opposites, but general anesthesia stresses the heart, and even having minor surgery can be exhausting.

That got Kin thinking — if you wouldn't run a marathon without training, why would you have surgery without preparing?

Kin's patients often asked her what they should do before surgery, but the standard answers she'd been trained to provide were vague — eat healthy, stay active, keep doing what you're doing.

"Patients are looking for something to do before surgery because they're nervous, fearful and vulnerable," Kin said.

So, to come up with better answers, she launched a study on prehabilitation, or "prehab."

In a 2014 pilot study, Kin enrolled 40 patients who were slated to have abdominal surgery — including removal of sections of their intestine because of cancer or inflammatory bowel disease. Twenty of the patients were told to walk 5,000 steps a day and to perform strengthening exercises in the weeks before surgery. The same patients also downloaded a mindfulness meditation app and were counseled to eat a diet rich in whole foods and low-fat proteins. Patients in the control group were given no specific instructions.

Four weeks after surgery, an analysis of pain outcomes showed that prehab patients' self-reported pain was one point lower on a 10-point scale than that of control group patients — an encouraging sign.

In a follow-up study from 2018 to 2019, Kin enrolled 250 colorectal surgery patients — including Notar — and instructed them to use an app that sent them information about the Mediterranean diet; it also reminded them to walk at least 5,000 steps a day and perform core-strengthening exercises three times a week.

Notar incorporated the exercises into an already busy schedule by waking up at 3:30 a.m. instead of 5 a.m. so she could squeeze in some of the exercises. And when she got home around 6 p.m., she'd prep dinner and finish the remaining exercises while her food cooked.

It was a grueling routine, but she lost 8 pounds during six weeks of prehab and felt stronger and more energetic. She was also much more relaxed about her upcoming surgery.

It turned out that Notar would need every ounce of her newfound strength to recover from the January 2019 surgery. Her surgeon had to remove more of her colon than was expected and, during the operation, Notar's spleen started bleeding and had to be removed.

By the time Notar was well enough to return home, she had lost about 30 pounds. Still, she credits prehab for her ability to return home at all.

BY THE TIME NOTAR WAS WELL ENOUGH TO RETURN HOME, SHE HAD LOST ABOUT 30 POUNDS. STILL, SHE CREDITS PREHAB FOR HER ABILITY TO RETURN HOME AT ALL. 'I DON'T THINK I'D BE HERE IF I HADN'T DONE THE PREHAB. THE RECOVERY WAS REALLY TOUGH, AND IF I HAD NOT BUILT UP THAT EXTRA STRENGTH I DON'T THINK I WOULD HAVE MADE IT.'

"I don't think I'd be here if I hadn't done the prehab," said Notar. "The recovery was really tough, and if I had not built up that extra strength I don't think I would have made it."

Overall, prehab seemed to pay off for other patients in the trial, too. After surgery, they used half the amount of opioids per day spent in the hospital than a group of 250 surgical patients who did not have prehab, though various medical and demographic factors also could have played a role, Kin said.

A member of Kin's research team presented these findings at a meeting of the American College of Surgeons in October. Kin and another Stanford surgeon, Brendan Visser, are planning a new app-based prehab study in which patients use wearable fitness trackers to monitor their heart rates, sleep patterns and activity levels. Patients will perform exercises that prepare for the first step of their recovery — getting out of bed. The researchers will track whether prehab reduces postoperative pain, narcotic use and infection rates.

Such prehab programs are in place at some health care centers, including at McGill University in Quebec, Canada, but are not widespread. Kin hopes her research will expand the scope of prehab and empower more patients to make concrete, evidence-based lifestyle adjustments that improve recovery.

"If your doctor suggests that you do prehab, do it," Notar said. "If your doctor doesn't suggest it, ask them about it."

TALKING IT OUT

Patients facing surgery are often full of questions: "Is what I'm feeling normal?" "What are the risks?" "How am I going to feel afterward?"

Underlying the questions are sometimes regrets, both spoken and unspoken: "I should have taken better care of myself." "I should have gotten the mammogram sooner."

Communicating surgical expectations and risks — and listening to what patients say in response — is a delicate art. It's also a requirement for physicians. The Accreditation Council for Graduate Medical Education, which sets the training standards for medical residency and fellowship programs, includes among its standards that physicians show compassion, respect and responsiveness to patient needs.

Kimberly Kopecky, MD, general surgery resident, was well trained in this arena during a one-year hospice and palliative medicine fellowship. She said she learned how to talk to patients with serious illnesses about their goals, fears and priorities in end-of-life situations.

But Kopecky knew that the amount of communication training other residents received varied greatly by specialty — and surgery was among the specialties that were lagging.

"Historically, surgical residency has not focused much at all on how we communicate with patients," Kopecky said. "It mostly has focused on our operative skill and clinical decision making."

So in 2018, Kopecky launched a series of courses to help residents strengthen their patient communication skills in preparation for the responsibilities they will eventually face as attending physicians. Her courses, which she teaches each quarter, cover empathy, discussing best- and worst-case scenarios, and how to break bad news.

In each session, 25 to 30 surgical residents gather to learn through a blend of presentations, group discussion and brainstorming.

"It's about practice," Kopecky said. "In the operating room, we practice suturing, stapling and cutting all the time. So why would we think we can learn these skills without practicing them?"

Kopecky is leading more sessions during the 2019-2020 academic year. During the fall course, residents are using a game Kopecky helped create called the Empathy Project. To play, residents draw from a stack of cards containing hypothetical patient statements — for example, that a tube running from a patient's nose to the stomach is uncomfortable and the patient wants it removed.

Participants take turns playing the roles of doctor and patient. The key is to acknowledge a patient's feelings rather than launching into a technical and procedural explanation of their ailment and the treatment they're undergoing.

"Most patients don't want the medical textbook answer," Kopecky said. "They want to be validated and they want to be heard and they want to be supported."

A NEW SPACE: THE NEXT FRONTIER

Perhaps the greatest boon to Stanford's care for surgical patients is the new hospital's surgical intensive care unit. Located on the fourth floor of the hospital, which opened in November, the surgical ICU holds 20 beds.

The new space allows providers to closely monitor patients after an organ transplant, trauma surgery or other major operation. Patients in the unit often need specialized equipment to help them breathe and circulate blood. Each ICU patient is cared for by a team of upward of 10 residents, fellows, specialized nurses, respiratory therapists, pharmacists, nutritionists, medical students and an attending physician.

"We not only receive a high volume of local patients, but also accept many transfer patients. These are often some of the sickest patients in the state, or sometimes the country, sent to receive specialized care at Stanford," said Lisa Knowlton, MD, assistant professor of surgery.

The surgical ICU won't just increase the number of patients who can receive care, it will also enhance the quality of the care they receive, said Mary Hawn, MD, chair of the department of surgery.

CONTINUES ON PAGE 43

ALL FOR ONE

Building a culture of teamwork in emergency care

BY MANDY ERICKSON

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

Early one August morning before the new Stanford Hospital had opened, about 20 nurses, physicians, physician assistants and technicians squeezed into a room at the Marc Andreessen & Laura Arrillaga-Andreessen Emergency Department.

It was time for the 7:30 a.m. daily "huddle," when they learned about the patients they would inherit from the night shift. Thirty had been admitted to the hospital through emergency — "a whopper of a night," according to Patrice Callagy, RN, executive director of emergency services. Patients had come in fearing they were suffering heart attacks, complaining of abdominal pain and experiencing headaches — typical emergency cases, just a lot of them.

Because too few beds were available, Karen Stuart,

Throughout Stanford Medicine, clinicians are training to harness teamwork, employing standardized exercises and developing their own. In one activity, clinicians participate in Lego-building competitions that illustrate the importance of good communication and collaboration in the operating room.

RN, manager of emergency services, asked the team to determine which of the patients could be treated on gurneys outside the patient rooms. Once the new hospital opened, the department's space would more than double in size, but that was still three months away.

Stuart urged the group to keep track of equipment — a resident had taken an eye-pressure reader to another department — and reminded them to complete their paperwork. Then she asked for "shoutouts," and a technician praised a coworker who had deftly whisked two patients away from another, who had become agitated.

These huddles, which take place four times a day when employee shifts overlap, ready emergency department workers for the shift ahead. But they also provide opportunities to share information broadly, so members of the team can step outside their roles if necessary. Anyone, regardless of job title, is encouraged to raise a concern, praise a coworker or ask a question.

