S T A N F O R D

M E D I C I N E

Issue 1 / 2026

special report

THE POWER OF RESEARCH

How discoveries translate into better health

plus

STANFORD MEDICINE

Issue 1 / 2026

CONSIDERING ASSEMBLOIDS AND ORGANOIDS

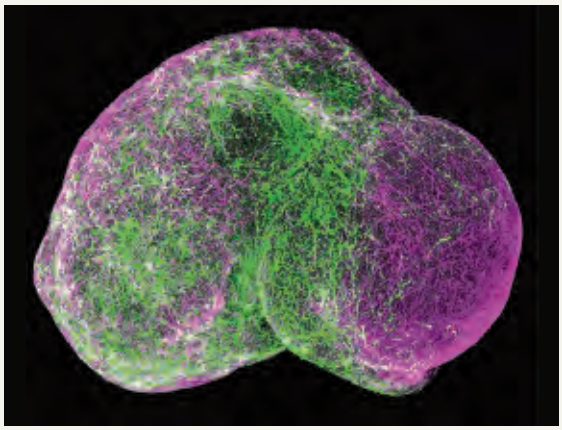
A CONFERENCE ORGANIZED BY STANFORD UNIVERSITY TACKLED BIOETHICAL QUESTIONS RAISED BY NEW TECHNOLOGIES FOR REPLICATING BRAIN PARTS IN A DISH

Over the past nearly two decades, stem-cell technology has enabled brain scientists to, as if by magic, transform virtually any living person's skin cells into diverse types of brain cells that, following their own hardwired instructions, coalesce into tiny spheres recapitulating different brain regions' structure and connectivity.

These tissue replicas, or neural organoids, can be strung together into interconnected concatenations called neural assembloids, which mimic the interplay between different brain regions. They allow neuroscientists to better understand neurodevelopmental disorders and the effects of oxygen deprivation or viral infections on the fetal brain.

This profound access to aspects of human neurobiology, difficult to impossible to study otherwise, promises treatments for severe conditions once thought intractable. But the field's rapid expansion raises concerns about the ethical and societal implications of neural organoids, assembloids, their transplantation into other species' brains for experimentation and more. "Technical advances, recent and imminent, are going to bring more attention to this field," said professor of law Hank Greely, JD, a longtime observer of looming bioethical quandaries.

As assembloid advances permit increased communication among different brain parts in a dish, and as animal transplantation or improved culture methods enhance organoid and assembloid development, might these laboratory tools become sentient — experience subjective sensations of pain, for instance, or even some form of consciousness? Will hookups between animals' brains and transplanted brain tissue of human origin trigger any unexpected, emergent properties, such as humanlike behaviors, in these animals?



Two tiny clusters of cultured brain cells — one stained green, the other, purple — fused and migrated to form this assembloid, which is a 3D lab-grown model used to study brain development.

PHOTOGRAPH BY PASCA LAB

Another issue: With a projected rapid expansion in the array of experiments that can be performed with organoids and assembloids, what additional steps should be taken to ensure that tissue donors' intentions are honored? Should they or their guardians be informed whenever new technologies enable their cells to be used to generate more-complex organoids, assembloids or interspecies hybrids?

To brainstorm about these concerns and whether regulations are needed — and if so, what they should be — Greely and Sergiu Pasca, MD, a professor of psychiatry and behavioral sciences and a neural-assembloid pioneer, spearheaded a conference, held Nov. 10 through 12, 2025, at Asilomar in Pacific Grove, California. The meeting brought together nearly 70 participants from the U.S., Europe and Asia, including neuroscientists, cognitive psychologists, philosophers, legal scholars, ethicists, editors of major scientific journals, journalists, patient advocates and representatives from scientific organizations. It was organized with support from the Dana Foundation and the Wu Tsai Neuroscience Institute, for which Pasca serves as the Uytengsu Family Director of the Stanford Brain Organogenesis Program. This initiative, launched in 2018, brings Pasca, Greely and others together to keep ethics at the core of brain organoid and assembloid advances.

The conference echoed a 1975 conference held at Asilomar — likewise organized by Stanford University scientists and bioethicists — to discuss the scientific, legal and ethical implications of recombinant DNA, or gene splicing. That new technology burgeoned and spawned everything from miraculous biotechnological cures to fears that the course of human evolution could be deliberately, and perhaps dangerously, altered.

At the 2025 conference, Greely said, participants largely agreed that the ethical questions regarding organoids and assembloids need more attention and that the public should be made aware of both the limits and capabilities of the technologies. However, another message that resonated broadly was that ethical considerations must not overshadow the impetus behind these scientific developments.

"Patient advocates articulated with striking clarity how urgent the need is for therapeutic advances and how important it is that ethical reflection does not become disconnected from the realities faced by affected families," said Pasca, the Kenneth T. Norris, Jr. Professor II of Psychiatry and Behavioral Sciences.

In the wake of the conference, the organizers' focus has turned to synthesis. They are now assimilating the insights and planning what comes next. — BRUCE GOLDMAN

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STANFORD MEDICINE

SPECIAL REPORT

The power of research

How discoveries translate into better health

Q&As with researchers who have translated their insights into health care advances.
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COVER: BRIAN STAUFFER

letter from the dean

"I have no special talent. I am only passionately curious."
— ALBERT EINSTEIN

Most biomedical breakthroughs don't begin with a plan. They begin with someone being curious about something — and deciding to follow it.

How does a cell decide when to repair itself, when to adapt and when to fail? Research driven by questions like this has reshaped our understanding of cancer, immune disease, neurodegeneration and aging, often in ways that were impossible to predict at the outset.

At Stanford Medicine scientists and clinicians pursue fundamental questions about biology, sometimes without knowing where they will lead. Over time, the insights they've gained have informed new approaches to prevention, diagnosis and treatment. Many of the advances patients rely on today — vaccines, medical imaging, complex therapies — grew from research conducted decades earlier that was once considered exploratory or even impractical. These outcomes underscore the value of basic inquiry and the scientific process and highlight the vital importance of academic medical centers that enable them to flourish.

While some research outcomes may be serendipitous, scientific discovery at Stanford Medicine does not happen by chance. The move of the medical school from San Francisco to the Stanford University campus in 1959 marked a turning point for Stanford Medicine's biomedical preeminence. This co-location of patients, data and laboratories brought researchers, engineers and clinicians into closer proximity to test ideas for addressing real-world clinical challenges. Combined with Stanford's culture of collaboration, investment in research infrastructure and forward-thinking programming, this connection accelerates discovery that is grounded in human need.

Today, many of the most promising biomedical advances are emerging at what have traditionally been considered the boundaries between fields, where biology meets data science, engineering and computation. Progress in these areas depends on even deeper collaboration, sustained investment and the freedom to pursue ideas whose value may take time to become clear.

Yet this prolific age of biomedical research presents a conundrum: an abundance of promising ideas and too few resources to investigate them all. Academic medicine often produces early discoveries that are deemed high-risk or have unclear financial upside for industry to commercialize. For this reason, Stanford Medicine has developed programs to accelerate the development of its own high-potential, early discoveries. Our Innovative Medicines Accelerator is one such example. This interdisciplinary program acts as both an incubator and accelerator for ideas, regardless of their commercial potential. Since 2020, the program has helped numerous faculty projects reach maturity and match them with pharmaceutical companies, venture capital investors or nonprofits best suited to develop therapies for conditions such as infectious diseases, cancers and metabolic disorders.

The accelerator is just one of many entities at Stanford designed to encourage researchers to embrace their entrepreneurial spirit across the research spectrum.

Supporting basic, translational and clinical research is more important than ever. By championing curiosity and enabling rigorous, exploratory science, we create the conditions that allow seemingly impractical discoveries to not only continue surprising us but to also improve lives.

Sincerely,

Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of Stanford School of Medicine
Vice President for Medical Affairs at Stanford University
Professor of Otolaryngology-Head & Neck Surgery

PHOTOGRAPH BY CAROLYN FONG

upfront

Paddington for preemies

HEARING THE SOUND of their mother's voice promotes development of language pathways in a premature baby's brain, according to a new Stanford Medicine-led study.

"This is the first causal evidence that a speech experience is contributing to brain development at this very young age," said the lead author, Katherine Travis, PhD, an assistant professor of pediatrics at Stanford Medicine when the study was conducted, who is now on the faculty of Weill Cornell Medical School.

The findings were published Oct. 13, 2025, in *Frontiers in Human Neuroscience*. The senior author is Heidi Feldman, MD, PhD, the Ballinger-Swindells Endowed Professor in Developmental and Behavioral Pediatrics.

Premature babies are often hospitalized for weeks or months, during which time they hear less maternal speech than if they had continued to develop in utero. They are at risk for language delays, and scientists have suspected that reduced early-life exposure to the sounds of speech contributes to the problem.

Forty-six babies who were born more than eight weeks early were in the study. They were randomly assigned to a treatment group or control group. Over the course of a few weeks, babies in the treatment group heard recordings of their mothers reading the children's book *A Bear Called Paddington* for 2 hours and 40 minutes every day. Members of the control group did not.

MRI scans were taken of the infants' brains before they were discharged from the hospital. The images showed the arcuate fasciculus tracts on both sides of the brain, which contain bundles of nerve fibers that help process and understand sound. The left arcuate fasciculus is specialized for language processing.

The scans revealed that the language-processing pathway was more mature in babies in the treatment group than in babies in the control group. The right arcuate fasciculus was less affected by the treatment — a finding consistent with known differences in how the two hemispheres of

the brain process speech, the scientists said.

"Babies were exposed to this intervention for a relatively short time," said study co-author Melissa Scala, MD, a clinical professor of pediatrics and a neonatologist at Lucile Packard Children's Hospital Stanford. "In spite of that, we were seeing very measurable differences in their language tracts. It's powerful that something fairly small seems to make a big difference."

'BABIES WERE EXPOSED TO THIS INTERVENTION FOR A RELATIVELY SHORT TIME. IN SPITE OF THAT, WE WERE SEEING VERY MEASURABLE DIFFERENCES IN THEIR LANGUAGE TRACTS.'

ILLUSTRATIONS BY HOI CHAN

Gentler cancer therapy

CAR-T THERAPY has been a boon for treating many blood cancers, but it's onerous. Immune cells called T cells are removed from a patient, genetically engineered and then returned. Patients must also undergo a procedure to deplete their original T cells, leaving them at risk for infection.

A study led by Stanford Medicine researchers suggests a gentler alternative. Although the method has not yet been attempted in humans, it was safe and effective in laboratory mice, the study found.

The method generates CAR-T cells with the same technique used for mRNA-based vaccines: mRNA is delivered into cells where it spurs production of the desired protein — in this case converting ordinary T cells into CAR-T cells. Unlike the suspension of T cells delivered in standard CAR-T treatment, the mRNA messages can be provided multiple times, amplifying its curative effects. Tumors in 75% of mice with B cell lymphoma treated with mRNA were eradicated after several doses. The approach requires no harsh pretreatment to deplete existing immune cells, and it allows researchers to track where the modified cells are in the body.

The study was published June 10, 2025, in *Proceedings of the National Academy of Sciences*. Katherine Ferrara, PhD, a professor of radiology and chief of the Molecular Imaging Program, was the senior author.

Surgery prehab

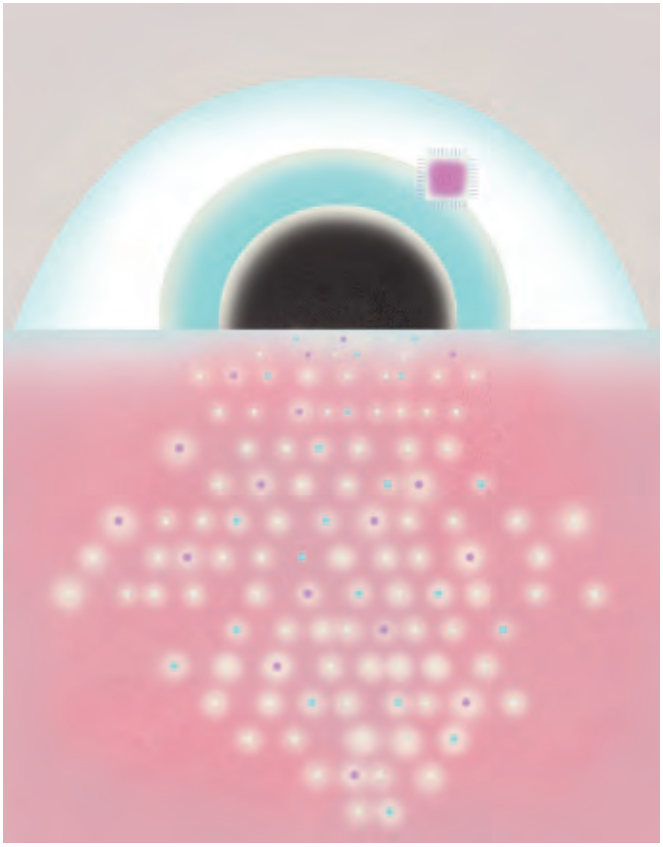
Surgeons often urge people to improve their physical and mental health prior to surgery — known as prehabilitation — to reduce complications afterward. A new Stanford Medicine study shows that people prehabilitate more successfully with a little one-on-one help.

In the study, standard prehab patients received literature about exercise, healthy eating, stress reduction, mindfulness and cognitive training. Personalized prehab patients received twice-weekly online coaching on the same topics. Within 30 days of surgery, 11 of the 27 standard prehab patients had moderate-to-severe post-operative complications, compared with four of the 27 personalized prehab patients.

Analyzing patients' immune cells, researchers found reduced overreactivity in some immune cells and lower baseline inflammation in the personalized group — surprisingly large shifts for a low-cost at-home intervention, they said.

"It's a measurable effect that you would expect from a pharmacological intervention, honestly," said Brice Gaudilliere, MD, PhD, a professor of anesthesiology, perioperative and pain medicine and a senior author of the November 2025 study in *JAMA Surgery*.

'I REALIZED WE SHOULD USE THE FACT THAT THE EYE IS TRANSPARENT AND DELIVER INFORMATION BY LIGHT.'



Help in sight

A MEDICAL DEVICE INVENTED by a Stanford Medicine researcher is the first capable of restoring functional sight to people with incurable vision loss, giving them the ability to perceive shapes and patterns, according to results published in October 2025 in *The New England Journal of Medicine*..

In a clinical trial, 27 of 32 participants with an advanced form of age-related macular degeneration, which destroys light-sensitive photoreceptors in the center of the retina, regained the ability to read within a year of being outfitted with the device.

The two-part prosthesis, called PRIMA, consists of a small, glasses-mounted camera that captures images and projects them via infrared light to a wireless chip implanted in the back of the eye. With enhancements enabled by the device, such as zoom and higher contrast, some participants could read with acuity equivalent to 20/42 vision.

"All previous attempts to provide vision with prosthetic devices resulted in basically light sensitivity, not really form vision," said Daniel Palanker, PhD, a professor of ophthalmology and co-senior author of the paper.

Palanker first imagined a prosthetic device 20 years ago, when he worked with ophthalmic lasers used to treat eye conditions. "I realized we should use the fact that the eye is transparent and deliver information by light," he said.

PRIMA provides only black-and-white vision, but Palanker is developing software that will enable the full range of gray scale, which is required for face recognition.

Pulmonary protection

A CHEMICAL messenger named after a small, spiny mammal of the Arabian Peninsula protects lungs from toxic damage in mice and might play the same role in humans, according to a Stanford Medicine study.

Neuroendocrine cells, which combine the properties of nerve cells and hormone-producing cells, make the desert hedgehog protein in the trachea and pancreas. An experimental drug that activates the protein in mice initiated a cascade of biological reactions that dramatically increased the survival of a variety of cells after the animals were exposed to sulfur dioxide gas, a pollutant that mimics damage from toxins such as wildfire smoke.

In treated mice, 66% of ciliated cells, which use feathery "arms" to sweep particles and viruses out of the lungs, and 82% of secretory cells, which make mucus to trap unwanted invaders, survived. Only 9.7% of ciliated cells and 43% of secretory cells survived in untreated animals. A similar protective effect followed infection with the flu or SARS-CoV-2.

Philip Beachy, PhD, the Ernest and Amelia Gallo Professor and a professor of urology and of developmental biology, was senior author of the study published in June 2025 in *Cell*. Scientists at University of California, San Francisco contributed to the work.

The researchers are studying how the hedgehog signaling pathway might be activated in humans to prevent lung damage in people who are exposed to airborne toxins.

Digital scientists

STANFORD MEDICINE researchers have figured out how to create digital "scientists" that work together with minimal oversight to solve real-world biomedical problems. A paper published in July 2025 in *Nature* describes how a virtual lab of artificial intelligence-powered scientists devised a better way to create a vaccine for SARS-CoV-2, the virus that causes COVID-19.

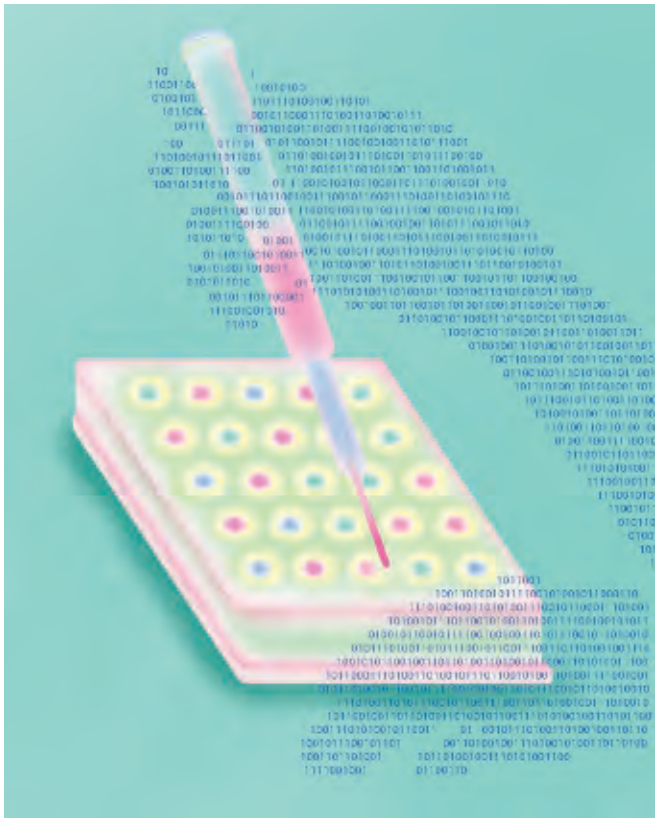
Advances in agentic AI, collaborative systems of AI models that interact to autonomously pursue certain goals, enabled the creation of a virtual lab, said James Zou, PhD, associate professor of biomedical data science and co-senior author of the study. This gave him the idea to train these software systems to perform like top-tier scientists.

In the virtual lab, a researcher poses a scientific challenge to an AI principal investigator, or AI PI. "It's the AI PI's job to figure out the other agents and expertise needed to tackle the project," Zou said.

For the SARS-CoV-2 project, the AI PI created an immunology agent, a computational biology agent and a machine learning agent. Another agent assumed the role of critic. Instead of proposing a traditional antibody, the AI team suggested a nanoscale fragment of an antibody.

A subgroup of researchers led by co-senior author John Pak, PhD, of the Chan Zuckerberg Biohub, created the nanobody and tested its ability to bind to one of the new SARS-CoV-2 variants — which is key to vaccine effectiveness — and found that it clung tightly to the virus.

Now, Zou and his team are analyzing the nanobody's ability to help create a new vaccine and feeding the experimental data back to the AI lab to hone the molecular designs.



Old mice, young muscle

SOME EXERCISE and one injection of a molecule that's part of the body's healing process are all it takes to turn back the clock on muscle vitality if you're over the hill. And are a mouse. Yet the discovery has compelling implications for people with age-related muscle loss or muscle-wasting diseases.

Stanford Medicine researchers determined that giving elderly mice a shot of prostaglandin E2, then allowing them to exercise on a treadmill over the next two weeks, dramatically increased their strength. The findings were published in June 2025 in *Cell Stem Cell*.

The research is the first to show that even a brief exposure to PGE2 rejuvenates muscle stem cells by erasing biochemical tags on their DNA that accumulate during aging and hamper the expression of genes involved in self-renewal, survival and muscle function.

An injection of PGE2 brokers the exchange in muscle stem cells of a lifetime's worth of genetic markers for a new set of instructions that enhances the function of individual muscle stem cells and is passed down to their descendants.

"PGE2 is restoring the cells' viability and ability to divide and rejuvenating their ability to regenerate and repair muscle damage," said Helen Blau, PhD, the study's senior author, the Donald E. and Delia B. Baxter Foundation Professor, and a professor of microbiology and immunology. "And it does so by inducing a heritable molecular memory."

we are Stanford Medicine

walk with me

TAG ALONG FOR A STROLL WITH SOME OF THE PEOPLE BEHIND THE RESEARCH, EDUCATION AND CARE AT STANFORD MEDICINE

In a new video series, called *Walk With Me*, Stanford Medicine researchers tell us not only about their aha moments of discovery but also about themselves — sharing insights into their work and lives as they show us around their home base on campus.

Read on for some short takes and see the videos at stan.md/walkwithme

Fatima Rodriguez, MD
ASSOCIATE PROFESSOR OF MEDICINE (CARDIOVASCULAR MEDICINE)

What inspired you to pursue this field?

My interest in the heart is very personal. My mom had a heart disease early, and technology saved her life with a mechanical heart valve. So, I always wanted to be a cardiologist. And as a researcher, you have the chance to treat populations.

Seung Kim, PhD
KM MULBERRY PROFESSOR AND PROFESSOR OF DEVELOPMENTAL BIOLOGY AND OF MEDICINE (ENDOCRINOLOGY)

What's one thing you wish more people understood about your work?

The wonderful thing about science is that it's a journey of discovery. Like any journey, there are false leads and things like that. But in the end, if you get a glimpse of the way nature might work, it's enthralling and addictive. Because no one else in history, perhaps, has had the thoughts that you might have at the moment when you have an aha.

Reena Thomas, MD, PhD
CLINICAL PROFESSOR OF NEUROLOGY AND NEUROLOGICAL SCIENCES

If you could give your younger self one piece of advice, what would it be?

Trust in the process, be curious enough to ask mentors and sponsors, early and often. And revisit those conversations. The path you set forth for yourself might have twists and turns, and that's OK, too.

Paul Mischel, MD
FORTINET FOUNDERS PROFESSOR AND PROFESSOR OF PATHOLOGY

What's your favorite lab tool or piece of equipment and why?

Oh, the microscope. I'm very visual. We've moved into reading the world as if we were sequencers, but to me, there's no substitute for seeing the world. Nature speaks in shapes, not letters. So, things that are visual — like advanced microscopes — I find beautiful.

Steven Artandi, MD, PhD

LAURIE KRAUS LACOB DIRECTOR OF THE STANFORD CANCER INSTITUTE, THE JEROME AND DAISY LOW GILBERT PROFESSOR

Why does research matter to you?

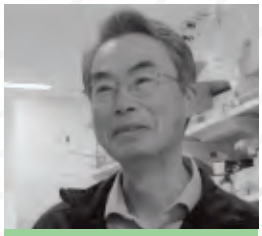
We want to improve the health of people. And research is the only means to accomplish that goal, to understand how the human body works and then to interfere in a way that would improve the health of individuals.

Sergiu Pasca, MD

THE KENNETH T. NORRIS, JR. PROFESSOR II OF PSYCHIATRY AND BEHAVIORAL SCIENCES

What inspired you to pursue this field?

My work, and literally my career now, has been to try to break this unbearable inaccessibility of the human brain and try to build these models that allow us to study these conditions noninvasively.



Joseph Wu, MD, PhD

SIMON H. STERTZER, MD, PROFESSOR AND DIRECTOR OF THE STANFORD CARDIOVASCULAR INSTITUTE

What is special about working at Stanford Medicine?

Working with trainees who are very hungry for knowledge. It's fascinating, as a mentor, to have a student come in who knows nothing about stem cell biology, nothing about drug discovery, nothing about genetics. After five years, they leave and set up their own lab. It's very humbling and satisfying.

Irogue Igbinosa, MD

ASSISTANT PROFESSOR OF OBSTETRICS AND GYNECOLOGY (MATERNAL-FETAL MEDICINE AND OBSTETRICS)

Why does your research on anemia during pregnancy feel especially urgent now?

Anemia is going up for everyone. We know it contributes to adverse events in pregnancy and it worsens disparities. We can do something about it. So why wait?

Carolyn Bertozzi, PhD

THE ANNE T. AND ROBERT M. BASS PROFESSOR IN THE SCHOOL OF HUMANITIES AND SCIENCES AND PROFESSOR OF CHEMISTRY

When do your best ideas come to you?

When I'm in conversation with the students in my lab. Sometimes I find that I can contribute and help mature the idea in a way that creates a new research project. So I don't know that I can take credit for any idea in a vacuum. I think I'm best when I'm in a conversation with other people.

TODD HOLLAND

the power of research

HOW DISCOVERIES TRANSLATE INTO BETTER HEALTH

Biomedical research is where medicine's next advances begin — turning curiosity into clearer diagnoses, better treatments and longer, healthier lives.

In this themed issue, we spotlight the people who take discoveries from the lab to the clinic, from molecules to all of us. Their work is powered not only by ingenuity and collaboration but also by sustained public investment, fueling high-risk ideas and large-scale studies vital for ongoing innovation.

Read on for articles that explore how research transforms care, starting with basic science discoveries, moving through the laboratory studies and clinical trials of the development process and, finally, making an impact in the lives of doctors and patients.

Also, tune in to the new season of the *Health Compass* podcast for conversations with some of the people behind the innovations (stan.md/health-compass).

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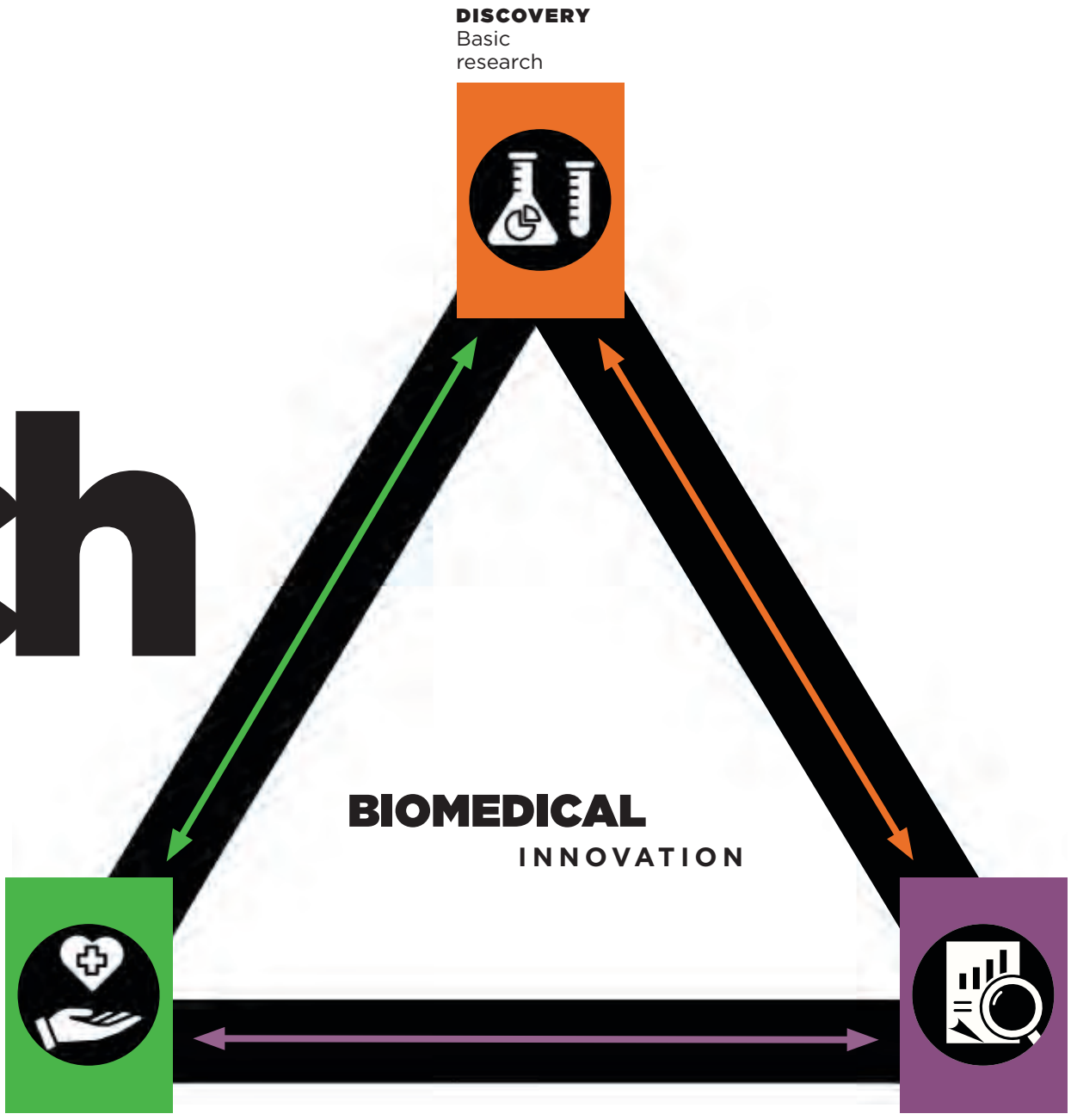

DISCOVERY
Basic
research
BIOMEDICAL
INNOVATION
IMPACT
New treatments,
diagnostics
and medical devices
RESEARCH &
DEVELOPMENT
Preclinical
research
and clinical trials

HOW CURIOSITY, COLLABORATION AND PUBLIC FUNDING GREW INTO A LIFESAVING THERAPY

innovation in bloom

Jack Gardella was 21 and a senior in college when a visit to Stanford Medicine revealed he had a serious heart condition. Overnight, his perception of his health altered.

"Obviously, it's not great news," Gardella, now 31, said.

But he was young and healthy and had no symptoms at the time.

As the years passed, that began to change. The fifth-generation cattle rancher living near a small town in the foothills of the Sierra Nevada became fatigued during routine work or hiking.

"Ninety percent of the time, when I walked up a hill, or stood up suddenly after lying down, I would feel my heart laboring," Gardella said.

By Krista Conger

ILLUSTRATION BY BRIAN STAUFFER

PHOTOGRAPHY BY MISHA GRAVENOR

During his regular checkups at Stanford Hospital, Gardella learned of a possible drug treatment for his condition, called hypertrophic cardiomyopathy. People who have this condition, in which the heart beats too forcefully, experience a thickening of the interior wall of the heart's left ventricle — the main pumping chamber that circulates oxygenated blood throughout the body. This thickening worsens over time, causing the heart to pump less effectively and may even block the flow of blood out of the heart.

About 1 in every 500 people in the United States are thought to have hypertrophic cardiomyopathy. Some have symptoms similar to Gardella's. But the disorder can also be silent; it's the leading cause of sudden cardiac death in young people. Gardella was lucky to be diagnosed early.

"I was always hopeful, but it also seemed a little pie-in-the-sky," Gardella said of the potential treatment. But in March 2024, his doctor told him he was a candidate to try the newly approved drug, called mavacamten. Within two weeks Gardella, a father of two young children, noticed a significant improvement. "I feel a lot better. I am not short of breath, and I can stand up from playing with my kids on the floor without getting lightheaded. I'm thrilled," he said.

"Mavacamten has been the single largest therapeutic advance for this group of patients — really since ever," said Victoria Parikh, MD, director of the Stanford Center for Inherited Cardiovascular Disease and an associate professor of medicine. "We've never had a precision therapy for hypertrophic cardiomyopathy until now, and patients often feel better almost immediately."

Mavacamten didn't spring into being overnight, however. It's the result of more than five decades and millions of dollars of publicly funded research, primarily in the laboratory of James Spudich, PhD, a professor of biochemistry, emeritus. Spudich, who received his PhD from Stanford University in 1968 under the tutelage of Nobel laureate Arthur Kornberg, MD, has dedicated his career to understanding the molecular intricacies of how myosin, the molecular motor that drives cell division and multiple other forms of movement in all cells, converts chemical energy into mechanical motion. Much of his work has focused on how muscle fibers contract to move our limbs, breathe in air and pump blood throughout our bodies. His research has been continuously supported by the National Institutes of Health for 55 years, with a five-year renewal grant starting in March 2026.

That body of work has paid off in the form of mavacamten, the first drug that attacks the cause of the heart's malfunction rather than simply mitigating symptoms. Since its approval by the Food and Drug Administration in 2022, mavacamten has been prescribed thousands of times, giving people like Gardella their lives back.

"It is like the clouds have lifted," Parikh said. "We've seen hearts responding in a way we had never seen before — patients hiking, running, climbing mountains. They are living full lives again."

The drug's development is just one striking example of how the power of research lies not only in sudden leaps forward but also in the long, patient accumulation of knowledge — much of it built through curiosity-driven, publicly funded inquiry with no immediate guarantee of clinical payoff. It is also a reminder that scientific progress depends on researchers who are willing and able to pursue difficult problems over years or decades, and on critical support from organizations like the NIH.

A vast tapestry of scientific effort, collaboration and sheer tenacity is required to turn a metaphorical twinkle in a test tube into a drug that can improve or even save lives — but even more is needed. Success also hinges on established pathways to move discoveries from academic laboratories to venture capital-supported biotech companies that can advance, test and manufacture potential therapies. In short, curiosity, teamwork and funding mechanisms must converge to push medicine forward.

WITH CURIOSITY AS HIS GUIDE

Spudich didn't set out to develop a blockbuster heart drug. But his unusual (at the time) focus on multidisciplinary training during the late 1960s and early '70s gave him an extraordinarily strong foundation in biochemistry, genetics and structural biology, and this allowed him to meticulously study the interactions of the two main molecules involved in muscle contraction — actin and myosin — at the nanometer level (1 billionth of a meter, or about 1/100,000 the width of a human hair). Over the decades his lab purified the proteins and studied them from every angle to ascertain exactly how they work. Along the way he founded three companies and raised tens of millions of dollars in venture capital to move his findings out of the lab and into the clinic. But

WHY IT MATTERS

- **One in 500 people have hypertrophic cardiomyopathy, a major cause of heart failure.**
- **A new drug provides the first precision therapy for the condition.**
- **The drug came about as a result of curiosity-driven studies of the interactions of the two main molecules involved in muscle contraction.**

'WE DIDN'T HAVE A SENSE THAT WE WERE WORKING ON SOMETHING THAT COULD BE TRANSLATED INTO CLINICAL USE. IT WAS REALLY JUST CURIOSITY... .'

his original studies were decidedly unrelated to drug discovery.

"The model organism I settled on in 1971 was an amoeba called Dictyostelium, which is so far flung from what might today be considered important for drug discovery that it would likely be difficult to receive government funding now," Spudich recalled. "I chose it because there was the potential of conducting genetic experiments. And it was a really good organism for growing in large numbers, which is important when trying to obtain purified proteins for biochemical study."

Also known (inaccurately, as it is not a fungus) as slime mold, Dictyostelium lives in damp, organic-rich soils, chowing down on a wide variety of soil-dwelling bacteria. It had much to recommend it as a model organism for studying muscle mechanics. It's a eukaryote — that is, an evolutionary step up from bacteria and the class shared by all higher organisms including humans. It also has a unique life cycle — able to exist as either a single-celled or multicelled organism. When the supply of bacteria to munch on grows sparse, many thousands of single-celled Dictyostelium migrate toward one another to form a multicellular slug-type conglomerate, which travels to the soil surface before differentiating into what's called a fruiting body for better dispersal to new environs and eventual survival.

All that moving around requires muscle. Well, not muscle exactly, but well-orchestrated movements of the cell's internal scaffolding — called the cytoskeleton. These movements are powered by the same duo of proteins, called actin and myosin, that trigger the contraction and relaxation of human muscles throughout the body, including the heart.

For the first years of his Stanford career, Spudich and members of his lab threw themselves into identifying and purifying myosin and actin in Dictyostelium and studying their function — harking back to his time as a graduate student in Kornberg's laboratory.

That's when the researchers stumbled onto something that made Dictyostelium even more powerful as a model organism.

"A graduate student in my lab at the time accidentally discovered — to the shock of everyone in the field — that it is possible to swap out the myosin gene in Dictyostelium through a process called homologous recombination," Spudich said. "So, we could make cells that were lacking functional myosin and replace it with genes for mutated forms of the molecule and observe the outcome. It was a very powerful combination of biochemistry and cell biology that is not done much today, because it's difficult to get funding for such model systems even though they are often uniquely amenable to such approaches."

MUTATING THE MYOSIN MOTOR

Enter Kathy Ruppel, a senior research scientist who came to Spudich's lab in the late 1980s as part of her doctoral studies as an MD/PhD student. Helpfully, Dictyostelium lacking myosin didn't die; they just couldn't divide when grown in liquid-filled test tubes. Instead, they morphed into large cells with multiple nuclei. That enabled Ruppel to clearly assess the effect of multiple mutations in what the Spudich lab had just shown was the motor domain of the myosin molecule — its head.

Researchers hypothesized from studies in the 1950s and '60s that muscle movement occurs when thick filaments of myosin II, a molecule with two heads and a ropelike tail, slide past neighboring actin-containing thin filaments. Contraction was proposed to occur when the myosin heads latch onto nearby actin filaments and, like teammates in a game of tug-of-war, pull in unison to shorten the fiber, called a sarcomere. The energy for this action comes from breaking a chemical bond in a small molecule called ATP.

"We could take out the myosin that the Dictyostelium needed to divide and replace it with different forms of mutant myosin and see which versions could rescue the defects," Ruppel said. "That was the first systematic study of how mutations in myosin affect motor function. We didn't have a sense that we were working on something that could be translated into clinical use. It was really just curiosity about how this motor turns ATP hydrolysis into movement and force, and we started to understand this well."

In 1990, shortly after Ruppel arrived in Spudich's lab, researchers at Harvard studying familial hypertrophic cardiomyopathy discovered that affected members of a large family spanning several generations all had a specific mutation in their myosin gene — a tiny, single-nucleotide change in the DNA sequence. It was the first inkling that myosin function was a key component of cardiomyopathies. But the Dictyostelium myosin was too different from the human version to test the effect of

these mutations directly. And the human version of myosin important in cardiac function, called beta cardiac myosin II, was notoriously impossible to make in the laboratory.

Lacking human myosin to study, the researchers in Spudich's lab further refined their understanding of the myosin motor during the 1990s, developing a way to precisely measure the movement of actin filaments across a lawn of rabbit skeletal myosin molecules affixed to a glass slide, and — working with Stanford Medicine Nobel laureate and physicist Steven Chu, PhD — designing a laser trap to measure the force of movement and length of displacement of actin due to the breakdown by myosin of a single molecule of ATP.

"This is the power of the reductionist approach," Spudich said. "Watching the actin filaments move across the myosin-coated glass at the same rate they move when your muscle contracts was a total wow moment. It blew everyone's mind. It transformed everything."

Their experiments were a tour de force in the field of muscle biology, identifying the power and distance that one stroke of one myosin motor produces. Finally, the molecular minutia of muscle movement had been revealed.

DRUGGING THE SARCOMERE

"At the time, I did not contemplate becoming involved in the world of biotechnology," Spudich recalled in a 2024 review article in *Frontiers in Physiology*. But in 1995, he was asked to join the discovery board of SmithKline Beecham Ltd., now GSK plc. Spudich lobbied heavily for new drug pipelines targeting the cytoskeleton for cardiac diseases and cancers, but the company had other priorities. In 1998, Spudich and several colleagues launched Cytokinetics to pursue cytoskeletal-based therapies — primarily looking for ways to ramp up cardiac myosin activity to combat heart failure.

"Jim had this idea for a very long time — that you could drug the sarcomere," said a former postdoctoral scholar in the Spudich lab, Masataka Kawana, MD, now an assistant professor of cardiovascular medicine and the medical director of the Ambulatory Heart Failure and Cardiomyopathy Service at Stanford Medicine. "But to do that you had to understand human cardiac myosin with absolute precision. No shortcuts."

Eventually, in 2010, researchers at the University of Colorado, Boulder, cracked the code of expressing human beta cardiac myosin II, and Ruppel, after clinical training as a pediatric cardiologist at Stanford Medicine, Harvard and the University of California, San Francisco, returned to Stanford to join Spudich to turn their joint lab's laser focus onto understanding what

Kathy Ruppel
SENIOR RESEARCH SCIENTIST AND CO-PRINCIPAL INVESTIGATOR IN THE SPUDICH LAB

'WE WERE ABLE TO GO FROM UNDERSTANDING THE BASIC SCIENCE TO MAKING AN EDUCATED GUESS, "WELL, IF THIS IS THE PROBLEM, IF WE TWEAK THIS, IT MAY HELP," AND THEN TO SEE THAT BE BORNE OUT IN A RELATIVELY SHORT AMOUNT OF TIME.'

James Spudich
PROFESSOR OF BIOCHEMISTRY, EMERITUS

'IT'S UNBELIEVABLE, AND SOMETHING I NEVER IMAGINED. I AM SO LUCKY TO HAVE LIVED SO LONG AND TO HAVE SEEN THIS VERY BASIC, ALMOST ESOTERIC BIOCHEMISTRY AND BIOPHYSICS RESEARCH END UP HELPING PATIENTS LEFT AND RIGHT, WHO ARE SAYING, "THIS IS TRANSFORMATIVE FOR ME."'

FOR FIVE DECADES, JAMES SPUDICH (AT RIGHT) LED A GROUP OF RESEARCHERS IN NIH-SPONSORED INVESTIGATIONS INTO THE MOLECULAR BASIS OF CELL MOVEMENTS INCLUDING MUSCLE CONTRACTION. KATHY RUPPEL (AT LEFT) JOINED SPUDICH IN 2010 TO CO-LEAD AN EFFORT TO UNDERSTAND HOW MUTATIONS IN CARDIAC MYOSIN CAUSE HYPERCONTRACTILITY OF THE HEART. THESE STUDIES WERE KEY TO THE DEVELOPMENT OF MAVACAMTEN AND AFICAMTEN BY MYOKARDIA INC. AND CYTOKINETICS INC., NOW APPROVED BY THE FDA TO TREAT OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY — ILLUSTRATING THE POWER OF COLLABORATION BETWEEN ACADEMIA AND BIOTECHNOLOGY.


Biosafety Manual
Safety Manual
Safety Manual
illumina

goes amiss in hypertrophic cardiomyopathies like Gardella's. Kawana joined soon thereafter to round out the team.

In 2012, Spudich and three others in the field launched another company, MyoKardia Inc., to focus solely on developing drugs targeting myosin's role in hypertrophic cardiomyopathy, raising nearly $40 million in venture capital within months. But the researchers at the company and in Spudich's lab quickly ran into a conundrum: The myosin mutations known to be associated with the inherited versions of the disease didn't substantially and consistently increase the intrinsic force a single molecule produced, the velocity of its movement or the rate of ATP breakdown, any of which could account for hypercontractility.

"So we knew something was wrong with the model," Spudich said. After months of contemplation, the answer came to him in a dream in 2014: The disease-associated myosin mutations weren't changing how the molecule functioned, but they increased the number of myosin heads available to latch onto the actin filaments. Like in a mismatched game of tug-of-war, the overall force of the contraction increased substantially with more enthusiastic participants.

Researchers at MyoKardia promptly began tinkering with small molecules identified and licensed from Cytokinetics for their ability to inhibit myosin. They struck gold. Chemically altering the twist of one of these molecules gave them an excellent inhibitor of the mutant myosin's function. "Little did we know that a decade later the molecule which we had in hand within the first six months of incorporating the company would prove to be the clinical lead molecule, and then the very molecule that the FDA approved ...," Spudich recalled in the 2024 *Frontiers in Physiology* article.

The molecule, which became mavacamten, worked by taking myosin molecules out of play, nudging some of the overactive myosin heads back into the "off" state — reducing the power of the heart's contractions to more normal levels. As the team at MyoKardia worked through preclinical experiments of mavacamten in mice and then in human clinical trials, big pharma took note. In 2020, Bristol-Myers Squibb Co. bought MyoKardia. In 2022, mavacamten was approved for use in humans.

VAULTING THE VALLEY OF DEATH

Mavacamten's rapid success is not the norm. Only about 10% of drug candidates entering clinical trials clear all the hurdles to become an approved drug. For Ruppel and Kawana, it crystalized the importance of basic research in drug development.

"It's really amazing," Ruppel said. "We were able to go from understanding the basic science to making an educated guess, 'Well, if this is the problem, if we tweak this, it may help,' and then to see that be borne out in a relatively short amount of time."

All told, the development of the drug required an investment of about $1 billion — far beyond what an academic institution can wager on an unproven drug.

"It was very meaningful to me to be involved in the mavacamten clinical trials at Stanford Medicine as a clinician," Kawana said. "I studied this drug in the lab, adding it to my experiments and learning how it worked at a very basic level. And now I'm prescribing this to patients in the clinic and witnessing their improvement. We were only able to do these studies because

Spotlight on Victoria Parikh

ASSOCIATE PROFESSOR OF MEDICINE (CARDIOVASCULAR MEDICINE)

Parikh runs the Stanford Center for Inherited Cardiovascular Disease, where she cares for patients and researches the genetic basis of cardiomyopathies. She is also the vice chair for strategy and innovation in the Department of Medicine — focusing on ways to implement precision medicine.

QUICK FACTS

- Received her undergraduate degree from Stanford University in 2005 and her medical degree from Stanford in 2011.
- Spent her Thanksgiving break hiking to Tiger's Nest monastery in Bhutan.
- Loves live music — most recently saw Lord Huron, the Preservation Hall Jazz Band and the Stanford University Singers.
- Favorite authors are Patrick Radden Keefe and Jhumpa Lahiri.

BROOKE GAZZOLI

IN HER WORDS

"I am researching these diseases to change the way people feel and help them live the lives they want to live. But the reality is that until now, it's been 95% perspiration and 5% celebration. We just didn't have the medications to target the cause of the problem. Mavacamten has really shifted that balance in favor of celebration. Now it's exciting to go to clinic thinking, 'I'm going to help somebody today with a really cool drug.'"

Bridging the gap

RESOURCES THAT ACCELERATE THE PATH FROM DISCOVERY TO TREATMENT

A brilliant insight is a great start, but it takes much more to bring a new diagnostic, therapy or device out into the world.

"Key to this endeavor are interdisciplinary groups and an organized infrastructure of resources that brings these vital teams together and supports them as they move from preclinical studies to human trials and finally to real-world interventions that improve health," said Ruth O'Hara, PhD, Stanford Medicine's senior associate dean for research and the Lowell W. and Josephine Q. Berry Professor in the Department of Psychiatry and Behavioral Sciences.

At Stanford Medicine, those resources include:

SPARK

Spark brings together Stanford University researchers and experts from industry to help develop promising, early-stage academic discoveries into viable candidates for clinical or commercial development. The program addresses common barriers researchers face, including limited experience with drug development and gaps in available funding for applied research. Spark provides practical guidance through coursework, seminars and mentorship as well as technical expertise, access to shared facilities and seed funding to support selected translational projects.

INNOVATIVE MEDICINES ACCELERATOR

Stanford University's Innovative Medicines Accelerator focuses on translating breakthroughs in understanding disease mechanisms into new drug therapies and cures. The accelerator includes a drug prototyping unit, a biobank that houses samples and data, and an offsite "freezer farm" to reduce the risk of sample destruction. This accelerator also includes a seed fund that supports promising research and facilitates the identification of therapeutic and diagnostic targets.

CATALYST

Stanford Medicine Catalyst helps turn later-stage discoveries — those with a working prototype or for which the basic science has been validated — into therapeutics or products including medical devices, software or systems innovations that could meaningfully impact patient care.

The program supports researchers with funding up to $1 million and hands-on assistance navigating the translation process, raising venture funding and working toward licensure and adoption of their discoveries in health care settings.

STANFORD BIODESIGN

The Stanford Mussallem Center for Biodesign focuses on improving health and health equity through innovation, education, translation and policy. Since 2001, Stanford Biodesign has trained thousands of fellows, students and faculty in the biodesign innovation process, which emphasizes identifying and addressing unmet health needs. Trainees have used this approach to develop solutions in a wide range of areas, including biotechnology, medical devices, diagnostics, health services and digital health.

SPECTRUM

Spectrum, Stanford Medicine's Center for Clinical and Translational Research and Education, offers guidance on study design, data management and research ethics. It also offers access to the Clinical and Translational Research Unit for conducting studies with human participants, as well as the Stanford Biobank for storing and sharing biological samples. Spectrum offers pilot grants and research training and connects researchers with community partners.

The National Institutes of Health-funded Clinical and Translational Science Award supports many of these efforts, including seed funding for SPARK and Stanford Biodesign; resources for storage of biosamples; and access to the Trial Innovation Network, a platform for all CTSA hubs that enables investigators to execute multicenter clinical trials.

Jim studied the Dictyostelium myosin for decades. You can't do precision medicine without precision science. Understanding myosin at the molecular level — down to a single amino acid — is what let us build a drug that treats the true cause of hypertrophic cardiomyopathies, not just the symptoms."

Parikh noted that the center now has more than 150 patients on mavacamten. "It's empowering for patients and for us," she said. "We'd been spending years just trying really hard to use what we had, which was a sort of mismatched collection of drugs, to a situation where it is just very clear that these hearts are responding in ways we've never seen before."

Patients like Gardella may soon have yet another option: A drug developed by Spudich's first company, Cytokinetics Inc., was recently approved by the FDA for treatment of the same condition. The drug, aficamten, works similarly to mavacamten, reducing the number of myosin heads bound to actin. But aficamten leaves the body more quickly, which may allow finer tuning of dosages and more precise control of contractility.

In 2019, Spudich, his wife, Anna Spudich, PhD, Ruppel and two former postdocs, Darshan Trivedi, PhD, and Suman Nag, PhD, co-founded Kainomyx Inc. to target the malaria parasite by disrupting its cytoskeleton. "Unlike MyoKardia, which garnered hundreds of millions of dollars from investors and pharmaceutical companies, venture capitalists don't want to fund malaria research," Spudich said. "We have some very good drug candidates. We're not going to make a nickel, but we feel we owe it to society. We've never been in this for profit, but it is gratifying to transfer basic research knowledge to medicines.

"It's unbelievable, and something I never imagined," Spudich said of the trajectory of his research career. "I am so lucky to have lived so long and to have seen this very basic, almost esoteric biochemistry and biophysics research end up helping patients left and right, who are saying, 'This is transformative for me.' None of this would have been possible without NIH funding for basic research." **SM** — *Contact Krista Conger at kristac@stanford.edu.*

DISCOVERIES ABOUT THE GENOME'S 'DARK MATTER,' DANCING DNA AND THE COLON'S NERVOUS SYSTEM ARE OPENING NEW DOORS IN SCIENCE

beyond the known

When Dan Jarosz, PhD, set out to study genetic mutations in yeast, he didn't expect to uncover principles that could help predict human disease.

But by analyzing a large family tree of yeast, Jarosz — a professor of chemical and systems biology and of developmental biology — was able to show how molecular changes in unstressed yeast cells could forecast how the cells would behave when faced with challenges. It suggests that the same could be done in humans: assemble detailed blueprints of healthy cells to predict how those cells may respond to diseases or drugs.

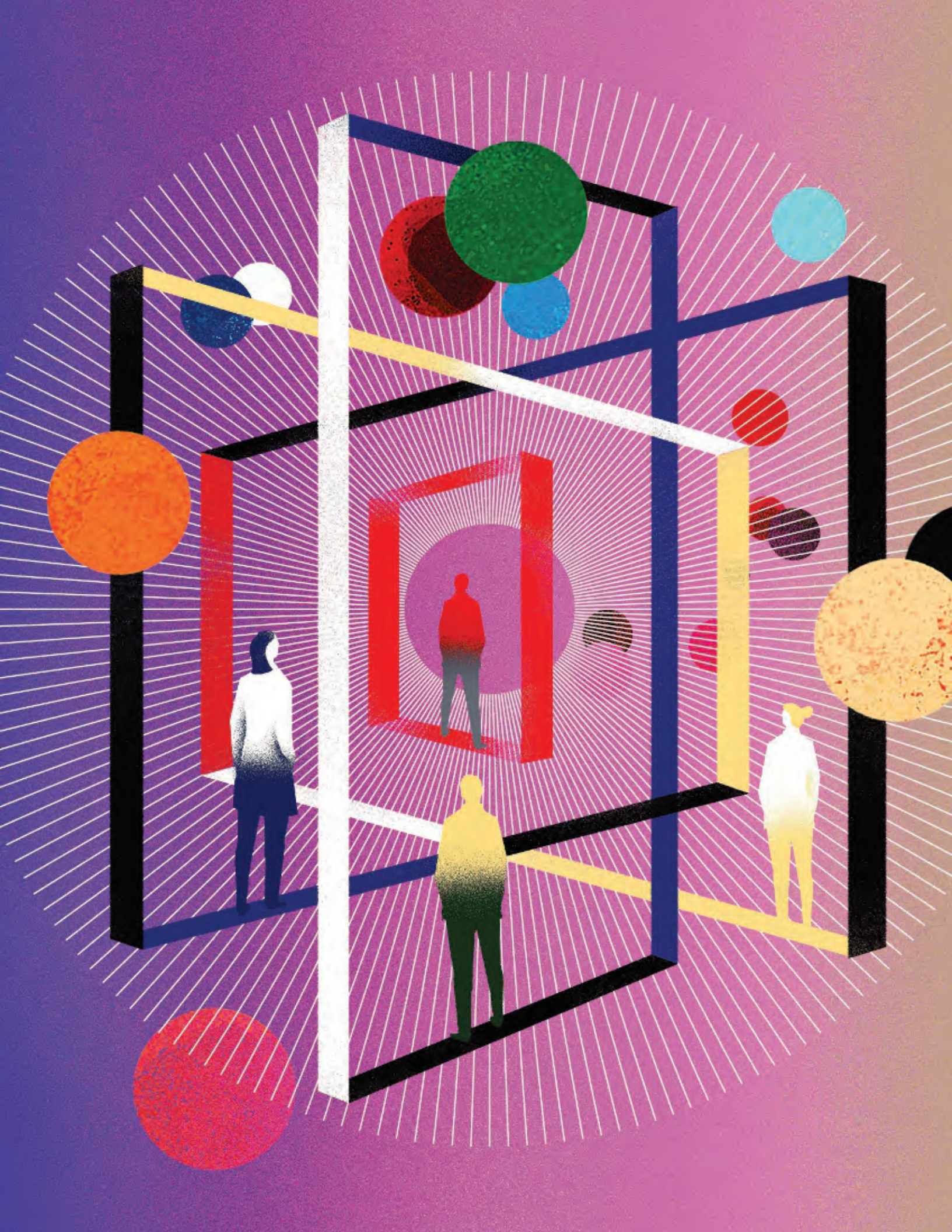
"We found way more than we initially expected," said Chris Jakobson, PhD, a postdoctoral scholar in Jarosz's lab who led the new work, published in *Science* in October 2025. "Following our nose, we got to places we didn't expect when we started."

That's precisely the point, according to Jarosz, who serves as senior associate dean for basic sciences at Stanford Medicine. "Basic research is about following curiosity wherever it leads," he said.

By Sarah C.P. Williams

ILLUSTRATIONS BY BRIAN STAUFFER

PHOTOGRAPHY BY MISHA GRAVENOR



"We're investigating fundamental questions about how biology works, and the insights that come out can have the most unexpected implications."

Why study yeast? Or ponder the repetitive regions of DNA once dismissed as "junk"? Or track how molecules move inside living cells? These questions might seem far from medicine, but they exemplify how discovery happens — by uncovering biological principles that could lead to entire new fields of study.

The researchers profiled here share Jarosz's commitment to discovery-driven science. They're decoding the "dark matter" of our genome, watching DNA fold and mapping the neurons that wrap around the colon. None set out to solve a specific clinical problem. Instead, they're propelled by curiosity and the desire to build foundational knowledge; it may take decades to reveal its full impact.

"There are only two kinds of basic biology," Jarosz said. "Those that are useful in medicine now and those that might be useful in medicine someday."

THE GUT'S 'SECOND BRAIN'

The enteric nervous system may hold clues to a variety of conditions

IF YOU'VE EVER FELT LIKE YOUR STOMACH has a mind of its own, there's some truth to that gut feeling. The human digestive system contains hundreds of millions of neurons — more than the entire spinal cord. This "second brain," called the enteric nervous system, coordinates the movement and digestion of food through the intestines and communicates with the rest of the body. Yet scientists know little about how it works, its implications in health and even what precise neuron types it contains.

Now, two Stanford University researchers are mapping the enteric nervous system and studying how these neurons mediate digestion and other essential processes. Their work could transform treatment of conditions ranging from irritable bowel syndrome to sleep disorders to Parkinson's disease.

"It's a really exciting moment for this field, because we're suddenly going from knowing only about individual neurons to being able put together the blueprint of the entire healthy enteric nervous system," said Julia Kaltschmidt, PhD, a faculty scholar at Stanford's Wu Tsai Neurosciences Institute and professor of neurosurgery. "Once we have that elemental knowledge, we can start to understand what goes wrong in diseases and how we can manipulate the neuronal network to ameliorate gut dysfunction."

Spotlight on Todd Coleman

ASSOCIATE PROFESSOR OF BIOENGINEERING

Todd Coleman's lab, the Stanford Neural Interaction Lab, focuses on the interaction between different neural systems in the body — the gut, heart and brain. They have developed new flexible, non-invasive electrodes to measure signals from these organs.

QUICK FACTS

- Coleman's high school, Dallas Carter, in Dallas, Texas, has been featured in ESPN documentaries about their sports teams, but Coleman excelled at math there.
- Studied electrical engineering and computer engineering at the University of Michigan and is still a big fan of their basketball and football teams (Go Blue!).
- Is passionate about sports psychology, mentoring, personal improvement and helping people define their own self-worth. One of his biggest heroes is mental performance coach Greg Harden, known for his work with quarterback Tom Brady and Olympic swimmer Michael Phelps.

PERSONAL MOTTO

"Things get easier when you stop assuming things will be easy."

IN HIS WORDS:

"I like to really get out of my comfort zone and collaborate with people who are experts in different fields, completely outside my area of expertise. I've gotten used to being OK with asking dumb questions."

Spotlight on Julia Kaltschmidt

PROFESSOR OF NEUROSURGERY

Julia Kaltschmidt's lab studies how groups of neurons in the gut and spinal cord develop and function.