And every Friday, a faculty member teaches the whole crew a particular aspect of emergency medicine, whether it's how to communicate with family members, use new equipment, manage blood loss or treat epilepsy.

Typically, physicians aren't trained to work with people in other health care professions, such as nurses and physical therapists, though all of them care for the same patients.

"Medical training is very siloed," said Megan Mahoney, MD, vice chief of staff for Stanford Health Care. Most health care organizations don't reward physicians for working well with others. Stanford Health Care is an exception, Mahoney said.

But as medicine has become more complex and specialized, taking advantage of each team member's skills is growing in importance. For example, members of a team scheduled to perform a cesarean section learn ahead of time what role each will play so together they can perform the procedure safely and efficiently.

But good teamwork also requires a shift from the traditional, top-down medical culture to a more level playing field. "Nurses need to be able to tell doctors if they see something that concerns them," said Andra Blomkalns, MD, chair of the emergency department and a champion

ALEXEI WAGNER, top left, monitors two groups of clinicians competing in a timed Lego-building team exercise that teaches the importance of using precise language and listening attentively in the operating room. For the exercise, one team member plays an attending physician who describes the Lego pieces and steps for building a model; another person plays a nurse who selects the pieces, then hands them to an intern who assembles the model based on the verbal instructions.

of empowering every member of the clinical staff. "Anyone should be able to say, 'I don't feel comfortable with this.'"

Throughout Stanford Medicine, clinicians are training to promote teamwork. They use standardized exercises and develop their own. Three examples from the emergency department — designing the work space in the new hospital, holding Lego-building competitions and running simulations of treating a pregnant trauma patient — illustrate some of the creative ways Stanford Medicine is building a collaborative culture.

A DESIGN WITH TEAMWORK IN MIND

About 10 years ago, as physicians and administrators at Stanford Health Care were envisioning the new hospital, they realized that the layout of the new work spaces could help facilitate more collaboration. "With the opening of the new hospital, there was an incredible opportunity to espouse teamwork," Mahoney said.

Clinical leaders in the emergency department invited various constituents — patients, lab technicians, guest services members, physicians and nurses — to create their ideal department. They placed empty moving boxes around an unused room on campus, marking the ambulance bay, the registration desk, the laboratory and other service locations.

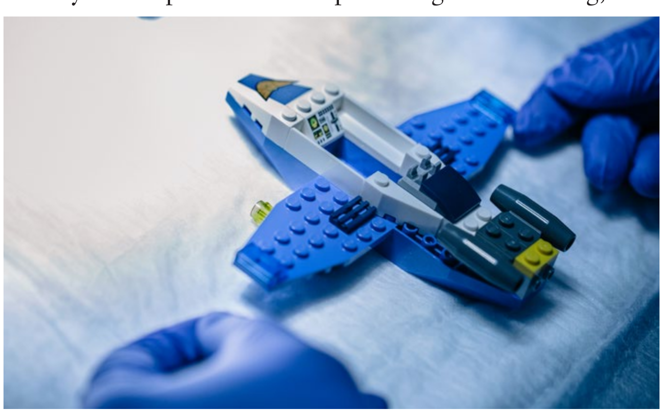
As they acted out typical scenarios of patients arriving with complaints ranging from chest pain to a head cold, they rearranged the boxes until they were satisfied they had the most efficient configuration — one that would ensure a rapid resolution for any condition.

For example, to encourage collaboration and efficiency, the new department has six zones, each featuring a "pod" surrounded by patient rooms. The pod is a group of desks formed into a square, with 10 or so computer screens. The computers belong to everyone, meaning a physician assistant can sit down between a lab technician and a translator, tap her badge on the reader and access her own data.

"It creates a faster pace for treatment, faster decision-making," said Vasiliy Rodin, RN, assistant care manager, who was in charge of the transition to the new ED.

Everyone can hear others' conversations, and that's the idea, Callagy said. "For example, a pharmacist may overhear an attending physician and a resident talking about medicating a patient and can butt in to say the patient is allergic to that medication.

"Or a social worker can overhear two nurses talking about an 80-year-old patient who keeps coming in after falling," she added. "They can say, 'That's someone who needs a referral to the Farewell to Falls program,' and make that happen."



The designers of the new department also reworked the entryway: Two teams — each including a registration clerk, a nurse and a medical technician — wait at podiums to greet arriving patients, then get to work immediately. The registration clerk gathers the patients' information as a medical technician takes their vital signs and the nurse determines the severity of their condition. "It's like during an auto race, when a car pulls into the pit stop," Callagy said. "The team works together to get the car quickly back into the race."

LEGO COMMUNICATION EXERCISE

Emilie Wagner, a lecturer at the Hasso Plattner Institute of Design at Stanford, was brainstorming with her husband, Alexei Wagner, MD, an assistant professor of emergency medicine, a couple years ago about a course she was teaching on communication in the operating room.

"We were trying to figure out a way to simulate an operation," Emilie Wagner said. "We asked ourselves, 'What can people build together?' We realized assembling Legos could be a stand-in for the procedure, and we could design an activity that mimics the communication dynamics of a real-world operating room."

The couple devised a three-person exercise that involves a pile of Lego bricks and a manual with wordless instructions on how to build a model helicopter. One person describes the instructions, similar to how an attending physician instructs an intern; a second, acting as a nurse, selects the pieces; and a third, filling the role of an intern, fits the pieces together.

In the exercise, the person playing the attending physician might tell the one playing the nurse, "Pick out the two dark-blue pieces that have six bumps on them," then tell the person playing the intern, "Place the pieces on either side of the white square with their shorter sides touching the white square."

During the exercise, participants wear masks and gloves, as if they were really working on a patient, and they're hearing pre-recorded background noise from the ED. The teams are also under time pressure as they compete against other teams. "It's very reminiscent of what it's like to do a high-risk procedure," Alexei Wagner said.

The exercise teaches the importance of using precise language and listening attentively, but it's most effective if participants step into different roles. When he runs the exercise for emergency department personnel, Wagner instructs the real-life attending physicians to act as interns, the interns to play physicians, and the residents to act as nurses. He wants attending physicians to realize how difficult it is to follow unclear instructions and how someone's tone of voice can affect outcomes. He hopes interns understand that while they may feel inadequate, their team members often disagree.

"It's an easy, low-cost, low-risk exercise to learn what it's like to walk in someone else's shoes," he said. "In emergency, when a team is unsuccessful, it's easy to blame the intern. But maybe the instructions were the problem."

Wagner oversees Lego exercises on occasion, for new clinicians and others who are interested in trying it. Emilie Wagner said that physicians are willing to participate, and afterward discuss what they learned — including how they failed — because they're dealing with toys, rather than patients or even manikins.

"They can have a difficult conversation pretty easily because they're just talking about Legos," she said.

MATERNAL SIMULATION

In a recent simulated trauma scenario, physicians and nurses crowded around a "patient" lying on a gurney. Kimberly Schertzer, MD, playing the role of a paramedic, announced that the patient had been in a freeway accident, was 32 years old and was 33 weeks pregnant. Everyone acted as if the manikin on the gurney with a distended belly was really a pregnant trauma victim.

The physician in charge stood at the foot of the bed, arms crossed, asking questions about the patient's vital signs and ordering tests. An emergency physician checked her breathing, her blood pressure and her limbs to see if any bones were broken. An obstetrician listened to the fetal heartbeat.

A nurse sitting behind a screen provided the voice of the patient; her moans echoed through a karaoke machine hidden under the gurney. "My stomach hurts," she said. "Is my baby OK?"

"The baby's OK," an obstetrician answered. The physicians discussed the possibility that the placenta had separated from the uterus, which can happen after trauma, but they needed a CT scan to learn more. As they ordered scans, the patient's "sister" walked in. "Is that safe for the baby?" she asked.

"If she's not doing well, the baby's not doing well," the physician in charge explained. "If we can fix her, the baby will be better off."

Because this was a simulation, the results of the scan were immediate: Schertzer, now playing the role of a radiologist, announced that the patient had an injured spleen, requiring her to stay in the ICU for observation. The patient would not deliver her baby just yet.