QUICK FACTS

- Kaltschmidt spent most of her childhood in Lüneburg, Germany, a small town dating from the Middle Ages known for its salt mining.
- Is grateful to her mentors during her undergraduate studies at the University of Madison-Wisconsin and as a PhD student in Cambridge, England, and is most proud to have been nominated by her trainees for the 2021 NIH Landis Award for Outstanding Mentorship.
- Recharges by early morning Stanford Dish walks, coffee and watching *The Great British Bake Off* with her family.

IN HER WORDS

"Stanford is an ideal place to be tackling this big problem of understanding the enteric nervous system because there's a lot of support for thinking outside the box."

'THE STOMACH ISN'T JUST PASSIVELY SITTING THERE DURING SLEEP; IT'S AN ACTIVE PARTICIPANT IN WHAT MAKES SLEEP RESTORATIVE.'

In addition to visualizing the full community of gut neurons, Kaltschmidt has marked individual cell types in the enteric nervous system with fluorescence and traced their shapes to learn how they interconnect. Recently, her team found that certain neurons in the gut come in two forms: some that run lengthwise down the intestine, and others — never before described — that wrap around the colon's circumference, creating dense, interconnected rings. When the researchers activated these cells in mouse colons, fecal pellets — the precursors to mouse droppings — moved through the organ nearly twice as fast as normal. The findings could pave the way to drugs to treat disorders in which the gut moves contents too quickly or too slowly.

"The enteric nervous system is not just sending information about the status of the gut to the brain," Kaltschmidt said. "It itself is processing information and independently coordinating gut movements. Finding these new cell types shows we're only beginning to understand how complex this system really is."

TAPPING GUT WIRES

DOWN THE HALL FROM KALTSCHMIDT'S LAB IN the Stanford Neurosciences Building, another Wu Tsai Neuro faculty scholar is taking a different approach to studying the enteric nervous system. Trained as an electrical engineer, Todd Coleman, PhD, an associate professor of bioengineering, shifted his research trajectory after his dad died from pancreatic cancer. He began building new tools to track the electric activity of the gut and understand how the digestive system communicates with the brain.

"Our technology works like an electrocardiogram, but instead of measuring the heart's activity, we're seeing the precise patterns of activity in the digestive system," said Coleman, who is also one of Wu Tsai Neuro's deputy directors.

Recently, Coleman's team recorded electrical activity from the brain and gut throughout the night to show that the stomach carries out a sophisticated dialogue with the brain during deep sleep. The stomach's rhythmic electrical pattern slows from its normal daytime pace to match the brain's firing pattern. And how closely the brain and gut synchronize with each other predicts how rested people feel in the morning.

"We tend to think of sleep as purely a brain state, but these findings show that restorative sleep involves coordination across the entire body, including the gut," Coleman explained. "The stomach isn't just passively sitting there during sleep; it's an active participant in what makes sleep restorative."

The discovery could help explain why patients with gastrointestinal problems so often experience poor sleep, and vice versa, suggesting that disrupted stomach-brain communication contributes to both digestive symptoms and unrefreshing rest.

TEAMING UP

AFTER MEETING IN THEIR BUILDING'S HALLWAY and discovering their overlapping interests, Kaltschmidt and Coleman began collaborating. In 2024, they joined forces to examine how the gut's nervous system springs to life.

Using Kaltschmidt's technology to measure gut motility patterns and Coleman's tools to analyze developing motility dynamics, they detected coordinated ripples of intestinal activity around day 16 of embryonic development, earlier than any previously known gut movements. The activity consisted of bursts of intense signaling, followed by periods of complete quiet — a rhythm also seen in the developing brain when sets of neurons are learning to fire together.

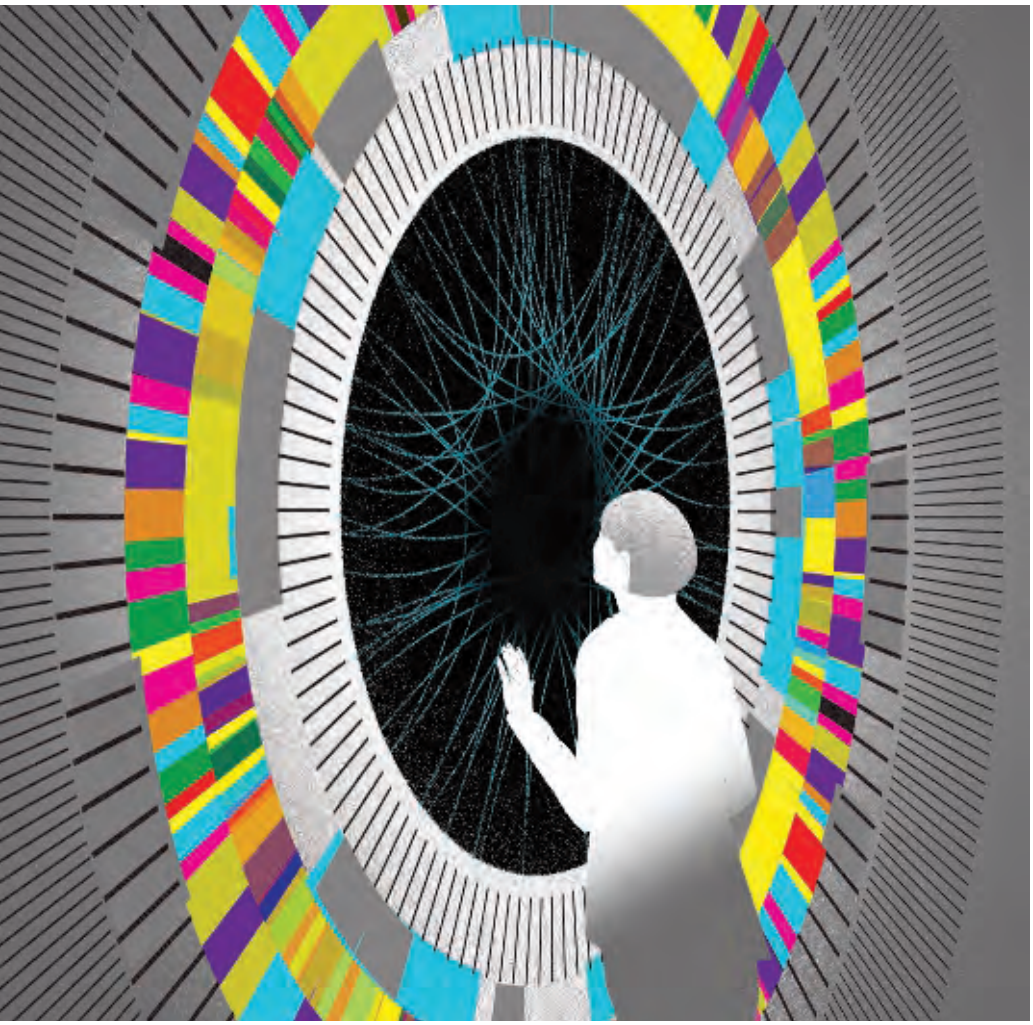
Kaltschmidt's team then showed that these early rhythmic movements depend on a nerve signal called acetylcholine. When they activated acetylcholine in developing intestines, the coordinated movements became more frequent and robust.

The finding could eventually help treat prematurely born infants, who often cannot digest food properly. Current medications used to stimulate gut movement in adults don't work in these babies, likely because their intestines and the surrounding nerves are still developing. But drugs already exist that safely boost levels of acetylcholine in newborns.

"We're excited to test whether these drugs can speed up the development of the digestive system," Kaltschmidt said.

Kaltschmidt and Coleman's collaboration reflects a broader shift in work on the enteric nervous system, they said, bridging basic research and clinical implications and bringing together long disparate fields of medicine. In 2025, the pair organized Wu Tsai Neuro's 12th annual symposium on the gut-brain axis and other brain-body connections, convening leading researchers from around the globe to discuss the field's frontiers.

"As we learn more, we're slowly but surely bringing these siloed fields of gastroenterology and neurology together," Coleman said. "I think it's going to challenge the status quo in medicine, but it's going to lead to really new important things."



THE GENOME'S 'DARK MATTER'

Repetitive DNA sequences once dismissed as junk may regulate how cells grow

MORE THAN TWO DECADES AGO, scientists celebrated the completion of the Human Genome Project — an international endeavor to identify and sequence all human genes — as a triumph of modern biology. But there was a caveat: Roughly 7% of our genetic code was missing from the published sequence, as vast stretches of repetitive DNA called satellite sequences were too complex to decode with the technology of the time. Many researchers were unconcerned, as they suspected these sequences had little biological significance.

Now, a team led by Nicolas Altemose, PhD, an assistant professor of genetics, is revealing that these mysterious regions are far from junk DNA. They may be enormous control centers that help regulate one of the most fundamental processes in biology: how cells decide when to grow.

"Finally, technologies have come along that let us peer into these regions of the genome," Altemose said. "It's like charting the unknown and, eventually, it may have implications for human health."

The sequences are called satellite DNA because they have a tendency to separate from other snippets of DNA in certain experiments, like satellites orbiting a planet, due to their unique properties. The sequences are highly repetitive, with short DNA patterns repeated hundreds of thousands or even millions of times.

Early genetic sequencing technologies could read only about a thousand DNA letters at once, and each of these decoded thousand-letter snippets then had to be pieced back together in the right order. When the genome has unique sequences, scientists can figure out where each piece belongs by matching overlapping edges. But satellite DNA is like a jigsaw puzzle made entirely of blue sky: millions of nearly identical pieces with no landmarks to distinguish them. For years, it was impossible to tell which repeat belonged where, or even how many repeats there were.

The breakthrough came with long-read DNA sequencing technology, which can process hundreds of thousands of DNA letters at once instead of merely a thousand. Altemose was part of the group of scientists who finally assembled these missing regions in 2022, completing the human genome in full.

"Seeing the complete genome assembly for the first time and seeing how these things were organized after decades of not really knowing what was in there was just so exciting," Altemose said.

But it was also the beginning of trying to figure out why the satellite sequences existed.

Altemose, who launched his Stanford Medicine lab in 2023, and his team decided to search for proteins that might bind to

HSat3 — a type of satellite DNA that is found in large blocks on many chromosomes, including the largest single satellite region in the human genome, which spans a staggering 28 million DNA letters (the length of about a thousand average genes).

Using computational analysis, Altemose's lab group scanned HSat3 for matches to known protein binding sites. Their hunt turned up thousands of spots that matched the precise sequences used as docking stations for transcription factors — proteins that normally attach to the genome to flip on or off nearby genes. But HSat3, because of its incredibly long repetitive nature, doesn't have any nearby genes.

"It was pretty surprising and almost, I would say, bizarre," Altemose said. "Why would these transcription factors be localizing in such high numbers to these areas of the genome?"

A HIDDEN SWITCH FOR GROWTH

HIS TEAM FOCUSED ON ONE OF the transcription factors, TEAD, which is known to help control genes related to cell growth and proliferation. Using microscopy, the researchers watched fluorescently tagged TEAD accumulating on HSat3 regions inside living cells. At the same time, another protein, YAP, was also accumulating with TEAD. More surprisingly, the clusters of protein and HSat3 DNA were found inside the cells' nucleoli, compartments where ribosomes are made.

The location gave Altemose's team a clue about what the HSat3-associated TEAD might be doing. Ribosomes are the molecular machines that manufacture all proteins in the cell. Making ribosomes is a rate-limiting step for cell growth; cells cannot grow faster than they can build these molecular factories. Meanwhile, TEAD is part of a group of molecules famous for sensing environmental cues — nutrient availability, cell crowding, mechanical forces — to decide whether cells should proliferate.

Altemose and his colleagues suspected TEAD could be directly controlling ribosome factories in the nucleoli as part of its role in mediating cell growth and division. To test this, they repressed HSat3. TEAD was no longer found in the nucleoli, and the production of new ribosomes plummeted. By concentrating TEAD and YAP right where ribosomes are being made, the scientists hypothesized, HSat3 helps cells more quickly make new ribosomes when cells sense the right conditions.

"We think that HSat3 is acting almost like a sponge, soaking up TEAD and concentrating it inside the nucleolus where it can directly regulate ribosome production," Altemose said. "It's an incredibly novel discovery."

The discovery may eventually have medical implications. Cancer cells are notoriously dependent on cranking out ribosomes to fuel their rapid division, so targeting the interaction between TEAD and HSat3 could be one way to slow their growth.

Altemose thinks the new findings represent one small step toward fully understanding satellite DNA. His team plans to follow up on other transcription factors beyond TEAD that are predicted to bind to HSat3. Each may represent a separate regulatory function of the repetitive DNA sequences.

Altemose's lab is also focusing on the repetitive regions of DNA found in centromeres — structures in each chromosome that ensure chromosomes are properly inherited when cells divide. The group has already shown how patterns of methyl chemical groups added to these repetitive regions can impact cell growth and division.

"This is all completely open-ended, brand-new biology," Altemose said. "We don't really know where it will lead, but we finally have the tools to do the hard work and study these regions of the genome that have been neglected for so long."

Spotlight on Nicolas Altemose

ASSISTANT PROFESSOR OF GENETICS

The Altemose Lab applies new tools and technologies to explore the biology of repetitive areas of the human genome.

QUICK FACTS

- Grew up in Hawaii and Southern California.
- Enjoyed graduate school so much that he completed two back-to-back PhD programs, first in statistics at Oxford and then in bioengineering at the University of California, Berkeley and UC San Francisco.
- Has applied for three patents for technologies used to map the interactions between proteins and DNA.
- Loves *RuPaul's Drag Race*, Björk and ice cream.

GREG KAHN/ HHMI

IN HIS WORDS

"Some of the most important future scientific discoveries are currently hidden in unexpected places. That's why we're following our curiosity to explore the dark corners of the genome. Who knows what else we might find?"

THE GENOME IN MOTION

DNA performs a dance that affects how cells function.

INSIDE EVERY CELL IN YOUR BODY, DNA is dancing. Stretches of the genetic material loop, twirl and wave until two sections — distant on a linear strand of DNA but now flung into proximity — find each other. They touch briefly, exchange information, then spin away again.

For decades, textbooks depicted our genome as a disordered tangle, a ball of spaghetti crammed into the nucleus with little organization. Alistair Boettiger, PhD, an associate professor of developmental biology, is among those scientists now proving that view wrong. With ultrahigh resolution microscopy techniques his lab has pioneered, he has shown how DNA's ever-moving structural dance is vital to cells' functions. The choreography of DNA inside heart cells makes them different from liver cells or skin cells — and missteps could cause disease.

"We can now trace, in exquisite detail, the structure of DNA in hundreds of thousands of cells from different tissues," Boettiger explained. "And it becomes clear that there is order to this structure; it is not a molecule crumpled together randomly."

In college, Boettiger studied physics, then began applying that knowledge to biology. He was fascinated by the way natural phenomena could be reduced to simple mathematical equations. Among the questions he was most drawn to: How can the same DNA strands encode every different cell in an organism? "Every organism develops with this balance of remarkable reproducibility and beautiful individuality," Boettiger said. "And when you put a strand of DNA in a cell, there is a predictable outcome. But we, as scientists, cannot yet read that code very well."

Scientists know how genes encode proteins, the workhorses of cells. But less understood is how cells flip those genes on and off, ensuring that proteins needed only for muscle cells, for instance, are not produced by brain cells. The answer lies partly in regulatory DNA — sequences called enhancers that can sit hundreds of thousands of base pairs away from the genes they control. Disrupting enhancers changes whether cells use a gene or ignore it. If these seemingly distant enhancers affect genes, they must somehow be brought close in three-dimensional space inside cells, scientists hypothesized. But how?

When Boettiger launched his Stanford Medicine lab in 2016, no imaging method was precise enough to answer that question. Fluorescent tags typically used to pinpoint molecules' locations within cells produced circles of light far bigger than a strand of DNA, making it impossible to map how different parts of a DNA molecule folded together.

"If you labeled a bunch of spots on a folded-up DNA molecule, you'd just see a blob," Boettiger said.

In 2019, his lab developed optical reconstruction of chromatin architecture, or ORCA, to solve that problem. The technique labels DNA segments with unique molecular barcodes, then lights them up one at a time rather than all at once. The result: a colorful thread winding through the nucleus and tracing DNA's path in 3D space.

THE CHOREOGRAPHY EMERGES

ORCA SHOWED THAT GENOMES' STRUCTURES are organized into distinct neighborhoods separated by clear boundaries. Within a neighborhood, DNA sequences frequently bump into each other. But they rarely reach across the boundary to interact with sequences in the adjacent neighborhood. Surprisingly, many of the boundaries were the same between cell types; it was the interactions within each neighborhood that varied.

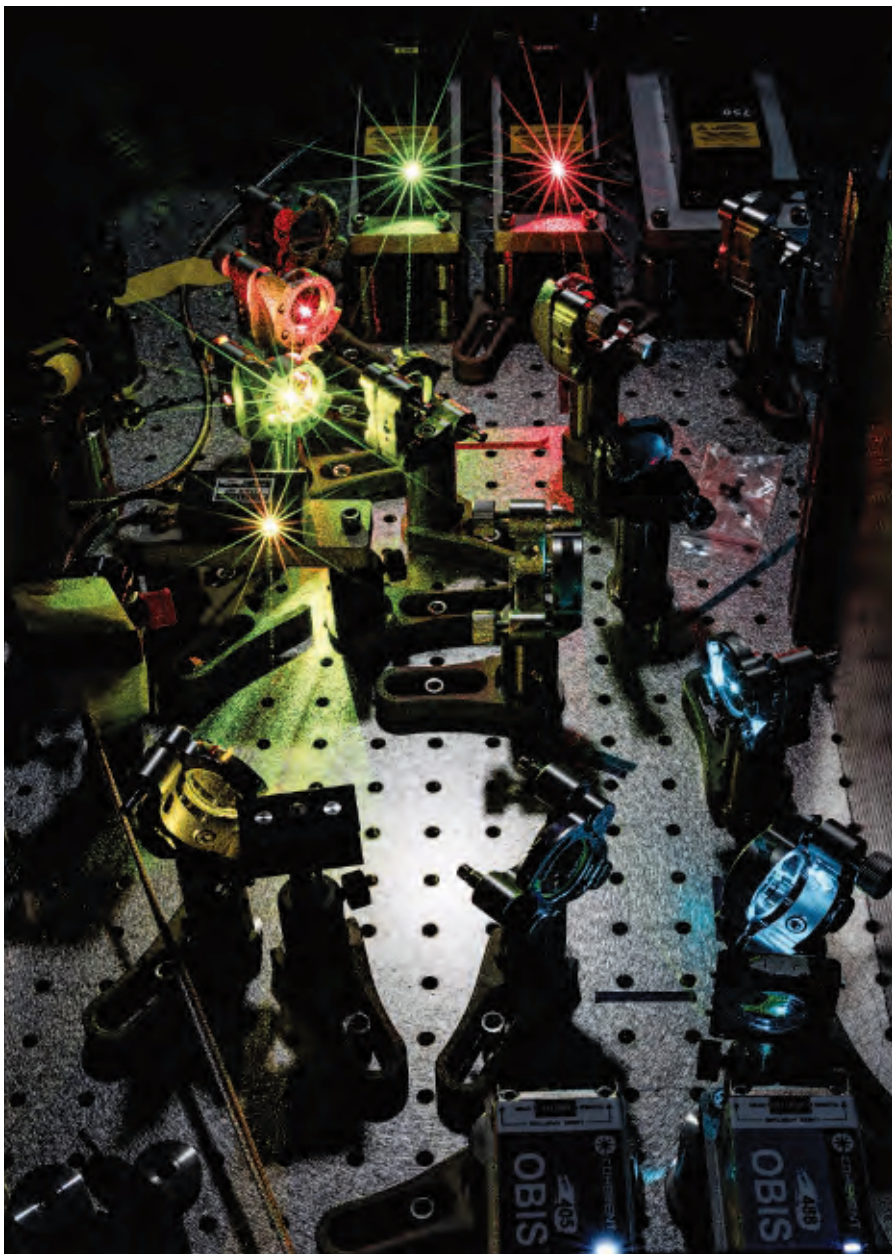
ORCA also upended another assumption. Some scientists had expected to find "hubs" — enhancers that bind to multiple genes at once. Instead, the data showed something more dynamic: Enhancers rapidly switched between partners, touching one gene, then another, but rarely both simultaneously.

"A lot of the data suggested that these interactions were incredibly transient," Boettiger said. "We wanted to know more about the timing of that movement."

In September 2025, Boettiger's group unveiled their newest tool, called TRACK-IT, which let them watch, in real time, how DNA moved in living cells. Specially engineered fluorescent tags lit up different places in the genome. Boettiger remembers getting it working for the first time: "I was literally singing at my desk," he recalled.

His lab team saw that within neighborhoods, DNA sequences could find each other in a matter of seconds, regardless of

IN SEPTEMBER 2025, BOETTIGER'S GROUP UNVEILED THEIR NEWEST TOOL, CALLED TRACK-IT… . BOETTIGER REMEMBERS GETTING IT WORKING FOR THE FIRST TIME: 'I WAS LITERALLY SINGING AT MY DESK,' HE RECALLED.



PART OF THE CUSTOM MICROSCOPE SETUP USED BY THE BOETTIGER LAB TO RESOLVE THE 3D ORGANIZATION OF INDIVIDUAL GENES AND THE SEQUENCES THAT CONTROL THEM.

Spotlight on Alistair Boettiger

ASSISTANT PROFESSOR OF DEVELOPMENTAL BIOLOGY

Alistair Boettiger studies how the structure and movement of DNA molecules are linked to gene activity and, ultimately, cells' identities and behaviors.

QUICK FACTS

- His identical twin brother is an associate professor of environmental science at the University of California, Berkeley.
- His accent is a mix of Philadelphia (where he was born); Manchester, England (where he spent some of his childhood); and Swahili and the Queen's English (which his mother grew up speaking in Nairobi).
- Advice from his graduate mentor that has most stuck with him: "Be serious about your science but never take yourself too seriously. It's important to remain humble as a scientist."

IN HIS WORDS

"I love working on the fundamental questions of how things work and developing new tools that push the field forward."

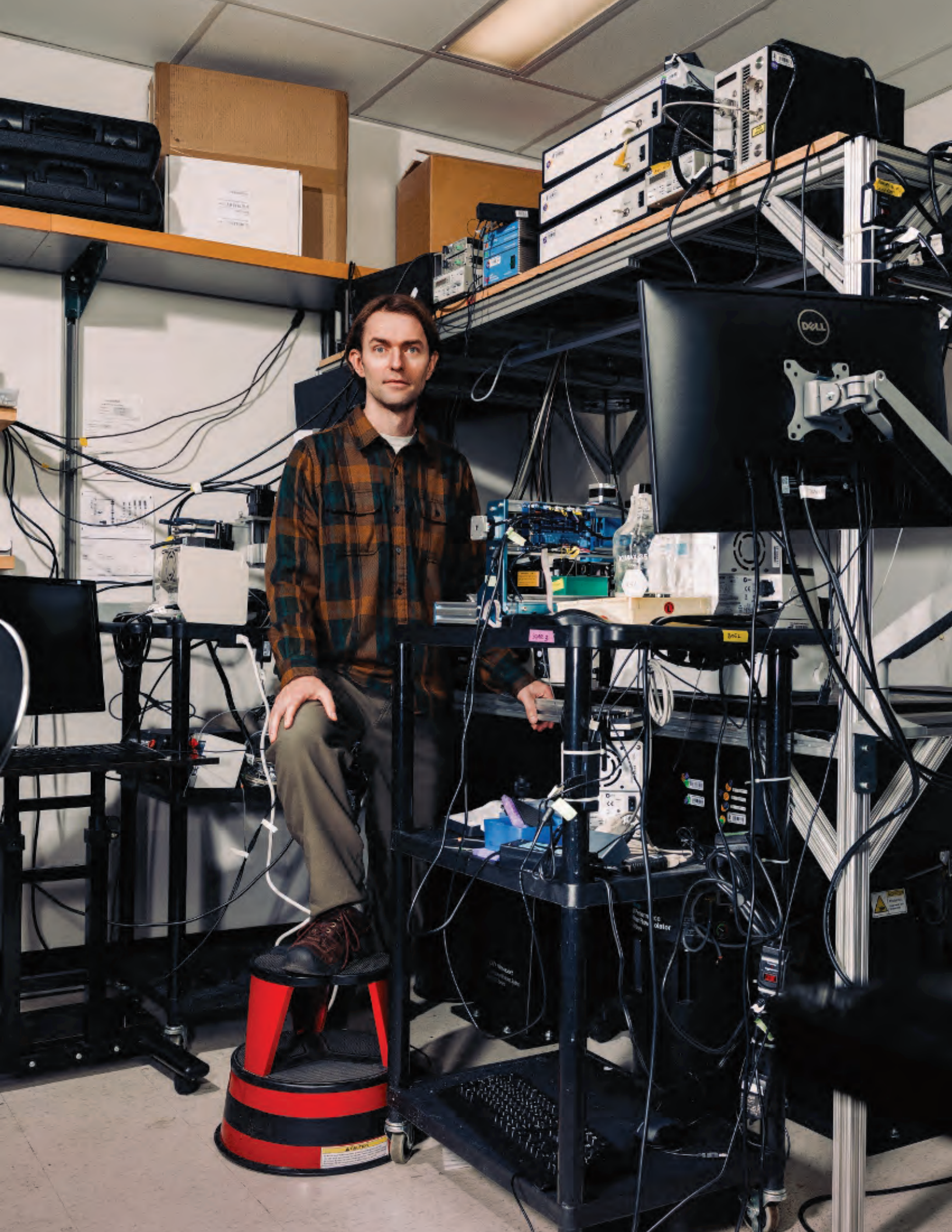
how far apart they sat on the linear chromosome. But at boundaries, everything changed. Search times jumped dramatically, as if the boundaries acted as invisible force fields. The boundaries, they then showed, depended on regions of the genome called insulators that block the formation of DNA loops.

"This kind of work helps us understand the fundamental principles of how a genome works," Boettiger said. "It gives us a wiring diagram of what areas of the genome can interact with each other, and which can't."

The implications ripple beyond basic biology. Understanding how genomes fold could help predict the effects of genetic mutations or explain why some bits of mixed-up DNA cause disease while others don't. Boettiger wants to create a set of physical rules that help scientists predict how a given strand of DNA will fold — and how that will dictate the function or health of a cell.

"I describe myself as a basic scientist, but I do derive meaning out of the belief that the things we discover will ultimately be useful to society," Boettiger said. **SM**

— Contact Sarah C.P. Williams at medmag@stanford.edu


DELL

CLOSING IN ON MEDICAL SOLUTIONS — FROM PREVENTING KIDNEY STONES TO STOPPING ALZHEIMER'S AND CURING OVARIAN CANCER

on the cusp

The path from an aha moment to a medical advance involves researchers climbing a series of confidence-building steps — each one meant to hone the resulting insights into a real-world patient benefit. In this section, we meet Stanford Medicine researchers who are on this path and spotlight their progress along the route, whether their stage is preclinical development, where they're analyzing molecular mechanisms, refining models and designing interventions, or they've made it to clinical trials, where they're putting early promise to the test in the place it matters most — among patients.

ILLUSTRATIONS BY BRIAN STAUFFER
PHOTOGRAPHY BY MISHA GRAVENOR

A BETTER ALZHEIMER'S DRUG?

A long trek nears its destination

By Bruce Goldman

FRANK LONGO SPENT A LOT OF TIME during his childhood in California thinking about brain science.

"I had a sister, a year younger than me, who was confined to a wheelchair and cognitively impaired," said Longo, MD, PhD, the George E. and Lucy Becker Professor in Medicine. "I asked my mother, who was a nurse, 'Why can't Patti walk?' She explained to me that my sister, born prematurely, had cerebral palsy due to her brain being deprived of oxygen pre-birth, and that there were no treatments for this and other brain conditions. That really stuck in my head somehow."

Driven by the desire to help people like his sister, Longo studied the brain and nervous system and, after attaining professorships at the University of California, San Francisco, and the University of North Carolina at Chapel Hill, joined the Stanford School of Medicine's faculty in 2006 as a professor of neurology and neurological sciences and, until 2023, as department chair.

For much of that time, Longo and his lab team have been exploring mechanisms that seem to slow or even reverse a correlate of brain aging and dementia: damage to and loss of synapses, the electrochemical junctions through which nerve cells in the brain transfer signals among one another. He sees this approach as a way to counter Alzheimer's and other neurodegenerative diseases.

The upshot: Longo has developed a compound that, unlike existing Alzheimer's drugs, could simultaneously tackle several mechanisms leading to neurodegeneration. This compound is now being tested in patients.

THE JOURNEY BEGINS

THE HUMAN BRAIN IS SAID TO CONTAIN ABOUT 86 billion neurons and at least hundreds of trillions of synapses, enabling cognitive feats from playing piano concertos or solving math problems to recalling events of your childhood or what you ate for dinner the previous night.

Spotlight on Frank Longo

PROFESSOR OF NEUROLOGY AND NEUROLOGICAL SCIENCES

Frank Longo is a pioneer in the development of an oral drug that's advancing in clinical trials as a therapeutic to counter Alzheimer's disease and, potentially, several additional conditions coalescing around a common symptom: cognitive loss. Longo is the co-founder and current chairman of the board of PharmatrophiX Inc., which has exclusively licensed the experimental drug to combat Alzheimer's.