Emergency physicians, trauma surgeons, obstetricians, neonatologists, obstetrical anesthesiologists, obstetrical nurses and emergency nurses together designed the pregnant-trauma-victim simulation. All the obstetrical residents, most of the emergency residents and many nurses in both specialties participated in the exercise. They didn't know the test results beforehand: They had to consider various diagnoses and discuss the possibility that the patient would need to deliver the baby immediately.

In a real trauma situation, "You don't have time when someone is critically ill to work out your systems and communications," noted Schertzer, an assistant professor of emergency medicine.

The 15-minute exercises were video-recorded. Afterward, the participants watched the video and discussed their performance. The different specialists learned from each other. The obstetricians now better understand the choreography of trauma medicine, including the primary and secondary surveys in which physicians check vital signs and then scan the patient for injuries. The emergency physicians were reminded not to keep a pregnant patient lying flat on her back; they also understand that lab results that appear normal are not necessarily OK for a pregnant woman.

Every few weeks or so, the department runs a simulation of a different treatment scenario, but it ran the pregnant-patient exercise 20 times from fall 2017 to March of this year. The team of clinicians from Stanford and Lucile Packard Children's Hospital Stanford focused on it after research showed that pregnant trauma patients are more likely to die, possibly because clinicians are reluctant to run scans or even treat them for fear of harming the fetus.

AS THEY ORDERED SCANS, THE PATIENT'S 'SISTER' WALKED IN. 'IS THAT SAFE FOR THE BABY?' SHE ASKED. 'IF SHE'S NOT DOING WELL, THE BABY'S NOT DOING WELL,' THE PHYSICIAN IN CHARGE EXPLAINED. 'IF WE CAN FIX HER, THE BABY WILL BE BETTER OFF.'

EMILIE WAGNER, RIGHT, a lecturer in the Hasso Plattner Institute of Design at Stanford, and her husband, physician Alexei Wagner, left, an assistant professor of emergency medicine, designed their Lego-building game so participants play roles outside their real-life operating room jobs. 'It's an easy, low-cost, low-risk exercise to learn what it's like to walk in someone else's shoes,' he said.

Since running the simulations, Schertzer said, the relationships between obstetricians, radiologists and trauma specialists have strengthened. "It was a great project," she said. "We really built a lot of bridges."

A TRIAL RUN

During a dress rehearsal before the new hospital opened, the emergency team enacted various scenarios. In one, Callagy, the executive director of emergency services, played a male car accident victim whose condition was so dire the Life Flight helicopter flew him to Stanford Hospital.

Her performance wouldn't garner any acting awards: She may have been stretched out on a gurney, but she was more involved in her real role, answering texts and emails on her cell phone. Pointing to a nurse who was taking notes on an iPad, she said, "Write down that we need to check all the doors and make sure they open quickly."

In separate cases, the team "treated" a psychiatric patient with violent tendencies and a patient who needed dialysis.

While the attending physician listed the accident patient's vital signs, a nurse adjusted the light over the gurney, and a technician rolled a chest X-ray machine into the room. Everyone accompanied the "patient" to the CT scanner room, then to the elevators that would take him upstairs to an operating room.

During the drill, team members frequently stopped to discuss how they could save time, where they would direct family members, who would retrieve blood. Because everyone was dressed mostly in scrubs or street clothes, it was difficult to tell who was a technician, a nurse or a physician, but everyone asked questions and offered solutions, stepping outside their real-life roles to address problems.

It was the kind of collegiality that encourages Mahoney. "We're seeing a flattening of the hierarchy," she said. "We want to be an organization where everyone is heard and everyone is valued." **SM**

— Contact Mandy Erickson at merickso@stanford.edu

Guided by lasers,
fluorescence and real-time imaging,
surgeons develop new ways to enhance precision

A NEW VIEW ON BRAIN SURGERY

Gordon Li stared down at a mass of pinkish-gray tissue. He turned to the neurologist beside him and, from behind his surgical mask, cued the next step of the procedure. "Really step it up for this part. Test her hard," he said.

Li, MD, associate professor of neurosurgery, was in the midst of an open-brain surgery and the "her" was Lisa Inouye, who lay awake on the operating table. Li was removing a tumor in a region of Inouye's brain that controls movement, and her lucid state allowed Li to ask Inouye to perform certain tasks, ensuring that he was not cutting out parts of her brain critical for those actions.

As instructed, the neurologist began rattling off a list of physical to-dos — touch your nose, tap your fingers, kick your leg out. Inouye touched, tapped and kicked as Li cut out bits of tumor.

"It was textbook," Li recalled.

That is, until he saw what appeared to be more tumor tissue — this part of the mass hadn't shown up on a pre-operative brain scan. After a bit of visual inspection and prodding — brain tumors feel mushier than healthy brain tissue — Li surmised the tissue was very likely part of the tumor and needed to be taken out. But before making the cut, he conducted one more review, this time using a new, experimental tool. Li had been collaborating with Eben Rosenthal, MD, a surgeon-scientist who is developing a targeted fluorescent dye that clings to and illuminates cancer. The idea behind this new dye — Inouye was the seventh Stanford patient to consent to its use during brain surgery — is to help surgeons spot cancer in real time, as they operate.

BY HANAE ARMITAGE

ILLUSTRATION BY STUART BRADFORD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He aimed a special camera at the possibly cancerous tissue, and from the screen emanated a glow of confirmation.

By the end of the surgery, Li had removed 98% of Inouye's tumor — a good bump from the 90% he had anticipated. Although it's still early in the dye's development, Li sees potential for its use in future operations. "It's clear how this dye could act as a guide for surgeons in murky territory," he said. "Determining where and what to cut is not always so obvious."

In fact, more often than not brain surgery requires a bit of guesswork. In search of more reliable guides than inexact visual and tactile cues, brain surgeons have turned to technology. Some, like Rosenthal, are developing newer imaging methods that they hope will let surgeons augment what they see with the naked eye. And some are turning to MRI — normally a diagnostic tool — to steer the course of their procedures.

MRI IN THE OPERATING ROOM

Beyond simple magnification, MRI used during surgery, known as intraoperative MRI — or iMRI — enhances the surgeons' view as they work. It enables them to see below the brain's surface. Operating suites outfitted with MRI machines are available in about 100 U.S. hospitals, including Lucile Packard Children's Hospital Stanford and the new Stanford Hospital, opened in November. It's one of the features of the new hospital that Li said he's most excited about.

MRI produces images using a combination of radio waves and powerful magnets, which is why earrings are not allowed in an MRI — the metal would skew the image, or the magnetic field could even strip the jewelry from the patient's ear. For this same reason, it's unwise to use an MRI in an operating room full of metal surgical tools. So hospitals and surgeons have taken precautions: The MRI, though still in the room, is located in a separate chamber away from metal, behind sliding doors that block radiofrequency.

In a typical iMRI surgery, a patient lies still in the central opening within the large, tube-shaped machine. Instead of using a scalpel to cut diseased tissue, surgeons use a laser.

Laser surgery with the iMRI happens in a series of small steps: With the patient's body inside the MRI and head poking out, the surgeon zaps parts of the brain tumor with the laser. To check on progress, the surgeon stops and moves the patient into the center of the MRI machine, turns it on, and takes images of the brain tissue and ablated tumor. (In an iMRI image, ablated tissue appears as a different shade than normal tissue.)

"Sometimes a tumor is so deep you don't want to resect it and risk injury to the brain," said Li. "But the iMRI setup lets you use the laser and monitor its whereabouts to precisely kill the cancer, which helps shrink the tumor and, most importantly, stops it from growing."

Shooting a scalding hot laser into the brain might sound a little brazen, but the laser is less like a lightsaber and more like a dynamic beam of heat that can be tuned in exquisite detail. Part of the iMRI imaging technique is something called magnetic resonance thermography, which produces a heat map revealing the temperature of the laser beam, allowing surgeons to closely monitor which parts of the laser are heated, and to what degree.

Cancer surgery is not the only use for iMRI at Stanford: Two other Stanford surgeon-scientists, Jaimie Henderson, MD, and Casey Halpern, MD, professor and assistant professor of neurosurgery, respectively, use iMRI to treat epilepsy on a routine basis. Before moving operations into the new hospital, they, like Li, made do with the diagnostic MRI outside the operating room.

"It was a little cumbersome," said Halpern. "We had to cart our surgical tools down to radiology and finagle a sterile setup, but we wanted to offer this revolutionary service to the patients who would benefit from it."

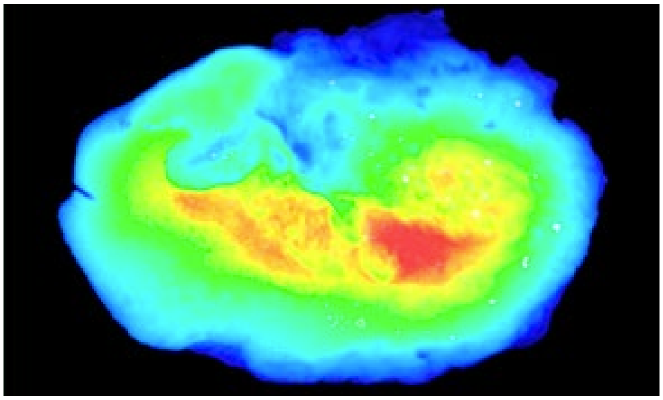
PRECISION HEAT

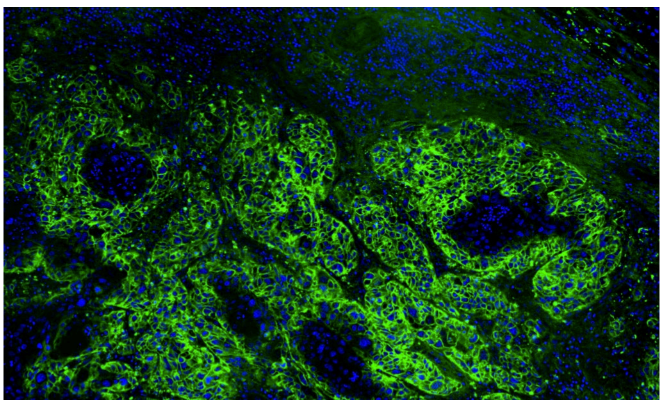
Halpern and Henderson use a laser paired with MRI to treat one of the most common types of epilepsy, known as mesial temporal sclerosis, which can be traced to a region of the brain called the hippocampus. Laser zapping aside, the go-to surgical therapy has traditionally been to remove the part of the brain that's causing seizures. And while it's effective and generally regarded as safe, not everyone is willing to part with a piece of their mental engine.

"MRI-guided laser ablation is a much less invasive way to kill the problematic tissue," said Halpern. "It's highly effective, and only requires a 3-millimeter incision, cutting down on complications and recovery time dramatically."

So instead of slicing out a chunk of brain tissue, Halpern and Henderson scorch the problematic tissue with a tiny laser and remove it to silence the seizures.

'iMRI won't be the answer for everyone, but it will be for some people. That's a big part of why we investigate new therapies, even if we have a few that work well already.'





Top: Tumor samples infused with the antibody-dye complex light up under an imaging instrument that detects photons from the labeled samples. The healthy tissue is in dark blue, and the tumor tissue is shown in green, yellow and red. **Middle:** Using a fluorescence microscope, scientists visualize the antibody-dye complex (green) on the membrane of brain cancer cells. In blue are cell nuclei. **Bottom:** Interactive surgical suites in the operating rooms of the new Stanford Hospital are equipped with MRIs so surgeons can have clearer views as they work, in near real time.

TOP, MIDDLE: ROSENTHAL LAB; BOTTOM: STANFORD HEALTH CARE

"It lets us oversee and precisely control the effect of the laser as it heats up and progressively burns the area from which the seizures originate," said Henderson.

Henderson and Halpern have conducted nearly 100 MRI-guided epilepsy treatments. "We do the whole thing in the MRI scanner, and we use MRI imaging to guide every step," Henderson said.

When the laser is initially turned on, at low power to avoid damaging any tissue unnecessarily, the patient is moved a few inches back into the bore of the scanner, where the surgeons can take MRI images and use them to guide the position of the laser if need be.

"We can see and move the laser in near real time," said Henderson. "We know exactly what the laser is doing, at the precise location that it's doing it, which lets us ablate the parts of the brain that are responsible for the seizures while ensuring that the normal brain structures in the vicinity are preserved."

While iMRI is a promising alternative for some epilepsy patients, it's not necessarily the right alternative, or possible, for everyone. And that's OK. The goal of much of the work by Henderson and Halpern, including the adoption of iMRI, is treatment personalization.

"Several years ago, before this surgery was an option, I had a patient with really debilitating seizures. She was a prime candidate for a more traditional, resection-based treatment," said Halpern. But she refused the treatment, not wanting her brain handled in such an invasive way. So when Halpern began pursuing iMRI, he presented the new option to her, which she embraced, and the procedure was successful.

"iMRI won't be the answer for everyone, but it will be for some people. That's a big part of why we investigate new therapies, even if we have a few that work well already," said Halpern. "We want to have an arsenal of therapeutic tools. That's really a big focus of our epilepsy program here — selecting the right procedure for the right patient so we can treat them in an effective, personalized way."

CONTINUES ON PAGE 44

plus

EXPLORING THE REALMS OF MEDICINE AND HEALING

FROM LEFT, MOHAMMAD ESFAHANI, MAXIMILIAN DIEHN, ASH ALIZADEH AND DAVID KURTZ HAVE DEVELOPED A COMPUTER ALGORITHM TO BETTER PREDICT TREATMENT OUTCOMES FOR INDIVIDUAL PATIENTS.

TIMOTHY ARCHIBALD

What are my chances?

USING IN-GAME WIN PROBABILITY TECHNIQUES TO PREDICT THE COURSE OF DISEASE

By Krista Conger

IT WAS LATE IN THE EVENING IN 2012, and oncologist Ash Alizadeh, MD, PhD, was emotionally exhausted. He had just lost a young patient to lymphoma, and the death had come as a shock. "Despite our best efforts, and a very strong, but ultimately mistaken, impression of successful treatment, the patient had relapsed unexpectedly," said Alizadeh, an associate professor of medicine (oncology). "It was a time of very raw emotion."

Although the majority of adults with the most common blood cancer, diffuse large B-cell lymphoma, are cured with the standard treatment protocol of six cycles of chemotherapy, about one-third will ultimately die from their disease. But it's difficult to know which patients will do well and which will do poorly. In fact, even the most experienced physicians making their best guess about whether any one patient will be cured of the disease or die of it are correct only about 60% of the time — just slightly more accurate than a coin toss.

That evening, Alizadeh and then-oncology fellow David Kurtz, MD, PhD, lingered to talk over the day's events.

"One of the most challenging things for patients is dealing with the unknown," said Kurtz, now an instructor in oncology.

"They want to know, 'What are my chances? How long am I going to live?' It's one of the most difficult questions to answer, but one that we face at every patient visit. And for most patients the most honest answer is 'I don't know.' It's very frustrating."

During the past several years Alizadeh, Kurtz, associate professor of radiation oncology Maximilian Diehn, MD, PhD, and postdoctoral scholars Mohammad Esfahani, PhD, and Florian Scherer, MD, have developed a computer algorithm to integrate many different types of predictive data to generate a single, dynamic risk assessment at any point in time during a patient's course of treatment. The data would include a tumor's response to treatment and the amount of cancer DNA circulating in a patient's blood during therapy. Such an assessment could be deeply meaningful for patients and their doctors. Alizadeh, Kurtz and Diehn treat patients at the Stanford Cancer Center.

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

The researchers have also found that the approach, which they've termed CIRI for Continuous Individualized Risk Index, may help doctors pinpoint those people who might benefit from early, more aggressive treatments as well as those who are likely to be cured by standard methods. They published their results on July 4 in *Cell*.

They are planning a clinical trial to test CIRI's utility in driving treatment decisions for lymphoma and are collaborating with investigators around the world to extend the CIRI concept to other common tumor types, including breast cancers and chronic lymphocytic leukemia.

But that night in 2012, CIRI was just the pipe dream of two exhausted physicians who wanted better answers for their patients and a way to prevent the wrenching situation Alizadeh had been part of earlier that day.

STATISTICIANS, BOOKIES, PUNDITS AND LATE NIGHTS: THE BIRTH OF AN ALGORITHM

Although Alizadeh had the terrible experience of patients dying unexpectedly, he had also occasionally treated people who experienced seemingly miraculous recoveries from severe and sometimes undertreated disease.