In addition to developing and testing treatments for Alzheimer's disease, Longo studies the mechanisms underlying Alzheimer's and other neurodegenerative diseases, including Huntington's disease.

QUICK FACTS

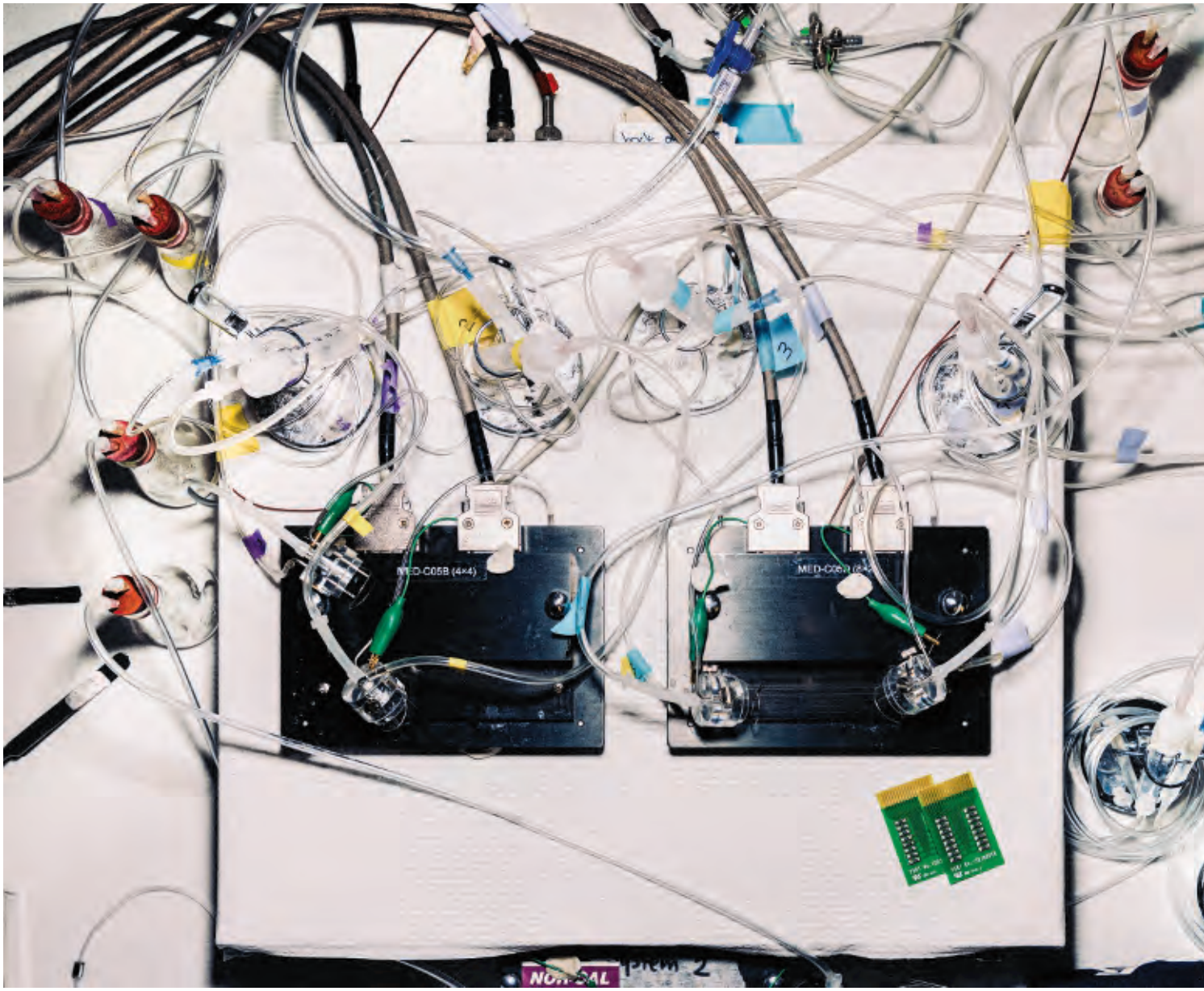
- Walk-up song: *Let's See Action* by The Who; Mood-lifting song: *Alive* by Pearl Jam.
- Loves pianos. He was a keyboardist in his Stanford department's cover band Hypertonics for a few years. He continues to play and to explore chord structures and progressions with curiosity about how they evoke different brain networks and feelings.
- A book that wowed him: *Cutting for Stone* by Abraham Verghese.
- Favorite place to visit: Desolation Wilderness (Lake Tahoe).
- Advice to students: Be systematic; don't rely on luck. Expose yourself to a lot of things and meet a lot of people to find the great mentors.

IN HIS WORDS

"I love research and I also love people. It's hard when research hits a roadblock, and to get through, I think about all the people who need help. What if we could do something for them? That keeps me going."

LONGO HAS DEVELOPED A COMPOUND THAT, UNLIKE EXISTING ALZHEIMER'S DRUGS, COULD SIMULTANEOUSLY TACKLE SEVERAL MECHANISMS LEADING TO NEURODEGENERATION.


AFG Bioscience
AFG Bioscience



THE ELECTROPHYSIOLOGY SETUP USED IN THE LONGO LAB TO MEASURE THE ELECTRICAL SIGNALS BETWEEN CELLS IN BRAIN TISSUE. THE BLACK PLATFORMS HOLD SLICES OF TISSUE AND RECORD THE SIGNALS; THE TUBES CARRY ARTIFICIAL CEREBROSPINAL FLUID.

In fetal and early childhood development, our brains acquire a surfeit of synapses. The resulting redundancy actually impedes cognition but, fortunately, is rectified by a brainwide pruning process that's regulated locally by a receptor on synapses' surfaces. A cell surface receptor that contributes to the trimming is called p75NTR. But this receptor, which quiets down after its childhood hyperactivity, becomes gradually more active in most of us as we age, or in the presence of Alzheimer's and other brain diseases — sometimes pronouncedly so, precipitating inappropriate synaptic pruning and loss of cognitive function. An unexpected finding within a large extended Alzheimer's disease-stricken family in Colombia has inspired Longo and his team to gain further insights into the capabilities of p75NTR.

Members of this family have inherited a mutation causing their brains to massively overproduce a substance called amyloid-beta (or A-beta) which is considered to be a primary contributor to Alzheimer's disease. Remarkably, one individual within this family who had large amounts of amyloid seemed to

'LM11A-31 COULD REALLY BE A BREAKTHROUGH IF IT GETS THROUGH PHASE 3. IF IT'S SUCCESSFUL, IT WILL BE THE FIRST NEUROPROTECTIVE DRUG TO PROVE ITSELF FOR ALZHEIMER'S DISEASE.'

have inherited a gene that renders synapses resilient to amyloid-beta and who remained dementia-free for decades. This gene controls many of the same nerve cell signaling mechanisms regulated by p75NTR. Longo and his team found that targeting p75NTR can create resilience to amyloid.

While still at UCSF, Longo and his colleague Stephen Massa, MD, PhD, identified a molecule that selectively interfered with p75NTR's activity to confer synaptic resilience, much like that promoted by the beneficial mutation. To develop the compound, dubbed LM11A-31, as a drug to combat Alzheimer's, he co-founded PharmatrophiX Inc. with his wife, CEO Anne Chun Longo, where he serves as chairman of the board. The company exclusively licensed LM11A-31 from UCSF and UNC.

Longo said he sees LM11A-31 as an alternative or adjunct to the current batch of pricey drugs recently approved for targeting amyloid plaque and the A-beta that precipitates to form those gummy deposits. Although small soluble clusters of A-beta are probably involved in the early stages of Alzheimer's disease, Longo said, the insoluble plaques those clusters eventually coagulate into may be more a fossil remnant than an active cause of the disease.

Other substances and processes become the primary causes of nerve cell and synapse degeneration.

Amyloid plaques may show up in brain-imaging scans two decades or more before outward symptoms develop, if they ever do. Many people with manifold plaques nevertheless have perfectly normal cognition, pointing to the phenomenon of resilience.

A Phase 2a clinical trial of LM11A-31 conducted among patients diagnosed with mild to moderate Alzheimer's disease (whose results were published in 2024 in *Nature Medicine*) confirmed its safety for use in humans.

LM11A-31 also inhibited accumulation of another Alzheimer's-associated protein called tau, protected synapses from ravages wrought by A-beta, and dialed down inflammation in the brain's in-house immune cells.

"The plaque-attack drugs are narrowly focused on removing amyloid," Longo said. "That's only one of several parallel mechanisms causing the neurodegeneration. LM11A-31 slows down a broad range of the degenerative cascade."

KEY ANSWERS LIE AHEAD

LONGO'S STANFORD MEDICINE LAB DOES no commercial-development work but continues to explore the degenerative mechanisms occurring in neurodegenerative diseases and ways various therapeutic target candidates might slow them down.

PharmatrophiX is working on funding a definitive Phase 3 clinical trial of LM11A-31 in Alzheimer's patients.

"That's the big mountain that needs to be climbed," said Howard Fillit, MD, a co-founder and the chief scientific officer of the Alzheimer's Drug Discovery Foundation, the largest nonprofit, nongovernment funder of dementia-focused drug development in the world — and an early investor in PharmatrophiX.

"LM11A-31 could really be a breakthrough if it gets through Phase 3. If it's successful, it will be the first neuroprotective drug to prove itself for Alzheimer's disease."

LM11A-31's multiple mechanisms of action confer unusual flexibility on its potential use. Preclinical studies indicate it could prove relevant to many indications, including Huntington's disease, HIV-associated dementia, stroke and traumatic brain injury.

A recent study Longo co-authored, published in early 2025 in *Brain*, found, in mice, that LM11A-31 prevented cognitive deficits that otherwise occurred due to perinatal oxygen deprivation. "That's exactly what caused my sister's cerebral palsy," Longo said. **SM**

— Contact Bruce Goldman at goldmanb@stanford.edu

IN SIGHT

New approaches to glaucoma, the leading cause of blindness

By Rachel Tompa

Spotlight on Jeffrey Goldberg

CHAIR OF OPHTHALMOLOGY

Jeffrey Goldberg develops and tests innovative ways to overcome nerve damage caused by glaucoma, the world's leading cause of blindness. In the more than 20 years he has studied glaucoma, Goldberg said, this is the first time the possibility of more effectively preventing vision loss, or even restoring lost vision, seems to be within reach.

QUICK FACTS

- Enjoys hiking and biking around the Bay Area with his wife and children.
- Earned both his doctoral degree in neuroscience and his medical degree at Stanford Medicine.
- Squeezes in a daily crossword puzzle.

IN HIS WORDS

"As a clinician-scientist seeing patients, I am very motivated by the burden of these diseases. These are real people with real families and real lives we are trying to help."

Listen to a ***Health Compass*** **podcast** with Jeffrey Goldberg at stan.md/health-compass

IT SOUNDS LIKE SOMETHING OUT of science fiction: an implant for the eye packed with genetically engineered cells that could restore vision to the blind. But Stanford Medicine's Jeffrey Goldberg, MD, PhD, is testing this and other innovative therapies in patients with vision problems and is finding promising initial results.

Goldberg, the Blumenkranz Smead Professor and chair of ophthalmology, studies glaucoma, the leading cause of irreversible vision loss and blindness, and related problems. Glaucoma damages the optic nerve, the bundle of fibers called axons that transmits all visual information from the eye to the brain.

Glaucoma treatments generally focus on reducing abnormal pressure in the eye. If you have annual eye exams, you've likely had your eye pressure checked with, for example, an instrument with a glowing blue light that rests on the surface of your eye.

Elevated eye pressure is a risk factor for glaucoma, and reducing that pressure through laser treatments, medicated eye drops or surgery can slow the condition's progression. But no treatments exist to fully stop this progression or to repair or rejuvenate the damaged nerve.

While existing treatments can slow or halt vision loss, especially if the disease is caught early, they don't work for everyone — up to 10% of people with glaucoma become resistant to the treatments. And vision lost to glaucoma is lost forever.

"Even among patients with great access to care, a significant fraction of them will progress to legal blindness despite our best treatments," Goldberg said. "So, there's a significant unmet need."

Goldberg and his colleagues hope to change that. For most of his career, no one was trying to advance treatments outside of pressure control for glaucoma. But there has been a recent shift toward developing and testing new forms of therapy, he said.

"Over the last 10 years, we've been pushing wherever we can to take advances out of the laboratory and into human trials," Goldberg said. Advances Goldberg studies include experimental therapies in the realm of neuroprotection, which prevent further degeneration of the optic nerve, and neuroenhancement or neurorecovery, where treatment restores damaged nerve cells. "This could actually even improve patients' vision," he said.

One such therapy is an implant filled with stem cells that secrete a hormone known as a growth factor, called ciliary neurotrophic factor, or CNTF. CNTF is found naturally in the eye and brain and helps support the growth of new neurons. Goldberg and his laboratory used it in preclinical animal studies of glaucoma, then partnered with a biotech company to test the implant device in patients with the eye condition.

The company had developed the device for a different, rare vision condition but Goldberg realized, based on studies of CNTF, that it might work in glaucoma, too. The tiny dumbbell-shaped implant, a bit more than half a centimeter long and a millimeter wide, is surgically placed in the eye's vitreous cavity, the gel-filled space in the eyeball between the lens and the retina.

A permeable membrane on the implant allows the release of CNTF secreted by the implant's stem cells, while also keeping the cells sequestered from the patient's eye. Goldberg's team recently completed a multicenter, randomized, Phase 2 clinical trial of the device and saw strong neuroprotective effects: The implant prevented severe vision loss caused by glaucoma, although in this smaller trial it did not seem to reverse vision loss.

EXPLORING GLAUCOMA'S MECHANISMS

IN OTHER TRIALS, GOLDBERG'S TEAM at Stanford Medicine is testing treatments that include electrical stimulation of the retina and growth factors delivered by eye drop.

"Jeff is a world-recognized authority on neuroprotection to detect and prevent vision loss from glaucoma," said Thomas Brunner, president and CEO of the Glaucoma Research Foundation, which has supported some of Goldberg's research. "His research on protecting and even replacing the retinal nerve cells that connect the eye to the brain could be a major breakthrough and effectively cure glaucoma."

In his lab, Goldberg studies what causes glaucoma and related eye diseases that lead to optic nerve damage. Interestingly, the damage is associated with high eye pressure but is not directly caused by physical forces of that pressure. Rather, increased pressure triggers molecular and cellular changes that cause nerve damage and neuron death.

Last year, Goldberg and his lab team discovered something interesting about cells known as astrocytes. While neurons convey information from the eye to the brain, "support cells" such as astrocytes influence how these neurons function. The team found that astrocytes can speed or slow glaucoma's progression, depending on how they react to the disease, and in a study in mice they uncovered a beneficial population of astrocytes that suppress the damaging astrocytes.

They also developed a gene therapy that, when delivered to the animals' eyes, flips the astrocytes from harmful to helpful, thereby preventing nerve damage, according to a 2024 study in *Nature*.

Goldberg said he sees gene therapies and growth factor treatments as additions to current treatments. "It would be like a belt-and-suspenders approach. One day our patients will have their eye pressure-lowering therapy and also their neuroprotective or regenerative therapy." **SM**

— To learn more about Goldberg's open clinical trials, click the "Glaucoma" tab at stan.md/GlaucomaTrials.
Contact Rachel Tompa at medmag@stanford.edu.

‘WE NEED A BREAKTHROUGH’

Trials of immunotherapy for ovarian cancer offer hope for patients with few options

By Ruthann Richter

EVERY DAY, OLIVER DORIGO, MD, PHD, has to confront the challenge of treating ovarian cancer, which is a frustratingly stubborn disease to manage. It’s hard to detect, at times resistant to drug treatment and, all too often, fatal.

“I don’t accept the fact that at least 60% of patients with ovarian cancer die from the disease. We need to change that. That has been my mission for decades,” said Dorigo, the Mary Lake Polan Professor at Stanford Medicine. “I’m very optimistic that there will be a time when we will be able to offer patients more effective therapies.”

That optimism springs from Dorigo’s recent work with two innovative therapies now in clinical trials that he hopes will improve the outlook for patients with the disease, one of the deadliest cancers among women. Some 21,000 women are diagnosed with ovarian cancer every year in the United States and, in 2026 alone, some 12,450 are expected to die from it, according to the American Cancer Society.

Because no definitive screening tools exist, patients are often diagnosed when the cancer is advanced, making it particularly difficult to treat, said Dorigo, director of the gynecologic oncology division.

Patients might initially respond to treatment, which typically includes surgery and multiple rounds of chemotherapy. But the cancer frequently returns and can cause patients to become resistant to drug treatment, leaving them with few therapeutic options, he said. Among patients with advanced disease, only about one-third live at least five years.

To change that, Dorigo and his colleagues have turned to CAR-T (chimeric antigen receptor) cell therapy, which is transforming cancer treatment. The therapy empowers a patient’s own immune system to attack cancer cells. It has been used with tremendous success in blood cancers, with clinicians just starting to test it in solid tumors.

“Ovarian cancer is one of these cancers that has been left behind in the immunotherapy revolution. It’s unfortunate because we need a breakthrough,” said Crystal Mackall, MD, founding director of the Stanford Center for Cancer Cell Therapy and a national leader in the field. “There’s no reason we shouldn’t be able to apply this in ovarian cancer.”

Spotlight on Crystal Mackall

PROFESSOR
OF PEDIATRICS
AND OF MEDICINE
AND FOUNDING DIRECTOR
OF THE STANFORD
CENTER FOR CANCER
CELL THERAPY

A pioneer in cancer immunotherapy, Crystal Mackall was among the first to show the value of CAR-T cells in pediatric leukemia, while working at the National Institutes of Health. More recently, she and Stanford Medicine colleagues showed these cells could be used to treat certain brain tumors. She has published multiple landmark papers in the field.

QUICK FACTS

- Came to Stanford Medicine in 2016 from the NIH and founded the Center for Cancer Cell Therapy in 2017.
- Grew up in northeastern Ohio, in a working-class family. Received her MD degree from Northeast Ohio Medical University.
- Recharges by spending time with family, hiking, doing other outdoor activities, reading and enjoying a good meal.

IN HER WORDS

“This work matters to me because I believe that cell therapies can have activity on more common solid cancers where we have major unmet needs. I think ovarian cancer is a good setting to test that.”

Spotlight on Oliver Dorigo

DIRECTOR
OF THE GYNECOLOGIC
ONCOLOGY DIVISION

Oliver Dorigo treats patients with gynecologic cancers, including ovarian, cervical, endometrial, vaginal and vulva cancer. His research and the clinical trials he leads are designed to develop and study new immunotherapies for patients with ovarian cancer.

QUICK FACTS

- Received his MD degree from the University of Heidelberg in Germany and a PhD in molecular biology from the University of California, Los Angeles.
- Was born and raised in Germany by a German mother and an Italian father, and still visits family in Italy and Germany.
- Has completed 21 full Ironman triathlons (2.4 miles swimming, 112 miles cycling, 26.2 miles running). To relax, he bikes, runs, swims, skis, surfs and spends time with family, including his three teenagers. “Everybody needs something to get their minds off the very challenging situations we encounter in patient care. Sports and family keep me active and give me something to look forward to.”

IN HIS WORDS

“I’ve treated ovarian cancer for decades. I see every day how challenging this treatment is for the patients and their families. We still lose way too many patients to this disease. For the patients and even for myself, it’s extremely frustrating to come to the end with no more options. We need more cures. With time, I am confident that we will get there.”

The therapy, which they are testing in a clinical trial, targets a protein called B7-H3, which is expressed in 90% of ovarian cancers, Mackall said. During treatment, clinicians extract a patient's white blood cells — the disease fighters of the immune system — and genetically modify them in the lab to recognize the B7-H3 protein. The new, highly active cells are then infused into the patient so they can zero in on and destroy cancerous cells.

Ovarian cancer is often confined to the abdomen, so clinicians can infuse the cells directly into that area using a soft tube, thus sparing other tissues.

"This might have an advantage," said Mackall, the Ernest and Amelia Gallo Family Professor and a professor of pediatrics and of medicine, who is collaborating in the trial. "We have seen this in brain tumors. Giving the CAR-T cells directly into the brain is shown to have benefit."

The researchers began the trial in late 2024 and have tested the treatment in seven patients, all with advanced, recurring disease that has resisted all other therapies. In all patients, the tumors stopped growing for some time, and in some, tumors decreased after two months, Dorigo said. "We have definitely seen initial benefits to patients — some positive signals," he said.

Dorigo noted that some patients in the trial experienced side effects related to the hyperactivity of the T cells, which can cause fever, low blood cell counts and leg swelling. To reduce these side effects, the research team has lowered the dose of the CAR-T cells. That made the treatment more tolerable while still controlling tumor growth, Dorigo said. Patients receive as many as three infusions to maximize the impact of the CAR-T cells, he said. The researchers now plan to treat up to 10 additional patients in the trial at the lower dose.

By summer 2026, the researchers may also begin using a next-generation CAR-T cell whose activity can be regulated through a daily pill that turns the T cells on and off, Mackall said.

This approach, developed in her laboratory, enables patients to use the pill to tune the potency of the T cells. For instance, a patient who begins to experience toxic side effects can stop taking the pill for a few days to modulate the dose and eliminate the toxicity, Mackall said.

CONTINUES ON PAGE 84

HOW A RIGOROUS FRAMEWORK IS SPURRING MEDICAL SOLUTIONS

By Nina Bai

catalyst

Five years is not a long time in health care innovations. It takes, on average, 10 to 15 years to bring a new drug to market and three to seven years for new medical devices. And that's if you have the funding and know what you're doing. More often than not, medical innovations tumble into the "valley of death" between bench and bedside, never crossing from initial scientific discovery to commercial product and patient care.

Five years ago, Susan Hiniker, MD, an associate professor of radiation oncology who treats pediatric cancers, didn't know any of that. But she knew what worked for her patients.

She knew that many young children have a hard time with radiation therapy, which requires them to lie still, alone in a room, for 30 to 45 minutes a day, sometimes five days a week for up to seven weeks. Children who cannot meet the requirements are put under anesthesia, daily, which comes with a laundry list of complications, including neurocognitive and cardiopulmonary side effects, not to mention more needles and more time in the hospital.

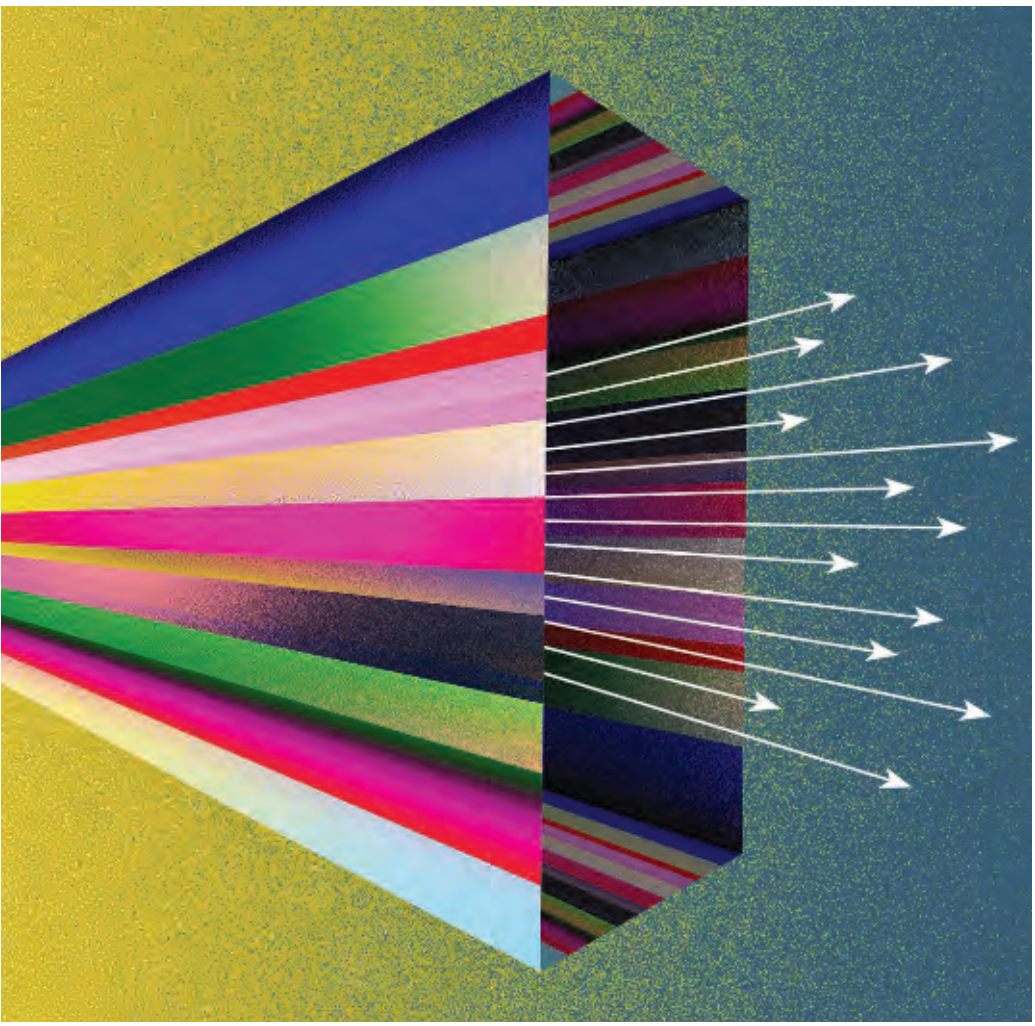
"We started to notice these little kids, 6- and 7-year-olds, coming in for consults, and in the waiting room they are pretty still, calm and cooperative — as long as they're staring at a tablet," Hiniker said. The immobilizing, entrancing power of a glowing screen is familiar to every parent. Hiniker and her colleagues Bill Loo, MD, PhD, a professor of radiation oncology, and Lawrie Skinner, PhD, an assistant professor of radiation oncology, wondered if they could replicate that effect during radiation therapy without interfering with the precisely calibrated radiation beams directed at the patient's tumors.

They imagined and built a device that projects video onto a small screen positioned just above the patient. The screen is a thin translucent plastic that does not block radiation.

The device, called AVATAR (audio-visual assisted therapeutic ambience in radiotherapy), worked like a charm. Kids as young as 2 willingly lay still day after day to watch their favorite shows. By 2020, the team was using AVATAR routinely at Stanford Medicine Children's Health. As word spread, they mailed devices to other cancer centers and were able to conduct a multicenter clinical trial, which found that the device helped 78% of kids aged 3 to 10 forgo anesthesia during radiation therapy, compared with fewer than half without it. Soon, the team was flooded with emails from other institutions asking how to get AVATAR.

"And then it was just three academic people kind of bumbling around. We had no idea how to actually scale anything," she said, noting that they were still assembling each AVATAR device themselves.

In 2023, they heard about Stanford Medicine Catalyst, a new-ish incubator and accelerator program that funds early-stage health care innovations and provides business, regulatory and investment guidance. With the vision of "invented here,



used everywhere," its aim is to help Stanford innovators improve the lives of patients around the world.

Catalyst sounded like exactly what Hiniker's team needed.

A MISSION OF COLLABORATION

THE CATALYST PROGRAM launched in the summer of 2020, during the height of the pandemic. Its first project was an inexpensive saliva-based COVID-19 test, which was later picked up and funded by the Gates Foundation.

The idea for Catalyst emerged from Stanford Medicine's Integrated Strategic Plan, a yearslong process that took stock of the strengths and weaknesses of the various Stanford Medicine entities to create a unified road map for the future. Part of the road map is more accessible support for innovation, particularly in the translation of basic science.

"Stanford has long been synonymous with innovation. Yet even with a history of faculty-led companies and technologies, many faculty felt they lacked the support needed to translate their ideas into impact," said the Department of Medicine chair, Euan Ashley, MB ChB, DPhil, the Roger and Joelle Burnell Professor in Genomics and Precision Health and Arthur L. Bloomfield Professor in Medicine. Ashley leads Catalyst with Michael Halaas, associate dean and chief operating officer of the School of Medicine, and Kevin Wasserstein, the program's executive director.

Catalyst was designed as a multiyear program that not only awards generous funding — up to a million dollars per project — but also partners closely with the awardees to bring their health care innovations to patients. Anyone at Stanford University can apply.

"We envisioned Catalyst as a way to address a vital need for our innovators across Stanford Medicine and the university at large — providing support for early-stage projects with great promise to break new ground in advancing health care delivery," said David Entwistle, president and CEO of Stanford Health Care. "As Stanford Medicine's flagship accelerator, Catalyst has truly embodied our commitment to nurturing and scaling transformative ideas for real-world clinical impact."

Stuart Scott, PhD, a professor of pathology, and Teri Klein, PhD, a professor of biomedical data science, were among the first round of applicants to Catalyst. Scott's lab had created new genetic tests to predict a patient's response to medications, and Klein's lab was developing software to translate such test results into actionable reports. Together, they hoped to design a streamlined clinical assay system that could quickly generate a complete pharmacogenomics profile of a patient. The profile would predict the likely efficacy and adverse side effects of various therapies for that patient to help physicians prescribe the best option. But Scott and Klein weren't sure if they had a commercially viable product.

After an intensive, monthslong review of their application and much back and forth, the Catalyst team surprised them with an ambitious proposal.

"We got more from Catalyst than we asked for, in a good way," Scott said. Catalyst didn't want to just develop a clinical tool, they wanted to take it through implementation in a large health care system — at Stanford Medicine.