He and Kurtz had begun to wonder whether every patient really needed six cycles of chemotherapy and their associated unpleasant side effects. "Treating every patient with the same protocol didn't seem to make sense," Kurtz said. "After all, each patient is different, and they come to us with varying disease statuses."

'We are trying to come up with a better way to predict at any point during a patient's course of treatment what their outcome is likely to be.'

At the time, Alizadeh and Diehn were developing sensitive methods to identify and quantify minute amounts of tumor DNA released into a patient's blood when cancer cells die. Tracking changes in the levels of circulating tumor DNA, or ctDNA, might help clinicians monitor the progress of the disease and predict whether it was likely to recur.

They published their technique, termed CAPP-Seq, in 2014. But they weren't done yet.

"Once we had CAPP-Seq in hand, we could start to think about the next step — how to incorporate all these various types of data, including ctDNA levels, into a tool that will actually help clinicians make better predictions for patients," said Kurtz.

To do so, the researchers used a technique that might be more at home in Las Vegas than in the clinic. For decades, bookies and pundits attempting to predict the outcome of the next hotly contested sports match or election have scoured every evolving scrap of relevant information and sifted through mountains of associated data. Their predictions can change on a dime, however, based on a player's poor pass or a candidate's stellar debate performance.

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

Would this approach work for patients in the clinic, they wondered? It seemed that it could be better than the snapshot-in-time approach on which clinicians currently rely.

When a diffuse large B-cell lymphoma patient is diagnosed, for example, clinicians assess the initial symptoms, the cell type from which the cancer originated, and the size and location of the tumor

CONTINUES ON PAGE 44

Burnout in brain city

WHEN NERVE CELLS' POWER PACKS GO WRONG

By Bruce Goldman

ADVANCED LIFE IS LARGELY A SUCCESS STORY OF A TINY BACTERIUM THAT KNEW A TRICK OR TWO ABOUT CUTTING A DEAL, over a billion years ago, with a larger cell capable of safely housing the wee magician. This was the deal: In exchange for a plentiful supply of oxygen, plus carbohydrates or fats, the bacterial boarder would transform these raw materials into energy the larger cell could use pretty much any way it wanted to.

This magic trick is the process we call respiration. Over time, the once free-living bacterium thrived and evolved to become the subcellular components, or organelles, we know as mitochondria. Mitochondria and the cells in which they dwell have been locked in a symbiotic embrace ever since.

There is a catch, though. The harder a cell has to work, the more energy its mitochondria have to churn out — and the more likely they'll burn out. Just ask a nerve cell. Or, better, ask a couple of Stanford scientists who have tied mitochondrial morbidity to neurological diseases and used that insight to make inroads in treating Alzheimer's, Parkinson's and more.

THE DARK SIDE OF THE DEAL

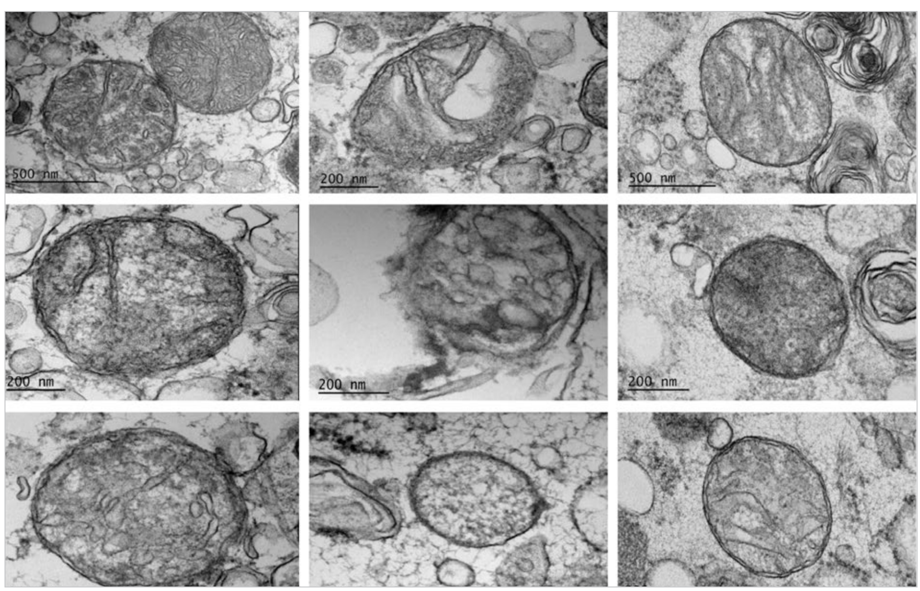
The downside of respiration is that it inevitably generates nasty byproducts called free radicals, which not only are harmful to the mitochondria but can also damage cells generally — not to mention deprive them of the energy they need to function properly. That cell damage, in turn, can set off a cell-suicide program called apoptosis. When things go wrong with mitochondria, they cough out far larger amounts of free radicals, and then things can go very wrong with us, too.

As free-radical damage takes its toll, battered mitochondria accumulate and overall mitochondrial function declines. While this happens throughout our bodies, some tissues get hit harder than others. The higher a cell's energy requirement, the more damage you might expect it to incur from the toxic exhaust of mitochondria in overdrive.

With this in mind, consider that about 20% of all the energy our mitochondria produce is used up by our massive, ever-busy brains. The roughly 100 billion nerve cells, or neurons, in the human brain contain hundreds to thousands of mitochondria apiece to generate that energy

With people living longer, age-related neurodegenerative disorders are more prevalent. The most common member of this club of undesirables, Alzheimer's disease, affects well over 5 million adults in the United States, with an estimated global prevalence above 20 million. Parkinson's disease is in second place, with 10 million people affected. Huntington's disease and amyotrophic lateral sclerosis — or ALS — are more rare, but are also tragically debilitating.

Each of these disorders is associated with the buildup in the brain of one or another protein that's toxic to neurons. Neuroscientists and drug developers



LEFT: HEALTHY MITOCHONDRIA. CENTER: DAMAGED MITOCHONDRIA (NOTE THE BROKEN OUTER MEMBRANES) EXPELLED FROM ASTROCYTES EXPOSED TO INFLAMED MICROGLIAL CULTURE BROTH. RIGHT: MITOCHONDRIA EXPELLED FROM ASTROCYTES EXPOSED TO CULTURE BROTH FROM MICROGLIA INCUBATED IN INFLAMMATORY SUBSTANCES — BUT ALSO PROTECTIVE PEPTIDE P110.

PHOTOS BY AMIT JOSHI

intent on finding cures have focused their attention on neurons and those neurotoxic proteins. But those considerable efforts haven't yielded drugs that stop the relentless progression of neurodegenerative diseases.

Meanwhile, researchers increasingly suspect mitochondrial mishaps are a driving force behind many neurodegenerative diseases — suspicions strongly confirmed in recently published studies by Stanford scientists. These insights stand to accelerate the rethinking of approaches that haven't been successful and speed a shift toward stamping out mitochondrial malfeasance. At least two promising drug candidates discovered at Stanford aim straight at mitochondria.

MITOCHONDRIA ON THE MOVE

Xinnan Wang, MD, PhD, has been on the trail of Parkinson's disease for several years. Her discoveries about mitochondria's role in Parkinson's are raising hopes that it can be caught before symptoms develop and, perhaps, arrested as soon as the disease is diagnosed.

Whereas 5% to 10% of Parkinson's cases are familial — the inherited result of known genetic mutations — the vast majority are sporadic, involving complex interactions of multiple unknown genes and environmental factors.

Parkinson's stems from the mysterious die-off of a set of especially hard-working midbrain neurons that fine-tune our every bodily movement. These neurons are referred to as *dopaminergic* because a substance they secrete, dopamine, transmits motion-modulating signals to other neurons. By the time a person manifests symptoms, an estimated 50% of these midbrain dopaminergic neurons have already died.

Why these particular cells, and not others, would die is unknown. One leading theory holds that the special intensity with which midbrain dopaminergic neurons perform their duties frazzles their mitochondria.

"Some cells in the body have a soft desk job," said Wang, an associate professor of neurosurgery. "But these fine-motor-control neurons are working 24/7."

No Parkinson's treatment in current use stops those neurons from dying, Wang said.

There also hasn't been any good way to *detect* Parkinson's disease early in its progression. "Early clinical diagnosis is entirely based on observing symptoms and querying patients," said Wang. The rate of misdiagnosis is about 10% to 20%, she said.

'Some cells in the body have a soft desk job,' said Wang, 'But these fine-motor-control neurons are working 24/7.'

Absent any reliable early marker, drug developers can't test potential treatments when they might help the most — before patients are symptomatic.

They're working in the dark, Wang says. "But our new study may provide them with eyes."

To do this, Wang's group focused on how mitochondria move within a cell. You might imagine that, like power plants, mitochondria wouldn't move much. But they're frequently shuttled from one part of a cell to another in response to the cell's internal energy needs.

"Mitochondria are very dynamic," Wang said. "Between 30% and 60% of them are on the move at any one time."

Not that they glide around the way their rustic, puddle-paddling, blown-by-the-breeze bacterial ancestors did. In fact, mitochondria's movements are quite orderly. But they don't travel on their own. Instead, they spend much of their time attached to a grid of molecular tracks that crisscross cells like elaborate urban-transit tracks, and along which they get hauled like cargo when need be.

Here's where mitochondria's hostile work environment (their own selves, that is) comes into the Parkinson's picture. Defective mitochondria have to be hustled off to cells' in-house dumpsters as soon as possible, lest their toxic output spur cell damage or death. For this purpose, our cells have a set of specialized proteins that yank them off the grid to be perp-walked to the cell's recycling centers. First, though, those proteins have to remove an adaptor molecule called Miro that staples mitochondria, whether damaged or healthy, to the grid.

Wang's group has pinpointed a cellular defect that stymies those "yanking" proteins' ability to shave Miro off damaged mitochondria. In a more recent study, published in *Cell Metabolism* in September 2019, the group found that cells from the great majority of people with Parkinson's and relatives considered at heightened risk for the condition had this same defect — unlike the cells of anybody else the scientists studied.

Using software belonging to Atomwise, a San Francisco-based biotechnology company, the investigators screened nearly 7 million drug candidates to identify compounds likely to facilitate Parkinsonian cells' ability to clear Miro from damaged mitochondria and expunge them. They identified a set of 11 compounds, which were also likely to be nontoxic, could be taken orally and could cross the blood-brain barrier.

Researchers tested the most promising compound, which appeared to target Miro almost exclusively, on Parkinsonian cells. It substantially improved these cells' ability to clear Miro after their exposure to mitochondria-damaging stress.

But these cells were skin cells, and Wang was interested in what this compound would do for neurons. So her team generated dopaminergic neurons from Parkinson's patients' cells, incubated them with the experimental compound, and found that these neurons rivaled healthy individuals' neurons in their ability to scrape Miro from damaged mitochondria and get rid of them.

To further test the compound, the scientists fed it to fruit flies engineered to develop the equivalent of Parkinson's. Fruit flies and people — whose ancestors diverged from some undoubtedly weird-looking common predecessor about 782.7 million years ago — share many similarities. The midbrain dopaminergic circuit that controls muscular movement works much as it does in them as it does in us. Giving the compound to those flies throughout their 90-day lifetimes prevented their dopaminergic neurons' deaths and improved their climbing ability, without toxicity signs.

"We're closing in on a drug that, instead of just providing symptomatic relief, might be able to address Parkinson's disease's cause and alter its course," said Wang. "We believe it could be a major step toward a cure."

Wang, who formed a company called CuraX to put her team's findings to work, said she thinks clinical trials of the compound or a close analog are no more than a few years off.

"Miro is a brand-new drug target — pharmaceutical companies haven't aimed at it before," she said. "Our hope is that if this compound or a similar one proves nontoxic and efficacious so we can give it repeatedly, like a statin drug, to people who've tested positive for the Miro-removal defect but don't yet have Parkinson's symptoms, they'll never get it."

Meanwhile, tantalizing evidence gathered by Daria Mochly-Rosen's group suggests that several neurodegenerative disorders — including Alzheimer's, Huntington's and ALS — are marked by identical inflammatory interactions among a few types of brain cells. Those interactions employ malfunctioning mitochondria as messengers of death: They travel from cell to cell, emitting inflammatory signals in the form of the toxic free radicals. And their mortal message can be countered by the systemic administration of a substance engineered in Mochly-Rosen's lab.

"We've identified a potential new way to prevent death of neurons in several diseases, regardless of their differing original causes," said Mochly-Rosen, PhD, professor of chemical and systems biology and the George D. Smith Professor in Translational Medicine. "A single pharmaceutical agent may be enough to slow progression of several different neurodegenerative conditions." She is poised to partner with biomedical companies that can help move this agent, known as P110, into clinical trials.

The new strategy came to light through experiments conducted by Mochly-Rosen, postdoctoral scholar Amit Joshi, PhD, and colleagues that implicate two types of normally protective brain cells called glial cells in triggering neuronal destruction. Collectively, these glial cells outnumber neurons in the brain. *Microglia* monitor the brain for potential problems — say, signs of tissue injury or invading pathogens — and scavenge protein aggregates and debris left behind by dying cells. *Astrocytes* release growth factors, provide essential metabolites and determine the number and placement of the connections neurons make with one another. The experiments, published in October 2019 in *Nature Neuroscience*, showed that mitochondria can convey deleterious inflammatory signals from microglial cells to astrocytes, and then from astrocytes to neurons.

Viewed close up, mitochondria are convoluted tubular networks that are perpetually being right-sized in a dance of fusion and fission. As mitochondria are frequently shuffled from one part of a cell to another, they must shift their shapes to accommodate their environments: Too much fusion, and they become too tubby to get around on the intracellular-transit grid or to work well. Too much fission, and they break into dysfunctional bits.

An enzyme 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 ALS. About seven years ago, Mochly-Rosen's team designed P110, a tiny protein snippet, or peptide, that blocks mitochondrial fission when it's proceeding at an excessive pace, as happens when a cell is damaged.

In the new series of experiments, the researchers kicked microglia grown in culture dishes into an inflamed state by simulating multiple neurodegenerative disorders, in each case by introducing a toxic protein whose aggregation heralds a specific disorder's onset. The inflamed microglia released some enigmatic something into their culture broth that was able to trigger inflammation in astrocytes that were immersed later in the same broth.

Likewise, a similarly mysterious something released by inflamed astrocytes into *their* culture broth was able to kill neurons steeped in that broth later.

Mochly-Rosen and her colleagues proved that the inflammatory agent being expelled by both microglia and astrocytes was one and the same: damaged mitochondria. What's more, adding P110 to the microglial culture dishes substantially blocked this faulty-mitochondria-driven transfer of inflammation from one cell type to the next.

Even healthy cells routinely release mitochondria into their surrounding environment. This can be beneficial if those mitochondria are healthy and can still generate energy. However, Mochly-Rosen and her co-researchers found that when microglia and astrocytes became inflamed, the mitochondria they released were more apt to be fragmented products of disruptive fission, which are lethal to nearby neurons. And blocking excessive mitochondrial fragmentation with P110 was enough to significantly reduce neuronal death.

"The ratio of damaged to functional mitochondria in the surrounding milieu determines whether neurons survive or die," Mochly-Rosen said.

The discovery has given her lab a new outlook, she noted: "We humans are as good as these little bacteria inside us. They are the ones who decide our fate." **SM**

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FEATURE

Tomorrow's hospital today

CONTINUED FROM PAGE 15

Advisory council member Moore and his wife, Lynn Fraher, had their first glimpse of the new hospital's construction in 2013 after he had a heart procedure and his doctors urged him to move around. As the couple wandered through the hospital hallways they noticed a big hole in the ground outside one of the windows.

As his health improved, they watched the building come to life. Moore had many Stanford Hospital stays over the years: In 2000, he was diagnosed with hepatitis C, and in 2007 he received a liver transplant and heart valve replacement in a back-to-back surgery.

These days they have a whole new relationship with Stanford Health Care. After more than 10 years of volunteering with the hospital — as patient advocates and on the advisory council, which Fraher led for four years — Fraher became a hospital employee last year in patient relations. In October 2019, she became a patient navigator in the new family and caregiver resource center.

For Entwistle, it's not the hospital that raises the bar for staff members like Fraher, but the other way around.

"The new Stanford Hospital is a setting worthy of our incredible physicians, nurses and staff," Entwistle said. "We've created an environment to match the high caliber of the care they provide, while offering patients and families an atmosphere that has been designed to promote healing at every step."