"That's when everything changed, because it went from really an engineering project to an implementation program," Scott said. "That was a huge thrill for us, to not only have the resources to build something nobody else in the country was doing but also to get the enthusiasm and momentum to implement it here."

Today, the Stanford Pharmacogenomics Implementation and Reporting Architecture, or SPIRA, is close to completing a pilot implementation program at Stanford Health Care, where it has received more than 100 requests for pharmacogenomics profiling and already helped some patients switch to more optimal medications. It's embedded in the electronic health records system and will soon roll out at Lucile Packard Children's Hospital Stanford.

NOT LIKE THE OTHERS

EVERYONE HAS AN INCUBATOR THESE DAYS — universities, global corporations and venture capital firms large and small, in just about any industry.

"When I first heard the idea of Catalyst, I thought, 'I've heard this before with other universities. Why does Stanford need one of these when, in fact, Stanford has already done so much in terms of innovation and producing a lot of translation?'" said Sue Siegel, co-chair of the Stanford School of Medicine's board of fellows and one of the industry advisers to Catalyst.

Indeed, Catalyst isn't Stanford's only incubator, not even the only one in health care. There's also Stanford Biodesign, which focuses on medical devices and biotechnology, and SPARK, which focuses on translating drug discoveries, and several others. But Catalyst stands out in several ways.

Most obvious, perhaps, is that Catalyst has deeper pockets. Catalyst can fund up to $1 million per project, whereas most incubators rarely grant more than a couple hundred thousand dollars. The team also takes an unusually hands-on approach, beginning with an intense due diligence review for every application. Catalyst team members then work side by side for a year with the innovators whose projects are accepted.

Some projects, such as SPIRA, can be piloted at Stanford Health Care, providing a real-world test bed, while also allowing Stanford to benefit early from these innovations.

Another consequential feature of Catalyst is its laser focus on making a difference for patients, whether through new drugs, diagnostics and medical devices, or by improving the quality and efficiency of the health care system.

"We truly start day one with a translational goal," said Wasserstein, who was a longtime venture capitalist and entrepreneur before joining Catalyst. "Our goal is not to increment the technology from early to slightly less early. It's to be a full bridge across the pond, to move a project from Stanford bench to bedside and to attract substantial capital, investment or partnership to enable the innovation to have lasting impact for patients and caregivers around the world."

"Catalyst has become truly foundational to our mission," said Lloyd Minor, MD, dean of the School of Medicine and vice president for medical affairs at Stanford University. "We have witnessed the success of this joint effort across the adult hospital, the children's hospital and the School of Medicine, enabling Stanford Medicine to catalyze these brilliant innovations and their translational impact on health care, first at Stanford, and then around the world."

While the North Star for most business ventures is a high return on investment or ROI, Catalyst's leaders measure the success of its projects by what Wasserstein has coined return by impact, or RBI.

As a result, Catalyst follows a slightly different compass than most incubators and can take on a wider range of innovations, including some that don't fit the typical model. "Catalyst has distinguished itself really nicely, in that many of the ideas that have come out of the university have a lot of impact but potentially wouldn't receive venture funding," Siegel said.

Of course, many of Catalyst's projects attract funding from venture capitalists and industry and spin out successful companies. But there's room for other ideas, too.

"Think of it as a democratized incubator for many different types of innovation," Siegel said.

An idea like AVATAR, for example, would never get funding from a venture capitalist.

A WHOLE NEW WORLD

BY 2023, WHEN HINIKER'S TEAM SENT IN their application to Catalyst, the program had more than a dozen projects under its belt, ranging from an organ-cooling device to extend kidney transplant longevity to a remote monitoring system for Parkinson's patients using finger movements.

At the time, Krithika Kumar, PhD, Catalyst's head of innovation, had recently joined the team to lead the review of projects. Now she heads a team of seven, including business analysts,

WHY IT MATTERS

- **Only about 10% to 15% of medical innovations that enter clinical development successfully make it to the marketplace.**
- **The Catalyst program provides know-how and funding of up to $1 million per project to bring health innovations to patients.**

'THERE'S SOME PROOF OF CONCEPT, SOME EARLY DATA SO THAT IF WE PUT MONEY AND TIME AND RESOURCES TOWARDS THIS, WE HAVE A REASONABLE CHANCE OF IT MAKING AN IMPACT.'

project managers and a technology architect, who consider each application. The proposals range from studying human organs on the moon to iron-supplementing biscuits.

"We sit around the table and talk about the projects across many, many rounds of review," Kumar said. "We're reading them line by line to ensure that we're doing justice to a project that's taken time to apply to us."

They interview the applicants, which have included undergraduates, staff and Nobel laureates. They research relevant markets, business models and competitors, as well as regulatory and reimbursement needs, and potential patient impact. They seek feedback from Catalyst's directors, deans and leaders throughout Stanford University and consult subject matter experts, including Catalyst's advisory board of experienced venture capitalists and industry veterans. In the final round, they work with the applicants to establish project milestones that are achievable in 12 months.

"We dig really deep," Kumar said.

The team tries to provide constructive feedback to every applicant, but to be selected a project must be more than a great idea on paper.

"We support what we call prototype-enabled innovations. There's some proof of concept, some early data so that if we put money and time and resources towards this, we have a reasonable chance of it making an impact," Kumar said.

The review process can take five to six months, during which time the Catalyst team meets regularly with applicants to refine their proposals. For many academics who apply, it's their introduction to a whole new lexicon of ROIs, J-curves (an investment trend with an initial decline followed by significant growth) and flywheel effects (when incremental successes build self-sustaining momentum) that all lead to Sand Hill Road (a street in Silicon Valley known for its concentration of venture capital firms).

"The questions you get are not going to be the same you'd get on a traditional research grant proposal," Scott said.

Once projects are chosen — four or five out of more than 100 applications are accepted per semiannual cycle — a 12- to 15-month development phase begins. That's when the Catalyst team rolls up its sleeves to help the project teams achieve the milestones they've set, often meeting on a weekly basis.

That collaborative relationship takes some getting used to for many academics, Wasserstein said. "They're used to consistently going after grants for their survival. They get grants, they receive their money, they go off and do the work, and then they report back. For us, we emphasize that this engagement is a true partnership. And we're going to be with you side by side through all the ups and the downs."

AVATAR was selected by Catalyst in 2024. "It's really not like a grant where they're evaluating you and you're just showing them what you want to show them," Hiniker said.

Kumar recalls many afternoons in the Catalyst office helping Hiniker's team assemble AVATAR devices to ship to sites around the world. Catalyst also provided technical support and built partnerships internationally. In just over a year, it helped deploy AVATAR in more than a dozen countries, including Tanzania, Kenya, Uganda, South Africa and Romania.

They found that AVATAR's benefits were even more profound in low- to middle-income countries, where patients may not have access to anesthesia. If a child can't lie still, they forgo potentially life-saving treatment. Recently, a 7-month-old baby in Romania was able to receive abdominal radiotherapy thanks to AVATAR, a device invented at Stanford only a few years ago.

AFTER CATALYST

THE CATALYST TEAM KNOWS THAT a year in their program is only the first leg of a project's journey and that even a million dollars can only go so far. So they prepare the projects for next steps, whether that's reporting metrics, making connections with industry leaders or practicing Shark Tank-like pitches to venture capitalists.

Radiopharm, a Catalyst project to create custom radiopharmaceutical technology that targets a patient's specific cancer, won a $35 million federal contract from the Advanced Research Projects Agency for Health (ARPA-H). That success was, in part, a result of the mentoring the team received and the progress they made through Catalyst, said Katherine Ferrara, PhD, a professor of radiology, who leads Radiopharm. The ARPA-H contract will allow the team to use computational techniques and artificial intelligence to design molecules that bind to disease-specific protein changes in cells, which could be a way to diagnose cancers that do not yet have screening tests.

CONTINUES ON PAGE 85

TWIRLING TO TREAT STROKE

HOW A SPINNING DEVICE SHRINKS BLOOD CLOTS IN THE BRAIN

By Sarah C.P. Williams

In the critical minutes after an ischemic stroke, when a blood clot is blocking an artery to the brain, time becomes the enemy. The sooner the clot can be removed, the higher a patient's chance of surviving and the lower the chance of brain damage. To remove a clot, doctors usually thread a catheter through blood vessels to vacuum or snag it, a procedure that became widely adopted within the past decade. But the removal succeeds on the first try only about half the time. For the toughest clots — dense tangles of protein that break apart when grabbed — success rates plummet to 11%.

A TRUE-TO-SCALE MODEL OF THE HUMAN CEREBRAL BLOOD VESSELS RESEARCHERS USE TO DEVELOP WAYS TO TREAT STROKE.

Now, Stanford researchers have developed a device, called a milli-spinner, that can dramatically shift those odds. The device rapidly twirls blood clots, shrinking them to a fraction of their size for easier removal.

"When you're treating a stroke patient, you want to get all of the clot out and get it out fast," said Jeremy Heit, MD, PhD, chief of neuroimaging and neurointervention and an associate professor of radiology at Stanford Medicine. "This new device could become the standard of care to get that done. We're looking forward to seeing what it can do in patients, hopefully in the near future."

The milli-spinner wasn't developed to shrink clots. Instead, Stanford University assistant professor of engineering Renee Zhao, PhD, was designing a tiny robotic device that she imagined could deliver drugs. But, when testing the device, which propels through blood vessels with spinning rotors, she noticed that the force created by the turning propeller created suction.

"We started to think, 'Can we use this localized suction to suck up clots?'" Zhao recalled.

Her team added a tether to the milli-spinner to guide it purposefully through vessels rather than leaving it to swim freely. They quickly discovered that it does much more than just suction out clots. It also condenses the clots into tiny, dense balls. The spinning motion applies compression and shear forces, rolling the proteins that hold clots together — called fibrin threads — into a tight tangle and squirting out trapped blood cells.

"It was beyond our imagination," Zhao said. "We could actually see the clot change color from red to white as the blood cells were squeezed out."

A colleague put Zhao in touch with Heit, and they began testing the milli-spinner in animal studies, with support from the Wu Tsai Neurosciences Institute and Stanford Bioengineering. It took hundreds of iterations before they got it right — able to be threaded through the catheters doctors already use, guided to the clot site, and spun and removed without fragmenting.

The combination of Zhao's engineering expertise and Heit's clinical knowledge was critical, both researchers said. Zhao's lab tweaked the design, 3D printing new versions again and again, while Heit ensured that the device would be compatible with existing clinical technology and useful for a real problem — the toughest clots in the brain.

Spotlight on Jeremy Heit

ASSOCIATE PROFESSOR OF RADIOLOGY AND CHIEF OF THE NEUROIMAGING AND NEUROINTERVENTION GROUP

Jeremy Heit specializes in treating stroke, brain aneurysms and other conditions in the brain's blood vessels using state-of-the-art technology. His research lab studies the underlying causes of reduced blood flow in the brain.

QUICK FACTS

- Received his MD/PhD degrees from Stanford Medicine in 2007 and 2008 and joined the faculty in 2018.
- Growing up in Colorado, Heit was his high school's valedictorian and the state champion in both gymnastics and diving. "I just had to remember when to land on my feet versus my head," he said.
- Spends most of his free time cheering on his four children in swimming and water polo.

IN HIS WORDS

"Taking care of stroke patients is among my favorite things to do because it can really make an impact. It's amazing to see a stroke patient get better right away and start moving in front of your eyes. I want that for every patient, and we need new technology to get there."

Renee Zhao

ASSISTANT PROFESSOR OF MECHANICAL ENGINEERING

Renee Zhao's lab focuses on making soft, intelligent robotic systems that can change shape, assemble, sense and navigate. Beyond applications in biomedicine, her materials are also useful in flexible electronics and sustainable energy.

QUICK FACTS

- Hometown: Xi'an, an ancient capital of China, where the Terracotta Army can be found.
- Received degrees from Xi'an Jiaotong University and Brown University and joined the Stanford University faculty in 2021.
- Recharges her energy by spending time in nature.

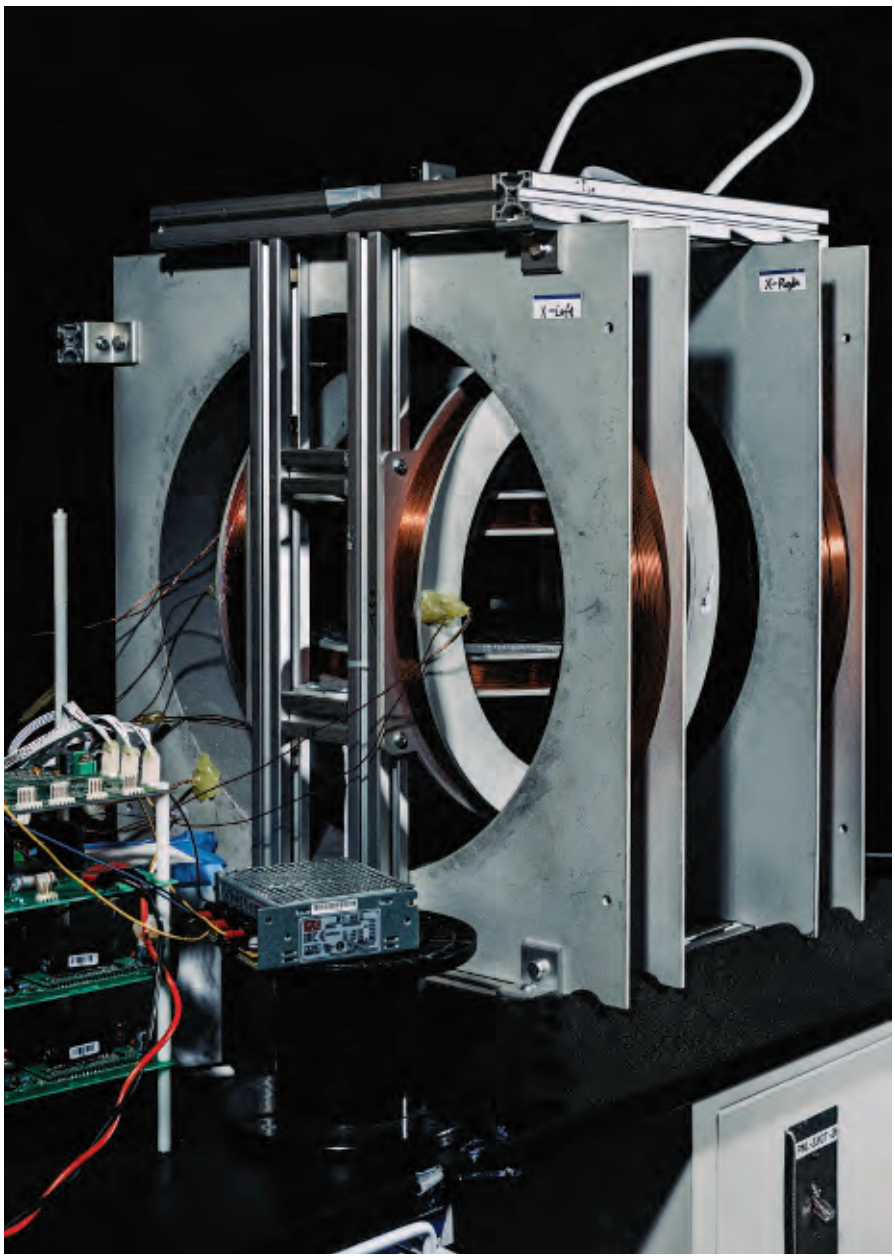
IN HER WORDS

"Collaborations with clinicians are really important so we make sure we're using our designs to address unmet needs in biomedicine rather than artificial problems that don't exist."

Listen to a ***Health Compass*** **podcast** with Jeremy Heit and Renee Zhao at stan.md/health-compass

'IT WAS BEYOND OUR IMAGINATION. WE COULD ACTUALLY SEE THE CLOT CHANGE COLOR FROM RED TO WHITE AS THE BLOOD CELLS WERE SQUEEZED OUT.'


RESPIRATORY SYSTEM



THIS ELECTROMAGNETIC COIL SYSTEM IS USED TO DRIVE AND STEER THE ROBOTIC MILLI-SPINNER FOR NAVIGATION WITHIN BLOOD VESSELS.

"A lot of people would say one plus one is two, but what you actually learn in this kind of collaboration is that one plus one is like four," Heit said. "The back-and-forth process of thinking and dreaming and being creative together exponentially amplifies what you're doing."

In June 2025, Zhao and Heit published the results of their animal trials in *Nature*. The milli-spinner, they reported, could shrink clots to as little as 5% of their original volume. For particularly stubborn clots, the device succeeded 90% of the time on the first attempt — dramatically better than current methods.

"The idea to actually change the morphology of the clot so it will pull out is a really novel concept; it's very different from anything else that's available right now," said Mahesh Jayaraman, MD, a professor and the chair of radiology at Brown University and former president of the Society of NeuroInterventional Surgery.

Jayaraman said he was skeptical when he first heard about the milli-spinner. "But as I looked into the science of it, it really struck me as a remarkable collaboration between scientists and physician-scientists," he said. "If it proves to be safe and effective, it could radically change how we treat ischemic stroke."

For patients, the new technology — if it can remove blood clots more quickly and effectively than today's approaches — could translate to improved quality of life and an easier path to recovery after a stroke.

"As a stroke survivor myself, I know how challenging the time after a stroke can be," said Debra Meyerson, PhD, an adjunct professor at the Stanford Graduate School of Education and author of *Identity Theft: Rediscovering Ourselves After Stroke*.

With her husband, Meyerson co-founded the nonprofit organization Stroke Onward to help stroke survivors in their long-term recovery.

The people they support often face dramatic changes to their relationships, jobs and hobbies.

"We would love for there to be far less need for our work," said Meyerson. "New innovative treatments like this blood clot removal technique give us hope that fewer people will face the devastating life changes a stroke all too often creates."

Zhao and Heit have founded a company to commercialize the technology and move the milli-spinner toward human trials. Meanwhile, they are researching other applications, including removing clots from the brain's smaller vessels and from vessels supplying the heart and lungs and treating peripheral vascular disease. **SM** — *Contact Sarah C.P. Williams at medmag@stanford.edu*

THESE TINY DEVICES ARE MILLI-SPINNERS, WHICH CAN SHRINK A BLOOD CLOT TO 5% OF ITS ORIGINAL VOLUME. THE DEVICE ON THE LEFT IS GUIDED THROUGH VESSELS BY A CATHETER. THE ONE ON THE RIGHT IS A ROBOTIC VERSION THAT CAN SWIM AND NAVIGATE MORE FREELY.

STOPPING KIDNEY STONES AT THE SOURCE

A Stanford nephrologist is developing drugs that could prevent kidney stones

By Sarah C.P. Williams

THE PAIN IS OFTEN DESCRIBED as worse than childbirth — a searing throb when a hard mineral deposit moves from the kidney into the ureter, blocking urine flow. Kidney stones strike about 1 in 10 people, and for those who develop recurrent stones, life becomes a cycle of intense discomfort, bloody urine, emergency room visits and surgical removals.

"For the patients who keep coming back, there's not always a good plan for how to prevent the next stone," said Alan Pao, MD, an associate professor of medicine in the nephrology division. "We can make some tweaks to their diet, and there are some medications that can reduce stones in some patients, but they don't always eliminate the problem."

Pao wants to change that. His lab is developing drugs that raise levels of citrate, a chemical naturally found in the urine that can block the formation of some types of kidney stones. Up to half of all kidney stone patients have unusually low citrate levels, and while a few existing drugs treat the condition, they raise urine pH, which unfortunately can promote a different type of stone. This is particularly problematic for people who have both low citrate and high urine pH — a combination more common in women.

"Most of the time those people are left untreated," Pao said. "I'm in an environment here at Stanford where I can collaborate with medicinal chemists, cellular physiologists and pharmacologists to come up with new treatments to help these people who don't have any other options."

A SOLUTION WITH NO SIDE EFFECTS

MOST KIDNEY STONES ARE MADE OF calcium that combines with other minerals in the urine to form hard deposits. But citrate binds to calcium, preventing that process and keeping the calcium dissolved until it is urinated out harmlessly.

That's why Pao started focusing on a specific protein, called NaDC1 (sodium dicarboxylate cotransporter 1), that is found in kidney cells. NaDC1 is a transporter — a kind of molecular pump — that pulls citrate from the urine back into the kidneys. When NaDC1 is too active, it reabsorbs too much citrate, leaving calcium in the urine free to form stones. By blocking NaDC1 directly, Pao hopes to increase urinary citrate without raising pH — avoiding the side effects that limit current medications.

Working with the Stanford Innovative Medicines Accelerator, Pao's team has developed a screening system that can test how well different chemicals block NaDC1. So far, they've identified two classes of compounds that work well in lab-grown cells. Next, they must determine whether the drugs can reach the kidneys in living organisms. Working with medicinal chemists, they're testing derivative compounds in mice to find formulations that make it to the urine while maintaining their inhibitory effects. If successful, the compounds could be patented and tested in clinical trials.

Pao has also launched clinical studies probing how lab tests might give early warning signs in patients with recurrent kidney stones, for instance, and what types of scans are best used in emergency rooms to diagnose kidney stones.

INSPIRED BY HIS PATIENTS

FOR PAO, THE WORK IN HIS LAB IS closely intertwined with the patients he sees in clinic, who have often exhausted their options to prevent stones. Some have even donated funds to support the research and regularly check in with him about how it's advancing.

"My patients have taught me to always think of ways at the bench to help patients by the bedside," Pao said. "My clinical work recharges my basic science work; it reminds me why we do the science."

One of those patients is Garrett Farwell, a software sales team member from Menlo Park, California. Two years ago, on his 39th birthday, Farwell ended up in the Stanford Hospital's emergency department with a kidney stone.

"It was completely unexpected and caught me totally off guard," Farwell said.

He wanted to do everything he could to prevent another stone but found that he kept getting generic advice: Doctors gave him preprinted information pamphlets without considering his type of stone or individual risk factors.

"When I found out Dr. Pao was doing work that could lead to more precise, personalized and effective kidney stone prevention, I was really inspired," said Farwell, who has since financially supported the research. "Those of us who experience kidney stones want to alleviate the constant anxiety of ending up back in urgent care or the emergency room. New drugs like those being developed by Dr. Pao could be life changing with both physical and psychological benefits." **SM**

— Contact Sarah C.P. Williams at medmag@stanford.edu

Spotlight on Alan Pao

ASSOCIATE PROFESSOR OF NEPHROLOGY

Alan Pao directs the Stanford Kidney Stone Clinic and runs a research program investigating how doctors can better diagnose, track and treat kidney stone disease.

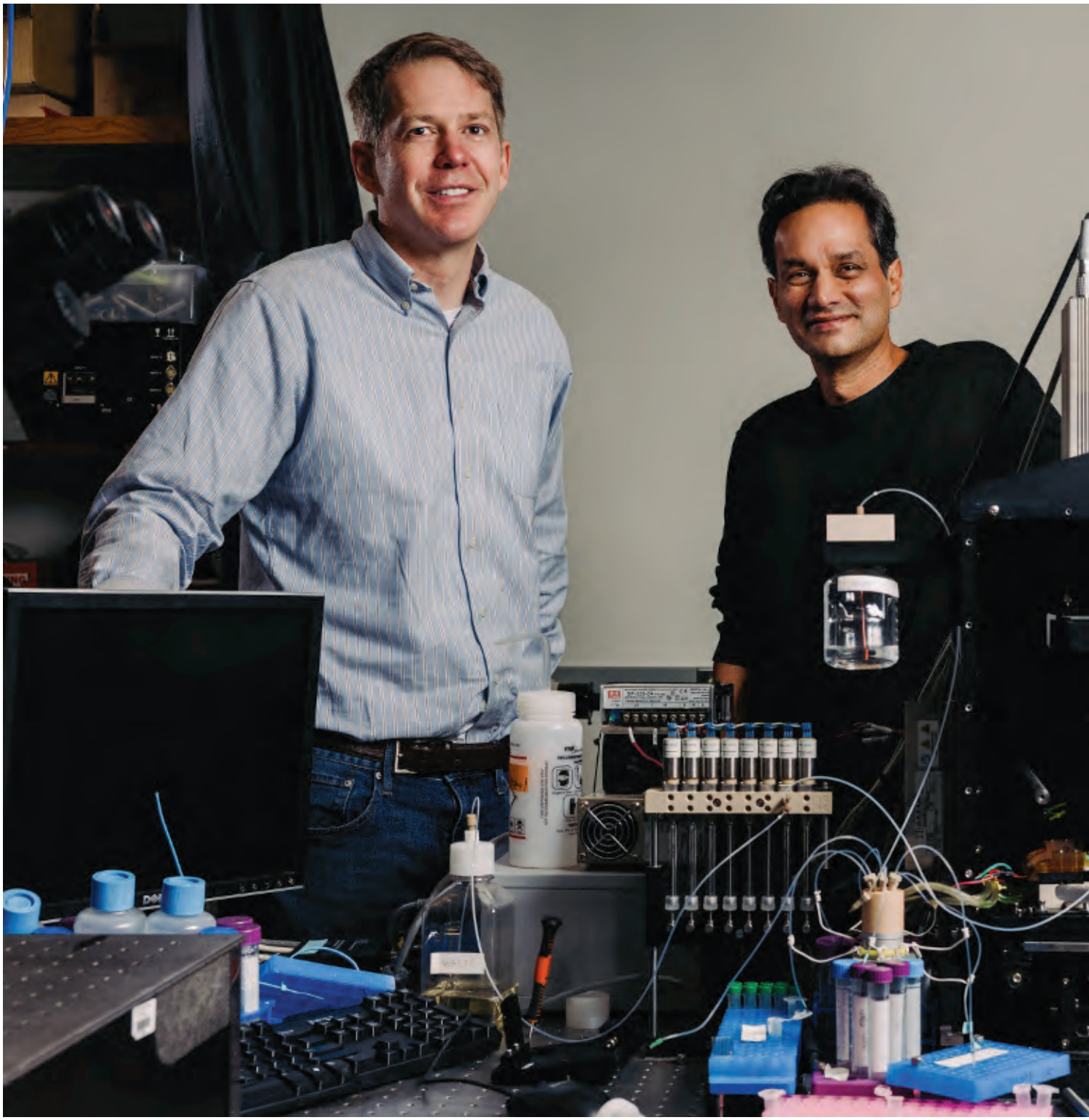
QUICK FACTS:

- Grew up in Chesterfield, Missouri, where he cheered on the "small ball" era St. Louis Cardinals.
- Received his undergraduate degree from Stanford University in 1994 before attending medical school at Washington University in St. Louis.
- Loves to visit art museums around the world. His favorite artists are J.M.W. Turner, Tsukioka Yoshitoshi and Gustav Klimt.

IN HIS WORDS:

"It's incredibly satisfying to be at the forefront of trying to push what's known in a way that could actually lead directly to new treatments for the patients who need them."

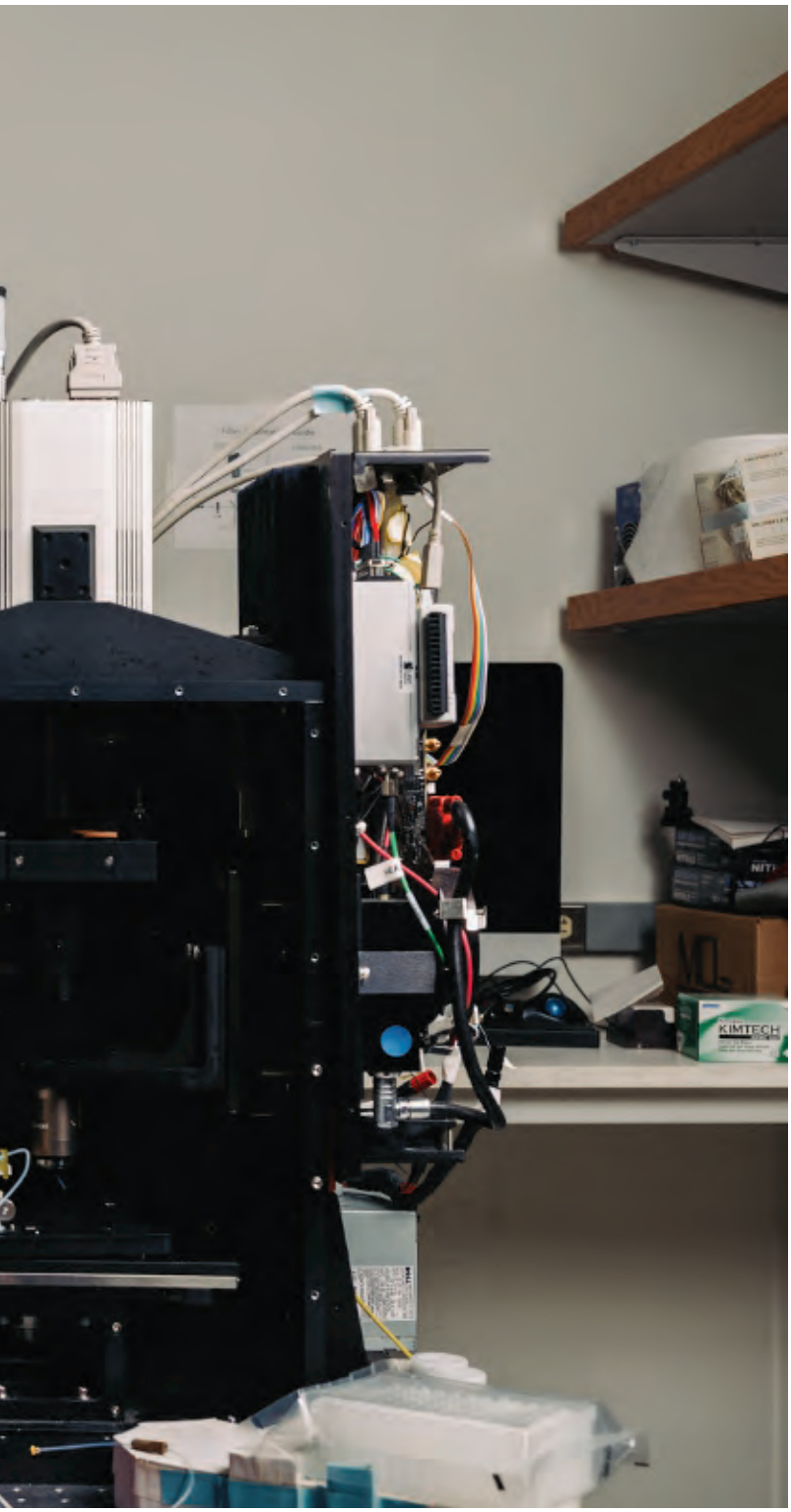
Listen to a ***Health Compass*** **podcast** with Alan Pao at stan.md/health-compass



GAME ON

Crowdsourced molecular computers open a path toward a better TB test

By Andrew Myers



THE HUNDRED THOUSAND OR SO players of the online video game Eterna have not done battle with digital terrorists or built synthetic worlds from imaginary resources. Instead, the players have been competing to design a molecule that would be able to perform specific functions — among them, acting like tiny computers. The molecule those players tinker with is

Spotlight on William Greenleaf

PROFESSOR
OF GENETICS

William Greenleaf links molecular biology, computer science, bioengineering and genomics to understand how our DNA controls when genes turn on or off, and how that affects what's happening in the body.

QUICK FACTS

- Grew up in Rochester, Minnesota.
- His favorite book is *The Making of the Atomic Bomb* by Richard Rhodes.
- He breaks through research roadblocks by "obsessive thinking about said roadblock."

IN HIS WORDS

"My long-term goal is to unlock an understanding of the factors that control how the genetic information is read into biological instructions — to develop a quantitative understanding of how cells maintain, or fail to maintain, their state in health and disease."

Spotlight on Rhiju Das

PROFESSOR
OF BIOCHEMISTRY

Rhiju Das first began to study computational protein folding as a postdoctoral scholar. He launched his Stanford Medicine lab in 2009, and in 2010, he co-founded Eterna, an open-science gaming platform that enlists amateur citizen-scientists to discover ways in which RNA molecules can bend into shapes that solve biological problems.

QUICK FACTS

- Grew up in Bartlesville, Oklahoma.
- Enjoys solving word and jigsaw puzzles with his daughters.
- His motto is Eterna's original tagline, "Played by humans, scored by Nature," "because it reminds us that scientific progress is not for people to evaluate, but for experiments. The whole thing, like life itself, is a cooperative game."

IN HIS WORDS

"What really keeps Eterna players going is the community. They motivate each other. They teach each other. They geek out over the experimental data. That's the coolest part about it all."

RNA, which carries out many roles in the body, most famously, translating DNA's genetic code into proteins.

Molecular computation could reshape modern medicine, said Rhiju Das, PhD, a Stanford Medicine professor of biochemistry and creator of the crowdsourcing Eterna gaming platform, which has the tagline "Solve Puzzles. Invent Medicine."

Das and his colleagues recently used insights from gamers to craft a molecule that could solve a serious public health challenge: identifying cases of active tuberculosis quickly and affordably.

"Molecules that compute can recognize infectious disease states and might also be able to distinguish cancer from healthy tissue. If put into therapies, molecular computers could deliver life-saving drugs directly to a tumor or autonomously edit faulty genes inside cells," Das said.

A quarter of the world's population is infected with the bacterium that causes tuberculosis, one of the leading causes of death from infectious disease. The microbe can lie dormant for years, causing no symptoms and resulting in no spread. But when the immune system can no longer contain the infection, the disease wakes up.

Unfortunately, there's no rapid, inexpensive diagnostic method that can indicate that TB has transitioned to this dangerous active state: Current strategies rely on costly tools to measure ratios of specific gene transcripts in the blood that signal the switch between dormant and active modes. The ratio is far more accurate than simply measuring any single gene, but it is difficult to compute. So Das and his collaborators set a challenge to identify, via the gaming platform, a molecule that can calculate the gene transcripts' ratios. Their thinking: Such a molecule could serve as the basis for a speedy, low-cost blood test. "Now we have a working, inexpensive proof-of-concept test," Das said. "It even creates a little pink line on a piece of paper, just like those antigen tests people use during COVID."

OPTICAL PARTS OF THE KIND USED TO BUILD THE INSTRUMENT THAT COLLECTED THE DATA FOR THE ETERNA PROJECT. THE INSTRUMENT IS PICTURED ON PAGES 50-51.

'IF PUT INTO THERAPIES, MOLECULAR COMPUTERS COULD DELIVER LIFE-SAVING DRUGS DIRECTLY TO A TUMOR OR AUTONOMOUSLY EDIT FAULTY GENES INSIDE CELLS.'

'HUMANS ARE JUST GOOD AT FINDING SHORTCUTS. THE PLAYERS CAN SEE THINGS IN THE MOLECULES AND THE EXPERIMENTS THAT OUR ALGORITHMS CAN'T.'

Stanford Medicine is filing a patent on a technology for nucleic acid amplification developed by Das' lab that is necessary to bring the test to market, and Das is looking for an industry partner to help develop a viable point-of-care test.

"TB kills more than 1 million people each year, yet it is still in need of better and cheaper diagnostics that are adapted to low-resource settings where TB is most prevalent," said Stijn Deborggraeve, PhD, an advocacy adviser for pediatric tuberculosis at Doctors Without Borders. "I encourage the researchers to translate their research into accurate, affordable and user-friendly diagnostic products. We need more innovative strategies to diagnose TB — especially in children."

MOLECULAR LOGIC

THE STORY OF DAS' RESEARCH, however, is not only about the introduction of a groundbreaking test for tuberculosis but also how Das and his team arrived at the solution. They invited an army of citizen-scientists to play the Eterna video game where the objective is to solve molecular puzzles by designing new RNA molecules. Those solutions, in the form of molecular diagrams, are then synthesized and tested for efficacy.

"Humans are key to this work. We can't just ask AI to churn through all the possibilities. Computationally, it's too hard, and we don't have any prior solutions that could be training data for an AI," Das said. "Humans are just good at finding shortcuts. The players can see things in the molecules and the experiments that our algorithms can't. We rely on this community of humans to figure out where the simulations are going wrong and to correct for it in future designs."

The key scientific principle behind Das' work is RNA's role as a sort of switch, changing its structure when binding to specific molecules — for example, a drug, a gene or a hormone. These folding patterns are a form of true-false computational logic, like 1s and 0s in an electronic computer. Fold one direction for true; another for false. "The molecules are computers," Das said.

"The idea is that when the computation reaches a certain threshold, a chemical signal would change the color of a line on a piece of paper," explained William Greenleaf, PhD, a professor of genetics and co-creator of the tuberculosis test.

Eterna's players, for their part, suggest novel molecular designs and predict how they will fold. Sometimes, they succeed; often they do not. Regardless, the results are fed back into the game for refinement until a solution is found. The players are then tasked with more difficult challenges. With the tuberculosis test, they designed a single RNA molecule that acts as a sensor able to detect whether concentrations of three particular RNA molecules are present in the ratio indicative of active TB.

"Humans are able to look at a problem and ask, 'Could this work?' in a way that a computer can't yet," said one of Eterna's top players, Andrew Kaechele, a key contributor to the molecular computation behind the tuberculosis test. "What I find most enjoyable is not just the challenge of complex RNA puzzles but also knowing that my contributions are helping science," he said, noting the game has had a positive influence on his neurodivergence. "Being part of this supportive community has helped me connect with others and feel less isolated, which is incredibly rewarding."

DEEPER IMPLICATIONS

BEYOND TUBERCULOSIS, THE RESULTS OFFER a pathway to a virtually unlimited array of RNA sensors for other conditions ranging from septic shock and cardiovascular disease to cancers.

"The authors chose a difficult problem to solve — TB ratio sensing encoded in a short RNA sequence — and successfully crowdsourced solutions and molecular designs," said Angela Yu, PhD, a professor of biochemistry and molecular pharmacology at Baylor College of Medicine, a peer reviewer of the paper who did not participate in the research. "This study is a great example of the game's ability to approach many challenges at once to expand our understandings of RNA. I think it will have deep implications for future medical applications."

Das said he can imagine molecular computers that go inside cells and weigh the collective signals as a neural network would to distinguish a malignancy from healthy tissue, for instance. A computationally enhanced cancer-killing drug might then turn itself on when in a tumor or off when in a healthy organ, like the liver, where it would otherwise prove toxic. Similar gene-editing molecular computers might one day seek out and repair faulty genes, while leaving healthy genes alone.

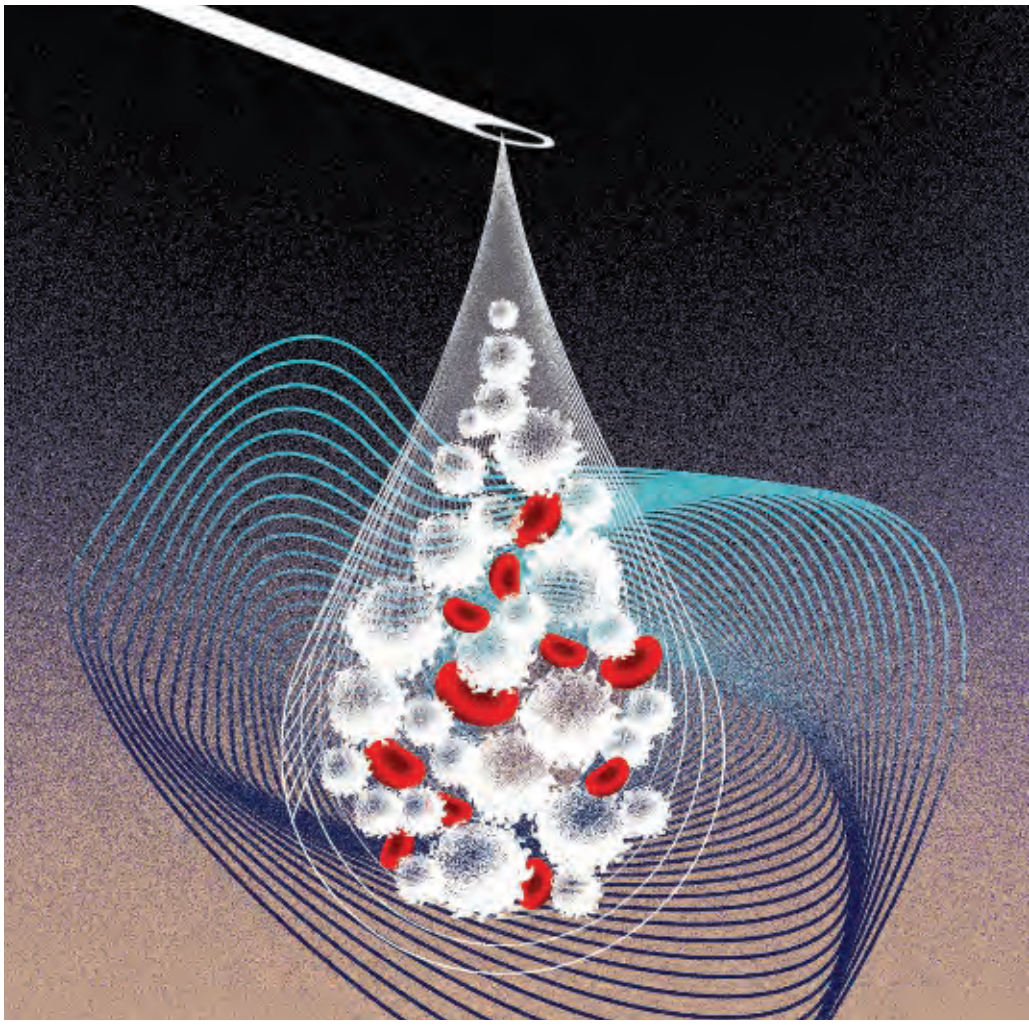
"These molecules are computationally aware of their surroundings and can autonomously calculate next steps," Das said. "You can imagine all sorts of possibilities from there." **SM**

— Contact Andrew Myers at medmag@stanford.edu

A SOFTER LANDING FOR STEM CELLS

A new transplant approach could spare patients chemo and radiation risks

By Erin Digitale



A SUCCESSFUL STEM CELL transplant can be lifesaving. But the procedure itself, which replaces diseased bone marrow with a healthy donor's cells, poses severe hazards, such as causing later cancers, for certain patients.

Now, physician-scientists are testing a way to resolve the conundrum, aiming to provide stem cell transplants free of chemotherapy and radiation. The transplants, commonly used for blood cancers and some immune disorders, typically involve destructive agents to eliminate problematic cells. But for several non-cancerous bone marrow diseases, the toxic approach is likely, quite literally, overkill.

The researchers recently tested a gentler method in children with Fanconi anemia, a genetic disease that makes standard stem cell transplant extremely risky. In a Phase 1 clinical trial published in July 2025 in *Nature Medicine*, the investigators swapped a targeted antibody into the procedure in place of radiation or a risky chemo drug called busulfan.

"We were able to treat these really fragile patients with a new, innovative regimen that allowed us to reduce the toxicity of the stem cell transplant protocol," said Agnieszka Czechowicz, MD, PhD, an assistant professor of pediatrics and co-senior author of the study. The three kids who underwent the new protocol are all at least two years out from the treatment and are doing well.

The first person with Fanconi anemia to experience the new approach was Ryder Baker, of Seguin, Texas, who is now 11. He received a stem cell transplant at Lucile Packard Children's Hospital Stanford in 2022 as part of the clinical trial. Today, the condition "doesn't slow him down like it used to," said Ryder's mom, Andrea Reiley. Before the transplant, she said, "He was so tired, he didn't have stamina. It's completely different now."

And the transplant saved Ryder's life.

"If they don't get a transplant in time, Fanconi anemia patients' bodies eventually will not make blood, so they die of bleeding or infections," said co-first author Rajni Agarwal, MD, a professor of pediatric stem cell transplantation. "The reason I am so excited about this trial is that it is a novel approach to help these patients, who are very vulnerable."

Other authors of the study included co-first author Alice Bertaina, MD, PhD, the Lorry I. Lokey Professor, and co-senior author Matthew Porteus, MD, PhD, the Sutardja Chuk Professor in Definitive and Curative Medicine.

FROM LAB TO TREATMENT

FANCONI ANEMIA INTERFERES WITH DNA REPAIR, impairing production of all three types of blood cells. With few oxygen-carrying red blood cells, patients fatigue easily, lack of white blood cells leaves them vulnerable to infections, and too few blood-clotting platelets lead to bruises and bleeding. By age 12, 80% of patients show signs of a life-threatening complication known as progressive bone marrow failure.

At that point, a stem cell transplant is the best option. To make space for the donor's cells, patients have traditionally received whole-body radiation or busulfan to eradicate their own blood-forming stem cells. But their impaired DNA repair process — which affects every cell in the body — makes people with Fanconi anemia especially vulnerable to DNA damage from busulfan or radiation.

"Right now, nearly all of these patients develop incurable cancers by the time they're 40," Czechowicz said.

So, Czechowicz's team tapped into discoveries about blood-forming stem cells from the lab of Irving Weissman, MD, the Virginia and D.K. Ludwig Professor in Clinical Investigation in Cancer Research and former director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine. Czechowicz joined Weissman's lab as an undergraduate student in 2004, before training as a physician-scientist and establishing her own Stanford Medicine lab.

Czechowicz, Weissman and others investigated a protein on blood-forming stem cells called CD117, which regulates the cells' growth and development. An antibody against CD117 eliminated the cells from mice in a highly targeted fashion, the team found. In the trial, patients received a single IV infusion of a similar, CD117-targeting antibody 12 days before getting donated stem cells.

The researchers made another key change to the transplant protocol, removing the donor's alpha/beta T-cells from the healthy cells given to the patient. (Otherwise, these immune cells can attack the recipient.) This cuts transplant complications and lets patients receive cells donated by someone who shares only half of their immune markers, such as a parent. Alpha/beta T-cell depletion, pioneered by Bertaina and now widely used at Stanford Medicine, also helps the donor's stem cells take over their new home — the hallmark of a successful transplant.

In the clinical trial, the researchers' initial goal was to help Fanconi anemia patients reach 1% donor chimerism, meaning 1% of the bone marrow cells would come from the donor. However, all three patients in the Fanconi anemia trial now have close to 100% of their cells from their donors. "We've been amazed by how well our protocol worked," Czechowicz said.

Since his transplant, Ryder has grown taller, gained weight and become much less susceptible to run-of-the-mill germs, his mom said. "It used to be huge hits when he would get sick at all, and I really don't have to worry about that anymore."

Now in sixth grade, Ryder is using some of his newfound energy to play sports. He loves pickleball and last year received an Up-and-Coming Player award from his school's soccer team.

The researchers are conducting a Phase 2 trial to expand the number of patients and find out if the antibody is essential. (In Fanconi anemia, where the bone marrow is failing, actively removing the patient's blood-forming stem cells may be unnecessary.) They also plan to expand to other conditions, including Diamond-Blackfan anemia, another genetic disease that causes bone marrow failure. And they're investigating how to remove the remaining chemotherapy drugs from the protocol.

"Our ultimate goal is a completely chemo- and radiation-free protocol for all patients who can safely use it, all over the world," Czechowicz said.

After more than three decades of administering stem cell transplants with the traditional approach, Agarwal said she loves explaining to patients' families how much better the new options are. "When I counsel families, their eyes start to shine as they think, 'OK, we can avoid the radiation and chemo toxicity,'" she said. SM — *Contact Erin Digitale at digitale@stanford.edu*

Spotlight on Agnieszka Czechowicz

ASSISTANT PROFESSOR OF PEDIATRICS

Agnieszka Czechowicz is developing safer stem cell transplants to improve treatment options for diseases that harm the body's ability to produce blood and immune cells.

QUICK FACTS

• Born in Gdansk, Poland ("hence my unique name with three Zs"). She was a child when her family immigrated to Minneapolis. Her parents were political refugees.

• Growing up, she was drawn to science, playing with chemistry sets and Petri dishes, then working in University of Minnesota labs. She also loved people, volunteering and working as a lifeguard. "Becoming a physician-scientist felt like the ideal career."

ROSANNE SPECTOR

• While earning her bachelor's, MD and PhD degrees at Stanford University, she considered the school "Disneyland for smart kids" because of its beauty and opportunities. She studied in the lab of Irv Weissman, MD, who discovered blood-forming stem cells, which sparked her interest in blood and immune diseases.

IN HER WORDS

"Being a scientist consists of solving many puzzles, which is something that I have always loved. And working with kids, families and communities affected by rare blood disorders provides an ideal environment to create both immediate and long-lasting impact."

spring forward

IN PURSUIT OF A MEDICAL DEVICE FOR CHILDREN WITH SHORT GUT SYNDROME

By Erin Digitale

When Lydia Garcia was a month old, she suddenly couldn't breastfeed. "She kept throwing up, and a lot of my milk was coming out through her nose," said Lydia's mother, Noemi Garcia. "Then everything just started coming out green."

Garcia and her husband, Ellis, rushed their infant to a hospital near their home in Santa Maria, a small town on California's central coast. Soon Lydia was helicoptered to Lucile Packard Children's Hospital Stanford, where doctors explained that she had signs of an intestinal blockage. "We did surgery to find out what had happened," said James Dunn, MD, PhD, a professor of surgery and division chief of pediatric surgery at Stanford Medicine. "Her intestine had twisted around itself so that a good portion of it had died."

Over a few weeks in November 2023, Lydia underwent a series of procedures to remove several segments of dead tissue, ultimately leaving her with just 9 inches, or 23 centimeters, of small intestine, about 10% of the normal amount for a newborn. "We had all sorts of different doctors talk to us about having a baby with short gut syndrome," Noemi Garcia said. "I had no idea what that was." She learned that Lydia was in a risky spot: In short gut syndrome, patients have so little intestine that they can't absorb enough nutrients to sustain themselves. They can't eat normally, depend on intravenous nutrition and often have a poor quality of life.

At the time Lydia ended up in his operating room, Dunn was in

LYDIA GARCIA LOST MOST OF HER SMALL INTESTINE AS AN INFANT. AN EXPERIMENTAL DEVICE HAS ENABLED IT TO EXTEND.

a challenging spot of his own. He had been trying for more than 20 years to develop a medical device that stimulates regrowth of lost intestine — just what patients like Lydia need. But progress on transforming it from a lab-validated concept to a commercially available device approved for infants was slow.

"It takes just a huge amount of effort to take a relatively straightforward device to the patient's bedside," Dunn said. This is especially true for medical devices intended for children. Each year, the U.S. Food and Drug Administration approves dozens of new devices for adults, versus just a handful for kids. As a result, some aspects of pediatric medicine lag years or decades behind care for adults. The gap is largest for patients with congenital conditions such as heart defects and for diagnoses like short gut that disproportionately affect babies and small children. Several Stanford University experts have formed collaborations with the FDA, with other academic institutions and with people inside Silicon Valley's innovation ecosystem to address the dearth of pediatric medical devices.

"Babies and children deserve the best, most advanced care we can provide, including medical devices tailored to their specific needs," said Paul King, CEO of Stanford Medicine Children's Health. "We want to develop new medical solutions for kids because it opens the door for decades of healthier life."

When he met Lydia and her family, Dunn didn't know if he'd be able to offer the new device to his tiny patient. But he had hopes for Lydia and, in his way, which is plainspoken and kind, he was able to transmit that hope to the Garcias during the harrowing weeks when Lydia was undergoing surgeries to remove dead intestine tissue.

"I remember Dr. Dunn coming in the room and reassuring us that she was going to be OK, she was going to get through this," Noemi Garcia said.

MIND THE GAP?

In the past 20 years, as medical device innovation for adults has accelerated, the boom hasn't reached children. Many new supposedly pediatric devices are first developed for adults, then approved only for adolescents, not smaller patients — an inadequate trickle-down approach.

"If you look at approval of devices specifically for children — for their unique diseases and problems — it's between zero and five per year," said James Wall, MD, a clinical professor of surgery.

The result, said Janene Fuerch, MD, a clinical associate professor of pediatrics, is that care for babies and small children often relies on jury-rigged solutions.

"We use lots of tape," said Fuerch, a neonatologist.

She means this literally: Neonatal nurses learn to handcraft three-dimensional supports from medical tape for catheters and other pieces of equipment. In adult medicine, a sterile, prefab device would be used instead.

"We're treating the most vulnerable population — my patients can't talk or advocate for themselves and sometimes weigh about a pound," Fuerch said. "We're not giving them the most up-to-date and precise medicine, which I find completely unacceptable."

Wall's specialty, surgery, is also full of instances in which pediatric experts must improvise. Concern about this inequity has motivated him and Fuerch to lead Stanford's efforts to accelerate medical device development for children.

The reason so few pediatric medical devices make it from idea to viable product lies in a combination of financial, practical and ethical challenges, the experts said.

"One argument from the medical device industry is that pediatrics involves small markets, and it's hard to rationalize an investment," Wall said. Although children constitute 25% of the population — "and 100% of the future," as Wall likes to say — most kids are pretty healthy.

Insurance reimbursement is another obstacle. To introduce devices for adults, inventors negotiate primarily with Medicare, which insures people 65 and older through a single federal infrastructure. By contrast, Medicaid, which insures about half of U.S. children, is administered by states or counties.

"There are 280 different entities that you need to negotiate with to get reimbursement through Medicaid," Fuerch said. "It's really hard for anybody to be incentivized to do this."

Kids' anatomy and physiology also change dramatically as they grow, presenting design challenges. A one-size-fits-all adult device may require multiple iterations for pediatrics.

In addition, ethical concerns result in inventors in pediatrics facing higher risk-tolerance barriers from regulators. Small

WHY IT MATTERS

- **The medical device boom has not reached children.**
- **Stanford Medicine programs are accelerating pediatric medical device development.**
- **A springlike device is being tested as a way to treat children whose intestines are too short to absorb sufficient nutrients. It works by gently stretching the tissue, which encourages it to regenerate.**

'IF YOU MOVE A CHILD ALONG THE ARC FROM DISEASE TO HEALTH WHEN THEY'RE A YEAR OLD AND THEY GET ANOTHER 80 YEARS OF QUALITY LIFE, IT'S REALLY MEANINGFUL.'

kids can't advocate for themselves, and regulators worry that new devices might cause worsening or lasting problems for children. So, the FDA often requires safety tests in adults before starting trials in children, although this, too, can raise ethical questions, Wall noted.

"It's with good intentions that the FDA says, 'Hey, test this in an adult first,' but it misses the point that you really should test in the population that can benefit, not on random other people," Wall said. Caution is appropriate, he added, "but these children have real problems that need to be solved."

The potential benefits of getting a new device through the approval process are enormous. Effective pediatric medical devices reduce the suffering of kids and their families, cut costs for them and the health care system and, most important, enable children to grow up in better health.

"If you move a child along the arc from disease to health when they're a year old and they get another 80 years of quality life, it's really meaningful," Wall said. "And it probably drives a lot of value for society.

"But who pays for that? It's unclear who is responsible for paying for that lifetime value of a solution in childhood."

STRETCHING WHAT'S POSSIBLE

Dunn became fascinated with the digestive tract's ability to remodel itself 25 years ago, when he was a pediatric surgeon-in-training. For instance, he learned that in intestinal atresia — a congenital defect in which an infant is born with two disconnected segments of intestine, one of which is very small — the small piece quickly expands to normal dimensions after the segments are surgically linked.

"I thought it was super intriguing," Dunn said. "I wanted to learn more about how the intestine does that."

Around the same time, he also met his first patients with short gut syndrome, babies like Lydia who had lost most of their intestines to volvulus (in which the gut twists on itself, cutting off blood supply), or to a prematurity complication called necrotizing enterocolitis.

Newborns usually have about 6 1/2 feet, or 200 centimeters, of intestine. Losing more than half creates lasting problems.

"If they're down to 40 centimeters, we can count on them being on intravenous nutrition for years, and if they're at less than 20 centimeters, it may be lifelong," Dunn said.

Though intravenous nutrition has improved in recent decades — older formulations caused liver failure — it costs more than $200,000 a year and decreases the quality of life for patients and their families. Some children gain enough intestine as they grow to be weaned off IV nutrition, but after months or years of not eating, they are averse to eating by mouth. Intestinal transplants often fail. The gut is one of the body's barriers to the outside world, making it difficult to give a just-right dose of immunosuppressive drugs: "It's a very tight rope to walk between infections and rejection," Dunn said.

What short gut patients really needed, he thought, was more of their own intestine.

His early inspiration hit when he was listening to a lecture about bones. The lecturer explained the procedure for lengthening a bone in someone whose legs are different lengths: You saw the short bone in half crosswise, brace the sawn ends a few millimeters apart, and let new bone cells fill the gap. A few days later, you enlarge the gap by a few more millimeters and repeat the process until the bone is long enough.

Or, as Dunn describes it, "You break the bone and pull on the bone, and it grows."

The idea of pulling on a living tissue lodged in his head.

"It struck me, 'Hey, maybe we can do the same to the intestine. If we stretch it, that mechanical signal will stimulate growth, and you'll have more intestine as a result,'" Dunn said.

FROM LAB TO LIFE

After finishing his training in 2001, Dunn was hired as a surgeon-scientist at the University of California, Los Angeles. For the next several years, his research team tested ideas for treating short gut, eventually designing a spring device that can be sutured inside the intestine to put tension lengthwise along the intestinal wall. Studies in animals showed that each spring could lengthen the intestine by up to four centimeters. After three weeks, when the spring had fully expanded and the su-


HOTLINE
Fluid Warmer

Spotlight on James Dunn

PROFESSOR
OF SURGERY

James Dunn is a pediatric surgeon and a bioengineer who conducts procedures ranging from the head to the toes — with babies who have birth defects as his most frequent patients. In his laboratory he seeks better solutions for children with short gut syndrome, which prevents them from absorbing enough water, nutrients and electrolytes from food and drink.

QUICK FACTS

- Grew up in Taiwan.
- Was inspired to become both an engineer and a surgeon by his childhood experience of seeing his grandfather walk into the room on two legs after an amputation for diabetes. This walk was made possible by a prosthetic device.
- Relaxes by playing beach volleyball most Fridays.
- Strategy for overcoming challenges: "Think about something different. Solutions and ideas will come to you."
- The medical device Dunn developed to lengthen the intestines was inspired by his desire to understand how our tissues adjust to different situations. "The body is just amazing," he said. "It can adapt in ways that are super fascinating."

IN HIS WORDS

"The best part of my job is seeing kids get better."

THE DEVICE DESIGNED BY JAMES DUNN TO TREAT SHORT GUT SYNDROME BY STRETCHING THE INTESTINE, WHICH SPURS TISSUE REGENERATION.

tures holding it in place dissolved, the device passed out in the animal's stool, leaving healthy new intestine. Dunn was granted a U.S. patent for the device in 2015.