As Stanford Health Care's staff, patients and families explore and feel at home in the new space, they're also learning that it's unique. "This combination of beauty, space, capacity, capability, technology and timelessness — I'm not sure how many places have that combination all in one," said Sam Wald, who oversees the interventional platform. "It's a renaissance hospital." **SM**

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FEATURE

From prehab to rehab

CONTINUED FROM PAGE 27

"ICU patients are quite different, depending on what the reason is for them needing critical care," said Hawn. "Having a dedicated ICU focused on surgical patients fits into our precision medicine ethos."

Each surgical ICU recovery room is 222 square feet, large enough to allow doctors to perform certain procedures, such as inserting a tube to help with breathing or feeding, at a patient's bedside rather than in an operating room.

There is a growing consensus in the medical community that if a procedure can be safely done at the bedside, it should be. That's because simply moving a sick, frail patient to an operating room risks infection or dislodging sensitive medical equipment.

Health care providers won't be alone at the bedside. Each recovery room has a fold-out couch that doubles as a bed so family members can spend the night with a recovering loved one.

"Treating patients in the ICU goes part and parcel with caring for their family members," said Knowlton.

POSTOPERATIVE PAIN

Pain is the body's natural response to being cut open. Yet while our pain responses wisely remind us to take it easy after surgery, they can also prevent us from starting rehabilitation. Ironically, the fear of pain during rehab can slow recovery and thereby prolong pain.

"Our mind and body perceive pain as something that we want to escape," said Beth Darnall, PhD, associate professor of anesthesiology, perioperative and pain medicine. "But it doesn't help us after surgery because there's nothing to escape. Those hard-wired responses actually work against us because they keep us in a heightened state of ongoing stress and tension."

Darnall doesn't speak only as a trained pain psychologist — she speaks from personal experience. Throughout her childhood and into her early 20s, she struggled with chronic gut pain so severe it once landed her in the emergency room.

Her doctors, unable to pinpoint the cause, sent her home from that visit with a bottle of Vicodin. But what Darnall needed most was someone to tell her how to reduce her suffering.

Darnall is now doing that for others. Her research shows that the mind shapes how we experience pain and that focusing on pain only amplifies it. We end up unwittingly getting more of what we fear. This may be part of the reason about 10% of patients develop chronic pain after surgery.

To test evidence-based pain management strategies, Darnall and her colleagues recruited women with breast cancer who were scheduled to have a tumor or a portion of breast tissue removed. Women in the control group of this randomized trial received general information about nutrition and movement rather than a specific pain relief strategy. Women in the test group viewed a 90-minute online video explaining what pain is and how our emotions and thought patterns shape it.

The video provided practical tips on staying calm by using muscle relaxation techniques and diaphragmatic breathing — or belly breathing. Participants also received an audio recording designed to induce relaxation by transmitting sound to each ear, and thus each hemisphere of the brain. Finally, the treatment included a personalized plan for surgical success. They were encouraged to complete it and apply the key skills daily after surgery.

Pain medication is not discussed in the video. Yet women in the test group stopped using opioids after surgery an average of five days sooner than women in the control group, according to results published in May 2019.

Darnall's team is now testing this program, called My Surgical Success, on orthopaedic trauma patients, and collaborators at Cleveland Clinic are testing it on spinal surgery patients. The video has been condensed from 90 to 45 minutes to boost the percentage of patients who complete it from the 56% reported in the latest study.

My Surgical Success is a digital version of a two-hour pain management course Darnall developed in 2013 called Empowered Relief. Stanford patients are offered the class for free, and it's been adopted by health care systems throughout Australia, Canada, Denmark, the United Kingdom and the United States.

"It's the class that my younger self needed back when I had pain," Darnall said.

Darnall's aim isn't to supplant the use of medication, but to give patients a range of options for managing pain in a more holistic manner.

"When we treat pain comprehensively and focus on empowering patients to best control their own experience, we will naturally observe that patients will need less medical intervention," Darnall said.

Managing pain, eating healthy and exercising regularly can benefit all of us, not just those preparing for and recovering from surgery. But surgical patients get to see the direct impact of lifestyle changes on their recovery — which can cement new habits.

"If patients see that what they did helped their recovery, that might spur them on afterwards," said Kin.

That brings us back to Notar, who still lives by the diet and exercise guidelines she learned during prehab and said that she always will. But she's not the only one in her household living by those rules. Four weeks into prehab, Notar was tired of preparing different meals for her husband and herself. So she delivered an ultimatum: "Look, you either eat what I eat or you make your own food."

He decided to join her, and Notar said they are both in better shape than they have been in many years. She's also working, volunteering and going to the gym again.

"Just the difference in how I feel is a blessing," said Notar, on her way to pick up a pregnant dog that she plans to care for until the puppies are born and go to new homes. "I have so much more energy and, I don't know how to explain it, but I'm a very happy person now." **SM**

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FEATURE

A new view on brain surgery

CONTINUED FROM PAGE 37

The quest for precision during brain surgery goes back decades. In Rosenthal's near 20-year career as a surgeon, the problem that motivated his creation of the cancer-targeted fluorescent dye remains. "Surgeons most often can't see cancer and, on average, they end up leaving anywhere from 10% to 40% of the tumor behind," he said. His solution has a simple premise: Mark the cancer with something you can't miss. "It's sort of like you've added phosphorous to illuminate parts of the ocean."

Rosenthal's efforts put him at the forefront of the development of fluorescence-guided surgery for cancer patients.

The luminescence agent developed by Rosenthal and colleagues combines two ingredients: an antibody that latches onto tumor cells and the bright green fluorescent label. When injected into a patient intravenously, the tandem molecules flow throughout the bloodstream, binding to cancer cells. Then, during a procedure, the surgeon shines infrared light onto the tissue. The light hits the fluorescent marker and sends a bright signal to a special camera that detects the light's refraction, forming an image that the surgeon observes on a nearby screen. The image reveals where those glowing markers have docked in the body and, by extension, where to cut.

The antibody-fluorescent dye hybrid Rosenthal works with first made it to the operating room on an experimental basis in 2015, in head and neck cancer. Once a surgeon has removed the glowing mass of tissue, it can be examined in greater detail. The hope is that the mass has "clean margins," with no sign of fluorescence bleeding through the edge of the sample.

"For decades surgeons have had to largely depend on pre-operative scans and the look and feel of tissue to determine what to remove during surgery. With this fluorescent-guided surgery, our goal is to enhance precision, clarity and the confidence that we're resecting to the best of our ability," said Rosenthal, a professor of otolaryngology-head and neck surgery. "Ultimately, I see this as a tool that could help surgeons confirm the absence of disease, detect any additional disease, or help determine where disease begins and ends."

For now, Rosenthal's dye is in the clinical trial stage: He and fellow surgeons administering the dye are collecting data for a study of the technique's safety in several cancer types, including brain, pancreatic, liver, and head and neck. If the results are positive, they'll expand the trials.

"Distinguishing tumor from normal or swollen surrounding brain can be really tricky under standard microscopes — sometimes indistinguishable," said Melanie Hayden-Gephart, MD, associate professor of neurosurgery who has used Rosenthal's fluorescent aid in surgery. "So this type of fluorescent-based excision could both enhance the efficiency of the operation — meaning that you would be able to more readily identify tumor versus normal — and it could improve the resection and overall outcome for the patient."

As a patient, Inouye fully supports the integration of science and clinical care. "After the success of my surgery, I've signed up for more studies because I believe that research can make a difference in patient care. When I came to Stanford, I told my doctors I needed them to buy me time," said Inouye. "I told them, 'Whatever time you can give me will make a difference.' I know I'm not the only patient who has felt or will feel that way." **SM**

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PLUS

What are my chances?

CONTINUED FROM PAGE 39

after the first imaging scan to generate an initial prognosis. More recently, some use CAPP-Seq to measure the levels of ctDNA after the first one or two rounds of therapy to determine how the tumor is responding and estimate a patient's overall risk of dying from the disease.

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

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

So, the team gathered data on more than 2,500 diffuse large B-cell lymphoma patients from 11 previously published studies for whom the three most common predictors of prognosis were available. Esfahani used the data to train a computer algorithm to recognize patterns and combinations likely to affect whether a patient lived for at least 24 months after seemingly successful treatment without experiencing a disease recurrence.