But he wasn't sure how to advance his idea to an approved-for-kids, commercially available therapy. In 2016, he came to Stanford Medicine, attracted, in part, by what he could learn from the university's expertise at commercializing medical innovations. He then began collaborating with Thomas Krummel, MD, his predecessor as surgeon in chief at Packard Children's and an experienced medical innovator.

Krummel moved into device development in the early 2010s and soon recognized that, to get their ideas to market, his colleagues had to give up on the idea of being, as he put it, "the Swiss army knife that can do everything."

"Doctors and scientists don't need to be good entrepreneurs; they need to identify and surround themselves with others with the skills they don't have," said Krummel, who is now an emeritus professor in pediatric surgery. He introduced Dunn to a biomedical engineer named Andre Bessette, who became the CEO of the medical device company that he, Dunn and Krummel co-founded, which they named Eclipse Regenesis.

SYRINGES FOR AN ENTERAL FEEDING SYSTEM, WHICH DELIVERS SPECIALIZED LIQUID FORMULA INTO THE SMALL INTESTINE OR STOMACH. IT FEEDS PEOPLE WHO ARE UNABLE TO OBTAIN ENOUGH NOURISHMENT FROM FOOD.

Krummel and Bessette began securing funding for the startup. Dunn had funded his discoveries using grants from the National Institutes of Health, academic societies, patient advocacy organizations and smaller granting mechanisms available to researchers at UCLA. But these pathways wouldn't cover the cost of commercializing their device. Instead, the team used funding from angel investors and from a seed grant from the UCSF-Stanford Pediatric Device Consortium, which receives funds from the FDA.

'DOCTORS AND SCIENTISTS DON'T NEED TO BE GOOD ENTREPRENEURS; THEY NEED TO IDENTIFY AND SURROUND THEMSELVES WITH OTHERS WITH THE SKILLS THEY DON'T HAVE.'

'WE ARE ALL ENTREPRENEURS AND INNOVATORS OURSELVES. WE'VE ALL STARTED PEDIATRIC HEALTH TECH COMPANIES, AND MANY OF US HAVE HAD TECHNOLOGY COMMERCIALIZED AND ACQUIRED.'

They also conferred with private health insurance companies about reimbursement to demonstrate to potential investors that the team's concept for short gut patients was on solid financial footing.

"The status quo of how we care for these kids is so phenomenally expensive," Bessette said. Unlike some pediatric medical devices, which might save money for the health care system — but only in the long run — the spring device could quickly benefit patients and decrease costs for insurers by getting patients off of intravenous nutrition, the team told the insurance companies.

"Our device is a much less expensive path to a permanent solution," Dunn said.

Bessette began seeking FDA permission for a human clinical trial. The FDA requested animal data on device effectiveness from an independent lab, as well as evidence that the company could reliably and safely make the spring device, following good manufacturing practices and using materials that are certified for humans.

"Academics are used to building prototypes in their lab — hand building one-offs — and putting them in animals to look at results. That shows proof of concept, but it's not a clinical device," Bessette said. "It's a big eye-opener for them to see what an actual medical device manufacturing process looks like."

FDA permission for a human trial came in late 2022, but it had a catch: The FDA wanted the developers to start by testing the device in adults. Short gut syndrome can occur at any age, such as in people who suffer a traumatic intestinal injury.

A 36-year-old man was the first to receive the device in a surgery performed at Stanford Medicine in early 2023.

WIDENING THE DEVICE PIPELINE

Wall and Fuerch are leading several efforts at Stanford Medicine to widen the pipeline of pediatric medical device development. The Stanford Mussallem Center for Biodesign offers a variety of fellowships for trainees and faculty, including in pediatrics, to help them understand the nuances of the medical design process and build networks of experts with the knowledge to help with commercialization. (Wall and Fuerch are both alumni of the program's innovation fellowships and help teach the current fellows.)

Wall founded a pediatric device initiative at Stanford Medicine in 2014, which expanded into Stanford's half of the UCSF-Stanford Pediatric Device Consortium, thanks to a 2018 grant from the FDA that made it one of five such consortia around the country. Fuerch now leads Stanford's part of the consortium; participants meet in weekly think tanks and can enter an annual seed funding competition. Eclipse Regenesis received the top prize in 2020.

In 2022, Wall and Fuerch founded Impact1, a pediatric, maternal and fetal device development program within the Mussallem Center. Co-directed by Fuerch and Kunj Sheth, MD, an adjunct professor of urology, Impact1 helps experts from around the world identify medical problems that a new device could solve through an iterative process of brainstorming and designing potential solutions. The group also assists inventors like Dunn who have a well-tested idea they hope to commercialize. In the past five years, Impact1 has supported more than 250 projects in 19 countries. (One of their success stories is a device that secures catheters threaded into a baby's umbilical cord in the neonatal intensive care unit — a sterile, prefab solution that lowers infection risk for a problem previously addressed with lots of tape.)

"We are all entrepreneurs and innovators ourselves," Fuerch said, of the programs' leaders. "We've all started pediatric health tech companies, and many of us have had technology commercialized and acquired."

The experience has helped Fuerch and Wall build a network of professionals they can introduce to up-and-coming innovators, including experts in biomedical engineering, regulatory processes, insurance reimbursement, intellectual property, business planning, hospital administration, venture capital and philanthropy.

Understanding that they need this network often requires a mental culture shift for academics.

"I sometimes say to them, 'You can own 100% of nothing or a part of something. Which do you want?'" Fuerch said. "That's the really difficult thing — letting go and realizing that there's a whole other side to this, the execution, which is just as hard, if not harder sometimes, than the idea itself."

By Lydia's first birthday, in October 2024, she'd been home from the hospital for a few months and was stable on intravenous nutrition. Dunn and his team had already published a peer-reviewed study of the spring device in the *Journal of Pediatric Surgery*, demonstrating its long-term safety when used in an animal model.

Following the FDA's guidance, the team implanted the devices in three adults with short gut syndrome who already needed intestinal surgery. For these patients, the device was safe, and one patient grew enough new intestine to stop using intravenous nutrition. The team published these results in November 2025 in *Surgery*, the first study documenting how the device works in people.

At the same time, the team kept asking the FDA to let them move the device into children. In mid-2024, they received permission through the agency's compassionate use pathway to try the device on their first pediatric patient, a preschooler.

NOEMI AND ELLIS GARCIA AT HOME WITH LYDIA.

'IT DEFINITELY CHANGED US. IT GAVE US HOPE OF HER BEING A REGULAR BABY, A NORMAL TODDLER. SHE'LL PROBABLY BE ABLE TO PLAY SPORTS AND DO ALL OF THAT.'

The pathway allows for case-by-case use of not-yet-approved devices for patients with unusual needs.

A few months later, the same permission was given for Lydia. She received her first spring shortly after her first birthday, and a second in March 2025, becoming the first person to have two springs placed.

She gained a total of about four centimeters of intestine, but that wasn't the only result that mattered.

Both springs were placed in Lydia's terminal ileum, the last part of the small intestine, which has special absorptive properties but was mostly destroyed when her intestine originally lost its blood supply. "People who have ileum can come off intravenous nutrition much more readily than those who do not," Dunn said.

In August 2025, Lydia had a third surgery to reconnect her intestines.

By then, she had spent a significant part of her life in the hospital — she stayed for eight months after the original series of intestinal surgeries — and was not very mobile or gregarious. But after the reconnection surgery, all signs pointed to Lydia feeling better.

"She was a totally different baby. She was climbing up the crib in the hospital," Noemi Garcia said.

"We saw a big difference in her wanting to crawl," her husband said.

Lydia now receives intravenous nutrition and nutrients through a gastrostomy tube to her stomach. (The tube allows nutrients to enter her digestive system gradually, helping her absorb more of them.) And, with help from occupational therapists, her parents are introducing Lydia to solid food.

"She's able to take food by mouth, but not a lot," Ellis Garcia said, likening her to "a baby bird." Lydia tends to gag, but the family knows it will take time for her to gain all the skills of eating. "We'll give her a little portion, and if she doesn't want it, there's no pressure."

The Garcias are grateful that Dunn's decades of research paid off at just the right time for their daughter. Although her journey hasn't been easy, Lydia is now a cheerful, chubby-cheeked 2-year-old who is learning to walk and loves to sing — *Jingle Bells* is her recent favorite.

"It made us happier," Garcia said of the real-world value of medical research to his family.

"It definitely changed us," his wife added. "It gave us hope of her being a regular baby, a normal toddler." The Garcias envision a life where Lydia will enjoy many of the same things as her two older siblings: "She'll probably be able to play sports and do all of that."

Eclipse Regenesis has secured FDA permission for a large clinical trial of the spring device in patients as young as 3 months old. It began in September and is accepting participants in five locations. The FDA will use data from the trial to decide whether to grant final approval to the spring device. Word about the trial has started to spread in the neonatal intensive care unit. Fuerch said she has heard her patients' parents say, "Oh, yeah, and then he'll get the coils," as if this were the most logical thing in the world.

"I always am shocked because it is just so novel," she said. "This is one of the very few places in the entire world where you could have a chance to get off intravenous nutrition and live a more normal life."

"As doctors and surgeons, we take care of one patient at a time but if this spring works, we may be helping thousands of patients every year," Krummel said.

"By developing a new technology that is applied not just in your own hands but also across the world, you maximize the good you can accomplish."

Although they don't know how things will turn out for Lydia, the innovators feel growing optimism for her and for all short gut patients.

"My hope is that she'll be able to come off intravenous nutrition," Dunn said. "More time will tell. If she doesn't, she's still a candidate for additional springs in the future." **SM**

— Contact Erin Digitale at digitale@stanford.edu

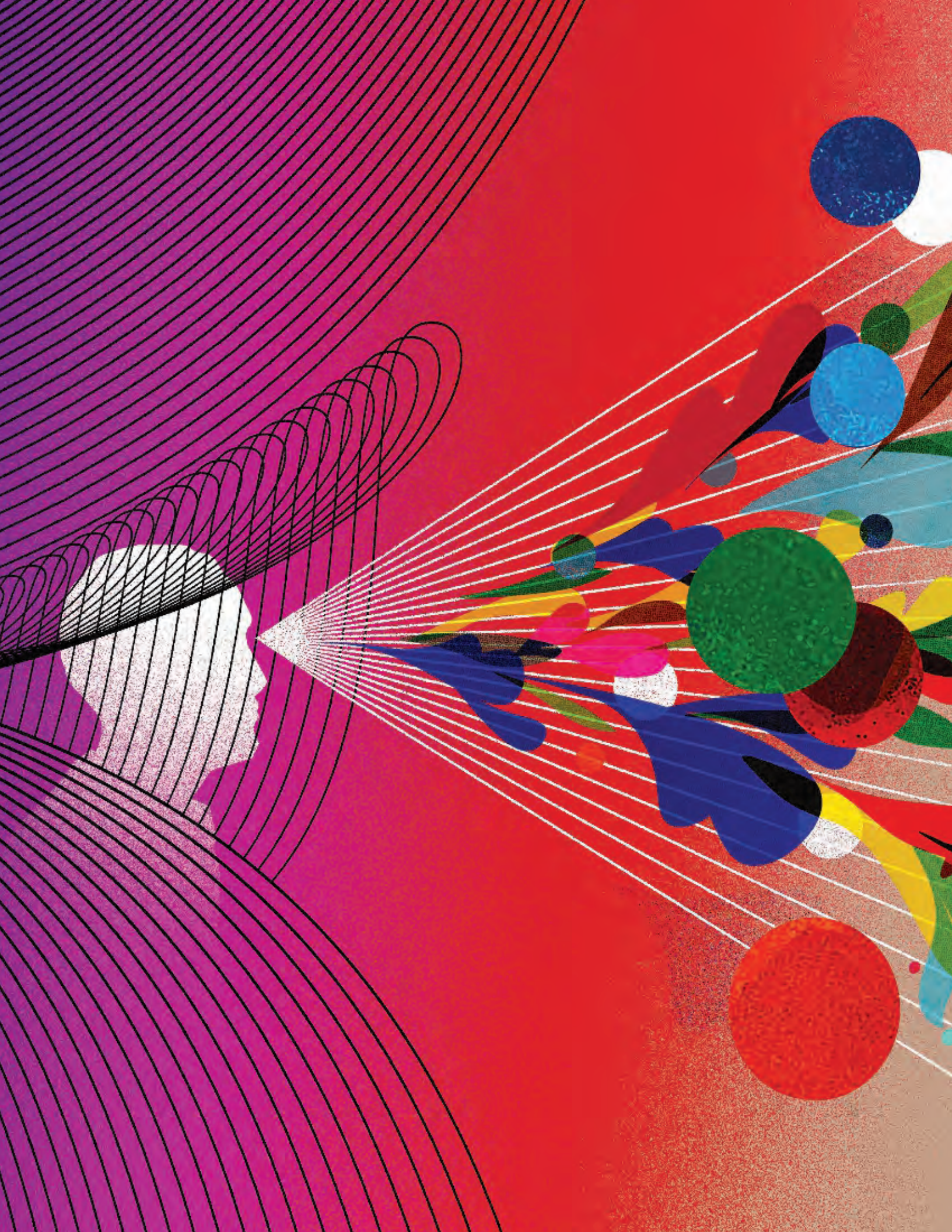
FIVE SUCCESS STORIES IN MEDICAL INNOVATION

from discovery to impact

The story behind a new medical treatment is usually an epic that unfolds over more than a decade. It often begins with the high of a fundamental insight, then moves through the hazards of preclinical studies, fundraising, regulatory hurdles and clinical trials.

There are milestones worth celebrating along the way, but setbacks are common — and most innovations never reach the clinic. Still, some of these tales do have a happy ending, delivering new therapies, devices and diagnostic tools that advance patient care. The articles that follow share a few of those success stories, told through conversations with Stanford Medicine researchers whose innovations are making an impact today.

ILLUSTRATIONS BY BRIAN STAUFFER



A HEART-PROTECTIVE MUTATION IN A PILL

Genetic insights lead to a new treatment for cardiomyopathy

By Rosanne Spector

TRANSTHYRETIN AMYLOID CARDIOMYOPATHY, or ATTR-CM, is a heart disease most of us have never heard of. ATTR-CM is fatal if untreated and — though still underdiagnosed — it is estimated to affect hundreds of thousands of people worldwide. With symptoms that overlap those of other heart conditions, doctors often fail to recognize ATTR-CM as the source of patients' heart failure.

For years, that lack of recognition made little difference because doctors had no approved therapies to stop the disease's progress. Care was limited to lessening symptoms or, in rare cases, a heart transplant.

The outlook for patients, though, has improved tremendously in recent years, due in part to a drug that got its start in a Stanford Medicine laboratory.

That drug, Attruby, was approved by the U.S. Food and Drug Administration in 2024 and is one of three targeted treatments available in the U.S. to treat ATTR-CM. Originally known as AG10, it is the first FDA-approved small-molecule drug patented by Stanford University. As a small-molecule drug, it can be taken as a pill and is able to easily pass through cell membranes to get to where it's needed. The active ingredient, acoramidis, was identified in 2010 by Isabella Graef, MD, then an assistant professor of pathology at Stanford Medicine, now CEO of Shenandoah Therapeutics Inc., and Mamoun Alhamadsheh, PhD, then a research associate at Stanford Medicine, now a professor at University of the Pacific. To develop the drug, they founded Eidos Therapeutics Inc., which was later acquired by BridgeBio Pharma Inc.

In this Q&A, we hear from Graef about how this advance came about and the emotional impact of the success.

WHAT GOES WRONG IN ATTR-CM AND HOW DOES ACORAMIDIS HELP?

Transthyretin, or TTR, is a protein secreted by the liver into the bloodstream that's composed of four identical subunits arranged like a four-leaf clover. In the blood of people with ATTR-CM, the TTR four-leaf clover assembly becomes unstable and falls apart, and the resulting subunits misfold, aggregate and deposit in the heart muscle. These misfolded protein clumps thicken and stiffen the heart walls and lead to heart failure. We designed acoramidis to stabilize TTR.

WHAT LED TO THE INSIGHT BEHIND THE DRUG?

The concept was grounded in human biology. An inherited stabilizing TTR variant protects people who carry that gene by stabilizing the four-leaf-clover assembly. We set out to reproduce that protective mutation pharmacologically.

Our key advance came from the realization that to truly stabilize TTR, a molecule couldn't just "sit" anywhere in the protein's binding channel. It had to engage the bottom of the binding pocket — the same area where the naturally protective gene variant helps hold TTR together. That idea ran counter to how many of the people in the field were thinking, and it led us to build one of the first screening efforts specifically engineered to find the right kind of TTR binders, not just any binders.

Guided by X-ray images to visualize the interaction of TTR with promising molecules identified by screening, Mamoun designed a compound that fit the TTR pocket extremely well and acted like the protective mutation. That is how AG10 — Alhamadsheh–Graef molecule 10, later named acoramidis — was born. This precision approach to protein stabilization, anchored in human biology and executed with rigorous chemistry, was what ultimately made meaningful clinical benefit possible.

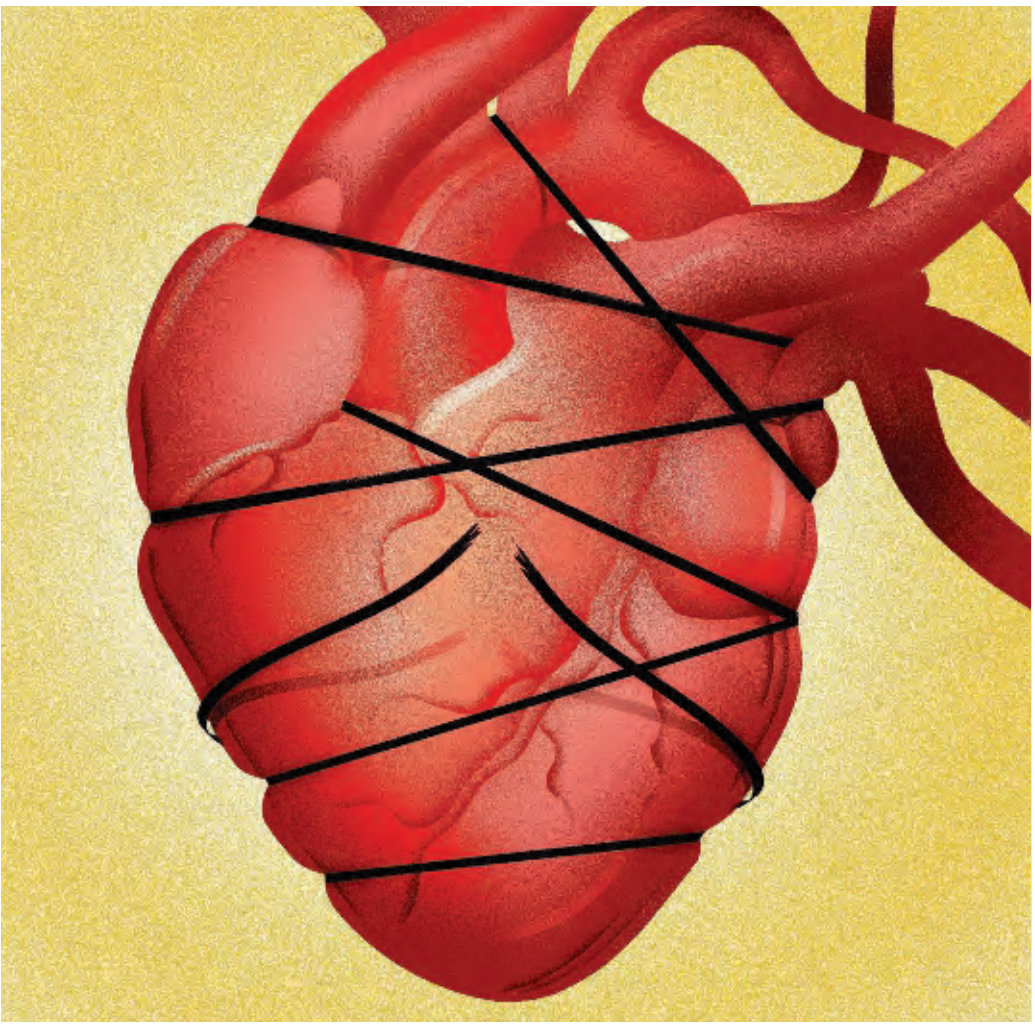
WHAT HAS BEEN THE IMPACT?

Acoramidis is authorized in the U.S., Europe, the U.K. and Japan, bringing a highly effective disease-modifying option into routine cardiology practice for a condition estimated to affect roughly 300,000 to 500,000 people worldwide, many of whom remain undiagnosed. What makes this feel like a true game changer is that the benefit extends to an especially high-risk hereditary subgroup found in about 3.5% of African Americans that's associated with rapid progression and poor survival.

WHAT HAS THIS MEANT TO YOU PERSONALLY?

Protein-misfolding diseases like ATTR-CM are not an abstract interest for us; they are personal. My path toward acoramidis began about 25 years ago, when I diagnosed my mother with a rare and rapidly fatal neurodegenerative protein-folding disease. Even as a physician, nothing in my training prepared me for the devastation of these disorders or the painful reality of how little we could offer. The most honest sentence I could say to my own family and to other families like ours was: "There is nothing we can do." Mamoun was driven by a similar motivation: He lost his mother in her early 60s to Alzheimer's disease.

So, the success of acoramidis isn't only professional satisfaction for us. It feels like a small reversal of that helplessness. It



is proof that stubborn, careful science can convert grief into something that helps other families keep the people they love.

WHAT KEPT YOU MOTIVATED THROUGH THE INEVITABLE FRUSTRATIONS?

Very early on, around 2010, when Mamoun and I were testing whether AG10/acoramidis could stabilize transthyretin, we worked with our clinical colleagues to collect serum from patients with ATTR-CM. I still remember one patient who was desperately sick, waiting for a heart transplant. He asked to speak with the researcher trying to build a better therapy, and when we met, he thanked me — not for a promise, not for a result, but simply for caring enough to keep trying. It was one of those moments where science and humanity collide.

That encounter became my gyroscope. Especially when it was hard to raise funding to develop AG10 into an FDA-approved drug, I would think of him and patients like him. It reminded me why we had to keep going. Mamoun's defining patient encounter came later, during the clinical trials: A patient advocate who had lost her mother to hereditary ATTR told him that she was fighting not just for herself, but for her children who might carry the same mutation.

And I am deeply grateful I wasn't doing it alone. Mamoun was there from the beginning — brilliant and steady — turning our ideas into molecules. Together we carried the emotional weight of a project that was never just academic for either of us.

WHO WERE THE ESSENTIAL COLLABORATORS?

When Mamoun and I began working side by side almost 20 years ago, something clicked in a way that's rare in science. We brought two complementary disciplines to the same bench — his precision and inventiveness as a chemist, and my perspective and drive as a physician-scientist grounded in human disease and patient need.

We were also carried forward by people who chose to believe early. The support and mentorship of the team at Stanford Medicine's translational research program SPARK, especially Daria Mochly-Rosen and Kevin Grimes, were pivotal; they helped us build the foundation when the project was still purely academic. Stanford Medicine clinicians Michaela Liedtke and Ron Witteles anchored the work in the realities of ATTR-CM for patients. Later at Eidos, CEO Neil Kumar, CSO Uma Sinha, and the clinical team provided the expertise to carry AG10/acoramidis through global trials and ultimately to approval. **SM**

'IT IS PROOF THAT STUBBORN, CAREFUL SCIENCE CAN CONVERT GRIEF INTO SOMETHING THAT HELPS OTHER FAMILIES KEEP THE PEOPLE THEY LOVE.'

AN OINTMENT TO QUELL ATOPIC DERMATITIS

Quieting the intense itch of a common skin condition

By Krista Conger

THE YEAR WAS 1999 AND LUCY SHAPIRO, PHD, was deeply troubled about the increasing ability of disease-causing microbes to defy the drugs used to thwart them. A professor of developmental biology at the Stanford School of Medicine, Shapiro responded by focusing on new anti-infective drugs.

Shapiro collaborated with Stephen Benkovic, PhD, a professor of chemistry at Penn State University, and Steve Baker, DPhil, at the time a postdoctoral researcher in Benkovic's lab, who were two of the most visionary chemists she knew.

Their plan: At a drug's active site, swap out carbon atoms for boron — its closely related neighbor on the periodic table. The logic: Carbon atoms are often at the active site of drug molecules. Replacement with boron would exploit boron's chemical properties, which might knock out pathogens in new ways.

In 2002, Benkovic; Shapiro; and her husband and colleague, Harley McAdams, PhD, a professor of developmental biology, emeritus, co-founded Anacor Pharmaceuticals Inc. to develop boron-based drugs. Their most recent success is crisaborole, an anti-inflammatory that received approval in 2016 from the Food and Drug Administration to treat the most common form of eczema. Pfizer acquired Anacor shortly before the approval.

Applied as an ointment, crisaborole helps calm skin inflammation and itch due to mild-to-moderate cases of atopic dermatitis — a condition that predominantly affects children. Unlike steroids, the most common treatment for the condition, crisaborole is safe for long-term use.

In this Q&A Shapiro answers our questions about crisaborole.

WHAT'S SPECIAL ABOUT BORON-BASED DRUGS?

The chemistry of boron is unique in its ability to change a compound's molecular shape, allowing it to access unusual targets. Moreover, the presence of boron in a compound improves its ability to permeate the cell membrane.

HOW DOES CRISABOROLE WORK?

It blocks an enzyme that interferes with the body's natural process for calming inflammation. That enzyme, phosphodiesterase-4, or PDE4, breaks down a chemical, called cyclic AMP or cAMP, that generally reduces inflammation. In short, when crisaborole blocks PDE4, it allows cAMP to do its calming work.

YOU WERE TRYING TO DEVELOP AN ANTI-INFECTIVE. HOW DID YOU DISCOVER CRISABOROLE'S ANTI-INFLAMMATORY POTENTIAL?

It was a surprise. We had created a library of small chemical compounds in which carbon at the active site is replaced by boron. And we tested these against all manner of bacteria and fungi to identify any that could kill the pathogens. We also tested the compounds on human cells to be sure they didn't adversely affect their growth or function.

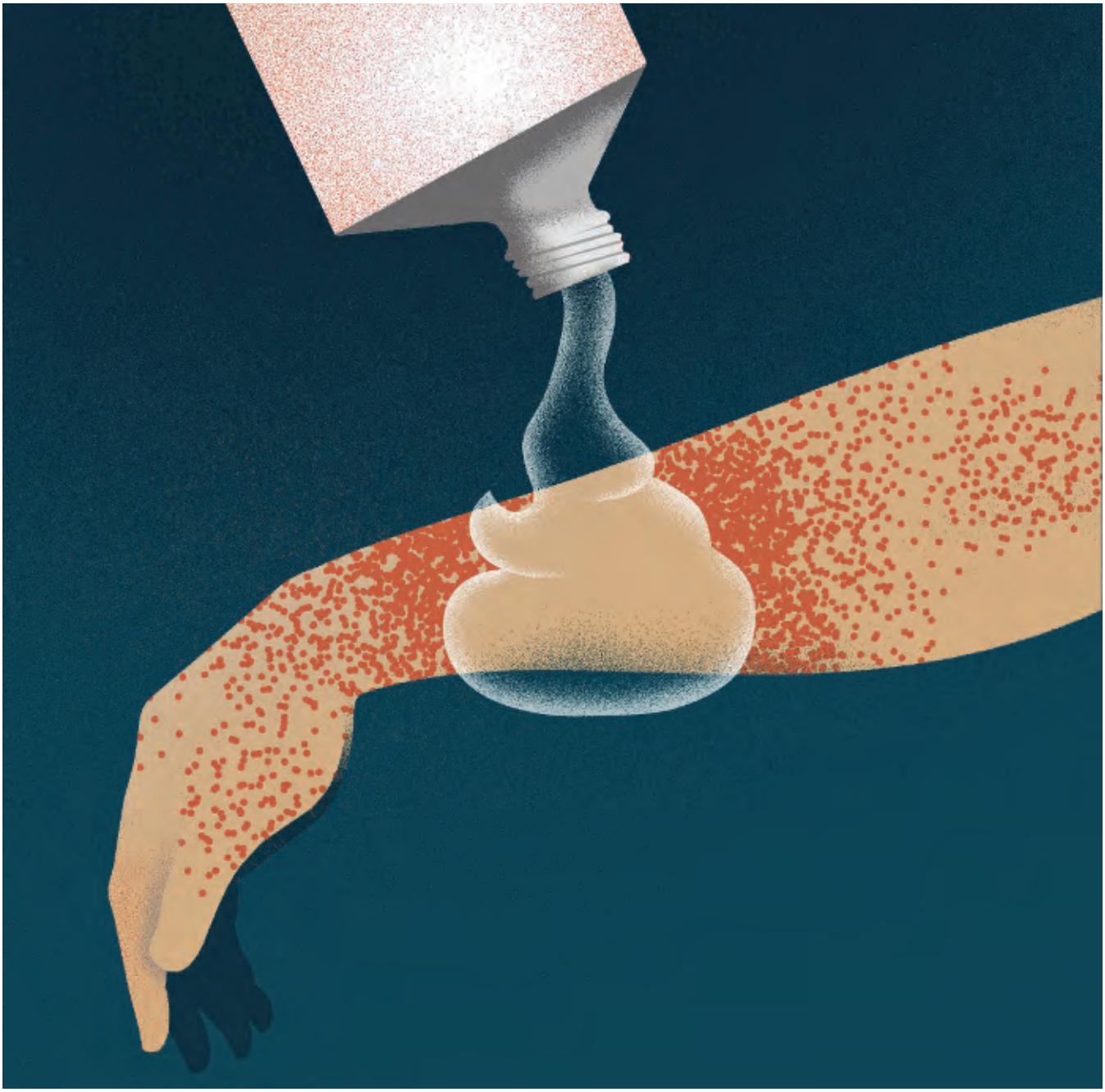
One of the small compounds was crisaborole, applied topically, and that was pretty good at stopping strep infections of the skin in studies in the lab. Children with atopic dermatitis are susceptible to strep infection, so we conducted a Phase 2 clinical trial of crisaborole in that population.