They also included information from 132 patients for whom data about circulating tumor DNA levels were available before and after the first and second rounds of treatment.

The researchers next tested CIRI's performance on data from previously published panels of people with a common leukemia and another panel on breast cancer patients.

Although the prognostic indicators varied for each disease, they found that, by serially integrating the predictive information over time, CIRI outperformed standard methods. If an experienced physician predicts a patient's outcome correctly about 60% of the time, CIRI got it right about 80% of the time. Not perfect, but a significant improvement.

Furthermore, the study suggested that CIRI could identify patients who might need more aggressive intervention within one or two rounds of treatment rather than waiting to see if the disease recurs.

"What I didn't initially expect was that aggregating all this information through time may also be predictive," Alizadeh said. "It might tell us, 'You're going down the wrong path with this therapy, and this other therapy might be better.'"

A clinical trial is necessary to learn whether CIRI can be used to guide the course of treatment in real time. But Alizadeh and Kurtz have seen tantalizing results when they've applied CIRI to some of their past patients with diffuse large B-cell lymphoma.

One patient with advanced disease chose not to complete the recommended six rounds of chemotherapy and checked himself out of the hospital after one round of treatment.

"At that point, I was sure I'd soon be arranging for end-of-life care for him," said Alizadeh. "He had the ugliest of the ugliest types of lymphoma — a huge burden of disease and the presence of all five of the standard risk factors we use to determine prognosis." More than four years later, however, the man is alive and has no evidence of cancer.

"It was completely shocking," said Alizadeh. "Conventional wisdom tells us there's no way we could achieve a curative outcome for this patient with just one cycle of chemotherapy."

Conversely, a young woman with few risk factors who appeared to be cured of her disease relapsed less than two years later and is now undergoing a much more aggressive form of treatment to try to save her life.

"All my training as an oncologist indicated that she should have had a full recovery," Alizadeh said. "If only we could have known 30 days into treatment that she would relapse, rather than two years later, we would have had more options for her."

When Alizadeh and Kurtz fed the patients' information into CIRI after the fact, the algorithm saw patterns that had escaped the seasoned physicians. It correctly predicted that the young woman would do poorly and the man might do well.

"For both of these patients, my professional judgment and CIRI's judgment were soberingly different," said Alizadeh. "Now we have to learn how to use this tool in a way that will be meaningful for patients and their doctors. What we know, however, from our retrospective studies is that if you compare CIRI's accuracy versus using any one risk factor alone, CIRI is head and shoulders better."

In short, the whole is better than any one component alone. And that's likely to help doctors help patients. **SM**

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HEALTH FOOD

BEHIND THE SCENES IN A HOSPITAL KITCHEN

At 12:17 p.m., Jose Tristan picks up the phone in his Stanford Hospital room to order lunch. It's a Wednesday in October. Four days earlier, Tristan, 43, missed a dose of medication he takes for chronic obstructive pulmonary disease and ended up in the hospital, struggling to breathe. As part of his treatment, Tristan was already on a low-sodium diet, and his doctor at the hospital has prescribed an even lower one. His phone call will start a countdown for delivering a meal of his choice.

"It's like ordering room service," said Jodi Krefetz, director of food services at Stanford Health Care. For the past eight years, anytime between 6 a.m. and 9 p.m. patients have been able to order from a menu of fresh, seasonal items designed with deliciousness in mind — including more than 30 breakfast items, a few dozen sides and snacks, and about 25 lunch and dinner entrees, many of which can be personalized to patients' taste.

But patients' needs go beyond flavor. The hospital's food service team prepares 1,300 meals a day to meet nutritional standards of more than 100 different diets. They count carbohydrates for diabetics, accommodate food allergies, puree food for people who struggle to swallow, and offer choices to fit varied religious and cultural dietary practices. And they do it all within a 45-minute time constraint.

"A lot of your choices are taken away in a hospital setting," said Helen Wirth, administrative director of hospitality services at the hospital. "For our patients, having some control is really, really important."

Diets prescribed for medical reasons limit patients' choices, of course. "Being a low-sodium patient, it's hard," Tristan said. His call to order lunch reaches a dietary assistant, who talks him through the menu. He asks about breaded baked fish, but it has added salt, which isn't allowed on his diet, she explains. Does he want steelhead trout? He chooses meatloaf. He also requests gravy, a baked potato with margarine and sour cream, peas, white rice, iced tea with sugar, and vanilla ice cream. The assistant enters everything into the food-service computer system and checks that Tristan's selections contain less than the 550 milligrams of sodium he's allotted per meal.

Three minutes after she starts his order, #519, the assistant saves it and it's automatically printed in the hospital's kitchen. There, staff on the hot-food line use clipped kitchen-speak while dishing up the potatoes whose aroma permeates the room. The place vibrates with activity: Equipment beeps, plates clank, people work shoulder to shoulder. (The new hospital, to which the team moved soon after this story was written, affords them 7,000 more square feet of space.)

By 12:27 p.m., a cook is heating Tristan's meatloaf in beef broth in a high-speed oven. When it's ready, a second cook adds the baked potato, gravy, rice, peas and a garnish in rapid succession. The plate goes in a warming vessel.

At 12:36, order #519 reaches a worker who adds utensils and condiments. At the refrigerator case, another staff member completes his meal. By 12:40, the team's checker is comparing everything on the tray with the original order.

The meal is loaded onto a cart at 12:42, headed to the hospital's third floor. The seventh and final person who handles Tristan's meal, the tray passer, scans the bar code on order #519. A computer at the kitchen exit, synced to Tristan's electronic medical record, would alert her if he had moved or his dietary requirements had changed while the meal was being prepared. The tray passer rolls the cart on a service elevator at 12:45.

Finally, at 12:49 p.m., the tray passer delivers Tristan's lunch to him, 32 minutes after he placed the order. It's a small but important step in helping him recover and head home. — ERIN DIGITALE

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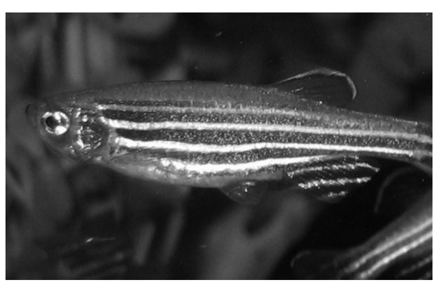
Night, night

UNDERSTANDING THE NEUROLOGY OF SNOOZING ZEBRAFISH COULD SOLVE THE MYSTERIES OF HUMAN SLEEP

It's hard to tell when fish are asleep because they keep their eyes open. But snooze they do, and recent research shows that sleeping zebrafish and sleeping people share striking similarities. In a study published July 10 in *Nature*, Stanford researchers found that when zebrafish sleep, their brains can display two states similar to those in sleeping mammals, reptiles and birds: slow-wave sleep and paradoxical sleep. The discovery marks the first time these brain patterns have been recorded in fish.

"The only real difference is a lack of rapid eye movement during paradoxical sleep," said Philippe Mourrain, PhD, an associate professor of psychiatry and behavioral sciences and senior author of the study.



The discovery means sleep research relevant to humans can be conducted on zebrafish, which are easy to study, in part because they are transparent, breed quickly and are inexpensive to raise. And unlike mice, the typical stand-in for humans in sleep research, zebrafish are awake during the day and sleep at night, just like humans.

Most neurological disorders are linked to sleep abnormalities — and zebrafish studies could help understand the connection, said Mourrain.

"Because the fish neural signatures are in essence the same as ours, we can use information about them to generate new leads for drug trials," added postdoctoral scholar Louis Leung, PhD, the study's lead author.

To record the brain and body activity of sleeping zebrafish, Leung built a scanning machine with a mini-aquarium. He transferred the zebrafish, one at a time, into the aquarium holding not only water but gelatinous agarose, which immobilized the fish so they were perfectly positioned for scanning.

Once the fish were asleep, researchers recorded changes in their heart rates, eye movements and muscle tone. The research revealed additional similarities to sleeping land vertebrates: The fish remain still, their muscles relaxed; their cardio-respiratory rhythms slow down; and they fail to react when they're approached.

Scientists aren't certain all animals sleep, but it appears to be a universal need among vertebrates and invertebrates. The benefits of sleep are still a mystery, however. "It's an essential function," Mourrain said, "but we don't know precisely what it does."

— MANDY ERICKSON

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