Although it showed only mild effectiveness against strep in the participants, the trial showed — unexpectedly — that it was an effective anti-inflammatory. We established that this compound is a unique PDE4 inhibitor.

WHAT CHALLENGES DID YOU ENCOUNTER: SCIENCE, DESIGN, REGULATORY, FUNDING?

We faced periodic challenges from all four, but we were fortunate enough to have an unusually capable CEO in David Perry, whose drive pushed all of us to overcome the roadblocks. Although we received our seed funding to develop new anti-infectives from the U.S. Department of Homeland Security (this was in 2001, after the bombing of the World Trade Center and the anthrax scares), I soon realized I wanted a company that designed drugs that would be available to everyone, worldwide. We live in a global village, and if we can't stop an outbreak of disease in Nigeria or Toronto we are not going to be able to control it here. So, Steve and I sought subsequent financial support for Anacor from venture capitalists.

'WE HAVE RECEIVED NUMEROUS LETTERS FROM PARENTS WHO HAVE BEEN ABLE TO RELIEVE THE TERRIBLE RASH AND ITCHING IN THEIR YOUNG CHILDREN.'



HOW DOES IT FEEL TO HAVE THIS TREATMENT AVAILABLE FOR PATIENTS?

Deeply satisfying. Because crisaborole is a nonsteroidal treatment for atopic dermatitis, the impact has been considerable at the pediatric level. We have received numerous letters from parents who have been able to relieve the terrible rash and itching in their young children. As one mother said, "My daughter has finally been able to sleep at night."

WHAT'S NEXT?

The success of crisaborole has led to the investigation of other PDE inhibitors, especially in neurological disease. In parallel with the discovery and development of crisaborole, Anacor also developed the first new antifungal in 25 years — tavaborole, which received approval from the FDA in 2014 to treat nail fungal infections.

At our current company, 5Metis Inc., boron chemistry is being applied to combat fungal infections of agricultural products, with significant success in the control of black sigatoka, a fungus that is killing the Cavendish banana worldwide. In addition, we are hoping to apply boron chemistry to antibiotic-resistant tuberculosis. **SM**

A TOOL TO DIAGNOSE SEPSIS

Speeding the time to treatment when minutes matter

By Rosanne Spector

IN THE UNITED STATES, at least 1.7 million adults develop sepsis each year and at least 350,000 die as a result, according to the Centers for Disease Control and Prevention. The condition is a life-threatening emergency in which the body's extreme response to an infection damages its own tissues and organs.

Purvesh Khatri, PhD, a professor of computational medicine, set his sights on developing the first rapid molecular sepsis test and in 2016 co-founded Inflammatix Inc., which licensed his Stanford Medicine research to commercialize it. TriVerity was approved by the U.S. Food and Drug Administration in 2025.

The assay helps doctors make better decisions in emergency situations, when it's not clear whether a patient has sepsis. Other tests that are in use take hours to days to produce definitive answers, so clinicians must make educated guesses based largely on symptoms. The new test can use one blood sample to quickly tell whether the patient has an infection, what kind it is and how serious it's likely to be — all within 30 minutes.

In this Q&A, we asked Khatri, a professor of computational medicine, to fill us in on the test and its trajectory of success.

HOW DOES THE TEST WORK?

It assesses how the patient's immune system is responding — measuring a panel of 29 mRNA molecules from a small blood sample — and applies machine learning to interpret those signals. Instead of hunting for a single pathogen, it reads the body's response and translates it into actionable insight.

WHAT SPARKED THE IDEA?

Tim Sweeney, MD, PhD, a postdoc in my lab and a co-founder of Inflammatix, was a resident in general surgery at Stanford Medicine from 2011 to 2015. The need became apparent during his time treating patients in the emergency department, surgery ward and intensive care unit.

The computational framework for how to get it done — combining multiple cohorts to find repeatable signals in the immune system — came from the method I had developed for an analysis of heterogeneous data.

The idea that immune response can diagnose infection without looking for a pathogen came from an analysis carried out by Charles Liu, who was a high school summer intern in my lab in 2013. His analysis of more than 8,500 blood samples from more than 40 diseases showed that a patient's immune response differed by the type of immune insult, such as infection, organ transplant, autoimmune disease or cancer.

WHAT KEY SCIENTIFIC OR ENGINEERING ADVANCE MADE THIS POSSIBLE?

Two things came together to turn noisy biology into clear guidance: the ability to measure many immune signals at once from a tiny blood sample and a computational framework that can spot patterns humans can't in highly heterogeneous datasets.

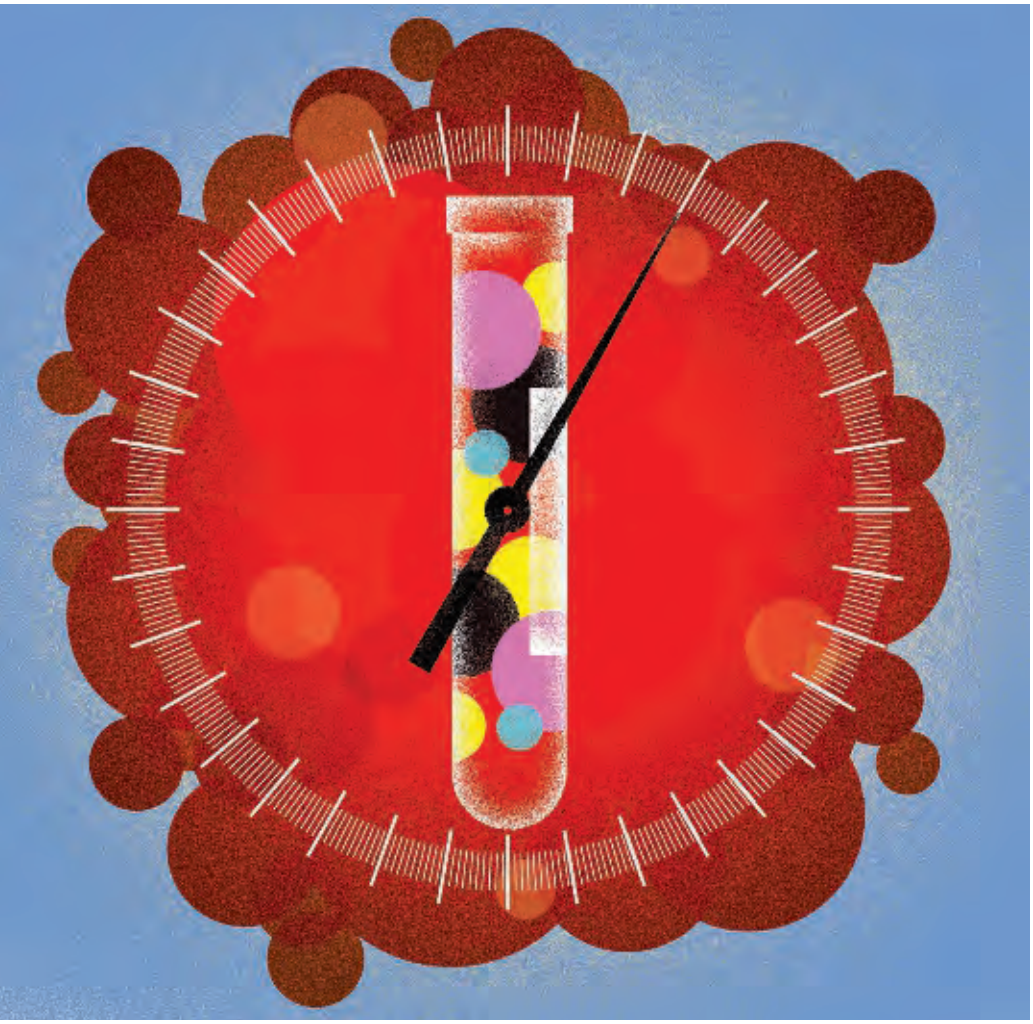
The test platform on which TriVerity runs is called Myrna (think: My RNA) and it took about nine years of development. The test can measure up to 64 genes simultaneously from a single blood draw, making it the highest multiplexed platform to date with FDA clearance.

The computational framework leverages machine learning and AI to flip the traditional biomedical research paradigm. Traditionally, those of us looking to create diagnostic tests believed a test would be a failure if it was built on data from a variety of sources — with biological differences between people, clinical differences due to their medical conditions and technical differences depending on how the data is collected, for example. Our framework turns this curse into a blessing in disguise to identify a signal that persists despite heterogeneity.

WHAT WAS THE TOUGHEST CHALLENGE AND HOW DID YOU OVERCOME IT?

Disbelief. Clinicians have always dreamed of being able to read out immune signals, but solving the technical challenges and aligning commercial incentives were thought to be impossible. I can't tell you the number of times we were told we would not be able to find a stable signal in the highly variable immune response and would not be able to build a sample-to-answer system with the 30-minute turnaround time. In addition, hundreds of millions of dollars have been spent on sepsis tests (usu-

'CLINICIANS HAVE ALWAYS DREAMED OF BEING ABLE TO READ OUT IMMUNE SIGNALS, BUT SOLVING THE TECHNICAL CHALLENGES AND ALIGNING COMMERCIAL INCENTIVES WERE THOUGHT TO BE IMPOSSIBLE.'



ally tests looking for bacteria in the blood), and they have all been commercial failures. In fact, someone once told me, "Sepsis is the graveyard of startups."

HOW DID YOU SHOW IT WORKS AND IS SAFE?

We had a successful trial designed to provide the evidence needed for FDA approval of the test's accuracy, sensitivity and specificity. The trial [published in September 2025 in *Nature Medicine*] enrolled 1,222 patients from 22 emergency departments in the U.S. and Europe. Most importantly, we were able to show that the test we developed could have substantially reduced the number of missed infections and patients who were judged to be clinically stable but were, in fact, critically ill.

WHAT EARLY OUTCOMES OR ADOPTION ARE YOU SEEING?

Several health care systems have implemented the test, and the results are extremely encouraging. In several implementations, we are seeing faster decisions, more confidence in care plans and substantially fewer unnecessary admissions.

CAN YOU SHARE A PATIENT STORY THAT CAPTURES ITS REAL-WORLD IMPACT?

Here is one of many: A man in his 60s arrived at the ED with a fever and shortness of breath. The team was working him up for pneumonia when the test score came back as low bacterial, low viral and high illness severity. Surprised that this was noninfectious, they ordered a heart attack workup — and it turned out he was having a heart attack. The patient had a good outcome. Thank goodness they didn't treat a heart attack with antibiotics!

WHAT'S NEXT?

First, we are improving the accuracy of the test and demonstrating its utility in improving patient care. Second, we are working to demonstrate that the test can also help identify which intensive care unit patients with sepsis would respond well to immune modulatory therapy — and which would have negative consequences.

HOW DOES IT FEEL TO SEE THIS TEST FDA-APPROVED AND AVAILABLE TO PATIENTS?

I have several overwhelming emotions. As someone who grew up in India and trained as an electronics engineer, I never imagined having opportunities to work on a disease that, according to the World Health Organization, accounts for 20% mortality globally each year. So, this success has given me a sense of fulfillment and accomplishment — to be able to go from an idea, which many people told us could not be done, to an FDA-cleared test with a potential for global impact. More importantly, it is humbling to realize how lucky I have been. I am eternally grateful for the singular privilege of mentoring and working with so many talented individuals both in academia and industry who committed to making that idea a reality. **SM**

Listen to a ***Health Compass*** **podcast** with Purvesh Khatri at stan.md/health-compass

A PACEMAKER FOR THE BRAIN

Treating Parkinson's by responding to the brain's rhythms in real time

By Sarah C.P. Williams

HELEN BRONTE-STEWART, MD, a professor of neurology and neurological sciences, has spent two decades studying what goes awry in the brains of people with Parkinson's disease. Recently, her work led to adaptive deep brain stimulation — a new technology to treat the disease.

Parkinson's, a progressive neurodegenerative disorder, disrupts the brain's ability to control movement, leading to slow movement, stiffness, tremors, and gait and balance impairment. These symptoms arise in part because certain brain regions develop abnormal rhythms of electrical activity. Since the 1990s, clinicians have used deep brain stimulation to deliver electrical pulses to the brain in hopes of restoring normal activity. But traditional systems deliver constant, around-the-clock stimulation to the brain, unable to adjust during sleep, changes in activity, or when a patient's medication is kicking in or wearing off.

Working with medical device company Medtronic, Bronte-Stewart, the John E. Cahill Family Professor, led the development of adaptive deep brain stimulation — a system that works more like a cardiac pacemaker, continuously monitoring the brain's electrical activity and adjusting stimulation immediately. Electrodes are implanted into areas of the brain affected by Parkinson's disease and the wires attach to a small, battery-powered device on the chest that controls the system. The U.S. Food and Drug Administration approved the therapy in February 2025.

In this Q&A, we asked Bronte-Stewart to walk us through the innovation and its journey from lab to clinic.

HOW DOES ADAPTIVE DEEP BRAIN STIMULATION WORK?

Think of it as a brain pacemaker. Traditional deep brain stimulation delivers constant electrical pulses 24/7, unable to sense what the brain is doing — like early cardiac pacemakers that couldn't sense the heart rhythm. In Parkinson's, a brain arrhythmia in the motor circuits jams the signals that result in normal movement. Traditional stimulation brings the brain arrhythmia down, but in a one-size-fits-all way with no feedback. Imagine taking two blood pressure medications but never measuring your blood pressure; you could end up too low or too high. That's what happens with traditional deep brain stimulation. Adaptive stimulation, on the other hand, senses a person's brain rhythms and adjusts in real time, delivering electrical stimulation only when needed and at just the right level.

WHAT SPARKED THE IDEA?

When I first started collaborating with Medtronic, we could deliver brain stimulation but we couldn't listen to the brain in return. I remember going on a trip to visit their headquarters and they left a pamphlet in my hotel room about the history of cardiac pacemakers. I'll never get those images of the earliest pacemakers out of my mind — people with wires leading to their chests from these huge carts of equipment. Just seeing the fortitude it took to develop today's adaptive cardiac pacemakers encouraged me to keep trying with the brain. I kept thinking, we're 10 or 15 years behind cardiology, but we can get there.

WHAT KEY ADVANCE MADE THIS POSSIBLE?

Two things came together. First, we had to figure out which brain signals actually mattered. My lab and others' built tools to precisely measure movement, then synchronized those with brain recordings from patients doing complex tasks. That let us figure out which brain signals corresponded to which movements. Through a collaboration called the Brain Radio project, groups around the world built a data bank which ultimately revealed that one type of signal, called beta oscillations, could be used to most accurately monitor patients.

From there, it was the technology. Medtronic developed a sensing-enabled neurostimulator that could deliver stimulation and record brain signals continuously. Once we identified the key brain signals, we could start testing their adaptive device.

WHAT WAS THE TOUGHEST CHALLENGE?

One of the biggest challenges is getting clinicians to use deep brain stimulation in the first place. There's been a disconnect going back decades. Early surgical procedures to treat Parkinson's led to some bad outcomes, and so neurologists really shied away from them. Then, the incredibly successful drug levodopa

'MY LAB AND OTHERS' BUILT TOOLS TO PRECISELY MEASURE MOVEMENT, THEN SYNCHRONIZED THOSE WITH BRAIN RECORDINGS FROM PATIENTS DOING COMPLEX TASKS.'

came along in the late 1960s, and that whole surgical era just completely went away. When deep brain stimulation came back in the 1990s, I think some of that wariness among neurologists lingered. Many clinicians still don't realize that deep brain stimulation is one of the safest neurosurgical procedures, and they wait too long to refer their patients. But as technologies like adaptive stimulation become available and word gets out about how well they work, that's slowly changing.

HOW DID YOU SHOW IT WORKS AND IS SAFE?

Initially, we were doing all this work in the lab with research devices, so we were using the adaptive technology on patients only for short periods of time at once. I was working with Medtronic on a feasibility study that would tentatively take it a bit further, but then they found out the regulatory bodies in the U.S., Canada and Europe were all on board with getting this out to patients. So the company shut down the feasibility plan and went straight to a full international trial where we sent people home for 30 days with the device, brought them back, then sent them home for another 30 days. That was the ADAPT-PD trial, published in *JAMA Neurology* last fall. We enrolled 68 patients, and the results were really encouraging. The trial showed that

adaptive stimulation was safe and provided comparable symptom control to traditional stimulation — the key was proving it worked just as well while people were at home going about their daily lives.

WHERE IS IT BEING USED TODAY?

It's now approved in both the U.S. and Europe. Europe got approval earlier and really picked it up quickly — I heard from colleagues that some centers had multiple patients on it within weeks. In the U.S., it's been available since the FDA approval in February 2025. Anyone with the Medtronic sensing-enabled system can now try it with their neurologist. It's still early, but the adoption has been encouraging.

HOW HAS THIS IMPACTED PATIENTS' LIVES?

What I'm hearing from patients is this overall sense of feeling like their disease is being treated better. It's hard for them to always pinpoint exactly why, but they report fewer side effects and more stability throughout the day. Some are noticing improvements in their most affected symptoms including tremors and sleep. The most telling thing is that 98% of patients who tried it in the trial chose to stay on it. That speaks to how well it's working in people's daily lives.

WHAT'S NEXT?

We're just at the tip of the iceberg. We're relying only on beta oscillations in these first adaptive devices, but there are other frequencies of brain signaling that we're investigating now that might let us fine-tune and personalize brain stimulation even more. My lab is also moving into Parkinson's and cognition — looking at new ways of stimulating the brain that could help with thinking and memory. There's also potential for using this technology in other conditions like obsessive-compulsive disorder and depression. The key is that we've unlocked this door of having adaptive technology that uses brain signals to drive stimulation. That opens up a whole new world of research.

HOW DOES IT FEEL TO SEE THIS TECHNOLOGY REACH PATIENTS AFTER TWO DECADES OF WORK?

I tentatively predicted this would happen — that eventually residents and fellows would look at us in shock and say, "You what? You used to stimulate the brain without recording it?" But watching it become real has been joyful. We've gone from complex lab equipment to a system that's just easy and normal; my students can pick up a tablet and intuitively figure out how to see a patient's brain recordings and adjust the settings on a brain stimulator. Most importantly, this is out there in the world, helping people. That's the best part. **SM**

GENE THERAPY FOR EPIDERMOLYSIS BULLOSA

Providing long-term relief from a debilitating skin blistering disease

By Erin Digitale

STANFORD MEDICINE SCIENTISTS HAVE developed two gene therapy treatments for a rare skin disease that causes severe blistering. Patients born with dystrophic epidermolysis bullosa, or EB, lack the gene for collagen VII, a protein that "staples" the skin together. Without it, their skin forms painful blisters at the slightest touch, many of which become long-term wounds.

Peter Marinkovich, MD, an associate professor of dermatology and director of Stanford Medicine's Blistering Disease Clinic, has devoted his clinical and scientific career to helping EB patients lead better lives. In this Q&A, we asked Marinkovich to describe the gene therapies he helped develop.

WHEN YOU STARTED, WHAT WAS MISSING FROM OUR TOOLBOX FOR EB PATIENTS?

These patients live with pain all their lives. From day one, they have blisters on their bodies and pain that would incapacitate anyone, but they somehow find a way to live with it. They also have to live with exaggerated scarring. In particular, their hands can get scarred to the point where each hand is like a mitt encased in skin. This severely limits their daily activities.

For decades, all we could offer was supportive care — good wound care and good nutrition, because the turnover of their skin meant they needed nutritional support. But the blistering would still happen. We were helpless to stop it.

WHAT KEY SCIENTIFIC ADVANCES MADE THE NEW GENE THERAPIES POSSIBLE?

When I was recruited to Stanford in the 1990s by Gene Bauer, an EB expert, researchers elsewhere were making great progress on identifying gene mutations responsible for EB. Gene said, "Instead of characterizing mutations, why don't we devote our energy to developing therapies from these advances?"

We took a technology developed for burn victims: You can grow large amounts of skin from the patient's own keratinocytes, a key type of skin cell. We also included a gene transfer step. Paul Khavari and his group, especially a researcher in his lab named Zurab Siprashvili, did one of the most difficult parts of this process: They made a viral vector that accommodates the very large

collagen VII gene. We could get the corrected gene into the patient's skin biopsy and multiply the cells to make a skin graft.

HOW DID YOU SHOW IT WORKS AND IS SAFE?

We started a clinical trial of the gene-corrected skin grafts around 2014, published results from the first four patients in *JAMA* in 2016, and got permission from the Food and Drug Administration to conduct a larger trial. I led this trial with Al Lane and, after Al retired, Jean Tang. We licensed the technology to Abeona Therapeutics Inc., which continued to prepare for a Phase 3 trial. That took a few years.

In the meantime, I started working on another technology, a topical gel gene therapy. It also uses a viral vector to deliver the corrected gene, but it's less invasive. We just put this gel on the wound. There's no manufacturing a graft, no going to the operating room or being hospitalized. Trials led by my team showed that the gel helped to durably heal EB wounds. In 2023, the gel, which is called beremagene geperpavec-svdt or B-VEC and is made by Krystal Biotech Inc., became the first FDA-approved gene therapy for epidermolysis bullosa.

The skin grafts, known as prademagene zamikeracel, received FDA approval in 2025. In the Phase 3 trial for the grafts, Jean Tang was the principal investigator evaluating wound healing and pain, while I was co-principal investigator ensuring that the grafting and other aspects of the trial were properly performed. We showed that the grafts helped heal patients' wounds and significantly reduced their pain, itching and blistering.

WHAT LONG-TERM OUTCOMES ARE YOU SEEING?

We now have more than five years' experience with each of the gene therapies for several of our clinical trial participants. Some have cleared up about 80% of the wounds on their bodies. It's a huge, life-changing event.

We're starting to see systemic effects. For the kids and teens, they grow more as their blisters clear, because their skin no longer demands so many nutrients. Chronic wound inflammation also caused anemia; as the wounds lessens, their hemoglobin increases, and they stop needing iron transfusions. And with healing, they are having much less pain. It's so nice to see that.

WHAT'S NEXT?

The skin grafts are effective, but the process of getting them is complex, requiring surgery and a one-week stay in the hospital. For this reason, I recommend the gene therapy gel as a first step and, in severe patients who have more wounds than the gel can accommodate, I recommend using the gene therapy skin grafts as well as the gene therapy gel.

Now my team is working on an additional option for patients: a treatment that's intermediate between these two therapies.

We're excited that these treatments that were born and came to fruition at Stanford Medicine, from preclinical work all the way through FDA approval, have the potential to improve the lives of these vulnerable patients that we really care about. **SM**

Listen to a ***Health Compass*** **podcast** with Peter Marinkovich and Jean Tang at stan.md/health-compass

Cells that heal

Offering hope to beat cancer when chemo falls short

BY RUTHANN RICHTER

PHOTOGRAPHY BY MISHA GRAVENOR

By the time Jordan Mulgado's blood cancer was diagnosed, dozens of tumors had penetrated her internal organs. One lung had collapsed; her pancreas was inflamed; and her liver, stomach and thyroid were not functioning well.

She was 18, with no history of serious illness. Now, she had bone pain and a dry cough and struggled to keep food down. The walk to the bathroom left her breathless.

After a week in a hospital in California's Central Valley, Mulgado learned that she had an advanced case of non-Hodgkin's lymphoma, a type of cancer that leads to out-of-control growth of cells in the immune system.

"When I first heard the word 'cancer,' I didn't cry, I just sat there in shock," she recalled. "I know it's silly, but the only thing I was worried about was that I had a test next day in class. I was more worried about the logistics of it, rather than the thought, 'Oh, I'm going to die.'"

That moment began a two-year odyssey of intensive chemotherapy, CAR-T cell therapy and, ultimately, a bone marrow transplant at Stanford Health Care that restored her to good health.

On a sunny day in October, Mulgado was one of about 1,000 recipients of bone marrow transplants or other cellular therapies who gathered with their families under white umbrellas for a patient reunion hosted by Stanford Health Care's Blood and Marrow Transplantation (BMT) and Cellular Therapy program. Together, they shared the joy of being alive.

"Patients are here because you've given them their lives back," said David Miklos, MD, PhD, chief of the BMT and cell therapy program, addressing the faculty and staff among the crowd.

More than 10,000 people have received cell therapies at Stanford Medicine in the past 40 years, making it one of the largest programs in the country, said Miklos, a professor of medicine and a member of the Stanford Cancer Institute.

In 2024 alone, some 820 patients received these treatments, double the number from 2020. The treatments all use living cells to fight disease, with bone marrow transplantation being the earliest form of the approach. It was first used, starting in the late 1950s, to replenish the blood-forming cells in the bone marrow after they were damaged by treatment for blood cancers. Bone marrow transplants and other cell therapies are still used mostly to treat blood cancers, but they are increasingly used for other conditions, including other types of cancer and diseases of the immune system and the bone marrow itself.

Better transplants

THANKS TO SCIENTIFIC advances in the field since those early days, patients with blood cancers are surviving longer, with 80% of people who have bone marrow transplants living for a year or more. In the early 1980s, most died within six months, Miklos said. Still, transplantation has its risks, most commonly a patient's body rejecting the donated cells as foreign, causing a war within the body known as graft-versus-host disease.

Robert Negrin, MD, a professor of medicine who preceded Miklos as director of the program, and his colleagues have developed a transplantation method that could prevent the condition.

The procedure calls for transplanting only a specialized group of powerful cells from a donor, rather than flooding the patient with all the donor cells. In a clinical trial published in 2025 in the journal *Blood*, Everett Meyer, MD, an associate

JORDAN MULGADO (RIGHT) RECOVERED FROM CANCER AFTER RECEIVING A BLOOD STEM CELL TRANSPLANT. SHE CALLS HER BROTHER DILLON (LEFT) A SUPERHERO BECAUSE HE DONATED THE CELLS THAT SAVED HER LIFE.

professor of medicine and of pediatrics, and colleagues showed that using the new approach made transplantation less toxic and very effective.

"By making a precise recipe we get better outcomes," Miklos said.

Another form of cell therapy, known as CAR-T (chimeric antigen receptor therapy), has revolutionized the field by enlisting the patient's immune cells to attack the disease. This involves removing some of the patient's cells and genetically editing them to recognize cancer cells. The new cells are living therapies that multiply in the lab, and once infused back into the patient, they seek and destroy the cancer beginning within a week of infusion, with astounding results.

"It seems like a miracle to some people, but it's not," Miklos said. "It's science. CAR-T redirects the patient's own cells to fight their cancer."

Stanford Medicine treated its first CAR-T patient in February 2016 and is a premier center for this form of therapy, treating 280 to 300 patients a year, Miklos said. Whereas only 12% of lymphoma patients previously survived a year, the new procedure has boosted that to 75%.

"Most of all, it's a one-and-done therapy," he said. "You are finished — no repeat chemotherapy cycles or daily pills."

Now, Stanford Medicine doctors are leading the cell therapy field by combining these two powerful techniques — CAR-T cell therapy and bone marrow transplantation — for even better results.

Mulgado began her treatment in 2022 with eight chemotherapy rounds, but they failed to control the cancer. She then had two different CAR-T infusions. The second was more potent than the first, with a compound manufactured at Stanford Medicine that is the first cell therapy to aim at a second target on the cancer cells. A recently published study in *The Lancet* by Matthew Frank, MD, PhD, an assistant professor of medicine, Miklos and others proved the second approach to succeed in more than half of patients with B-cell lymphoma whose disease had worsened despite standard therapy.

But for Mulgado, her lymphoma recurred after these two CAR-T therapies. She also developed a temporary neurologic side effect that left her unresponsive, as if she were in a coma. She woke up confused a few days later and initially struggled with simple tasks like chewing her food and writing legibly.

She practiced daily exercises, penning the sentence, "My favorite flower is a sunflower." Over the months that followed she recovered from the side effect and prepared herself for a blood stem cell transplant.

CONTINUES ON PAGE 85

Getting to know your mitochondria

An excerpt from **The Life Machines: How Taking Care of Your Mitochondria Can Transform Your Health**

BY DARIA MOCHLY-ROSEN AND EMANUEL ROSEN

What are mitochondria, how can you keep yours happy and why would you want to? To answer these questions for curious readers without a science background, protein chemist Daria Mochly-Rosen, PhD, and her husband, writer Emanuel Rosen, wrote a book about these tiny structures that power our cells.

Mochly-Rosen, a Stanford Medicine professor of chemical and systems biology, has studied mitochondria for two decades — a period that has seen an explosion of research on the organelles and a boom in interest among the public. Yet, she has observed a major gap in knowledge about mitochondria and found it frustrating.

"Yes, mitochondria are the cells' fuel sources, but we now know they are much more than that, said Mochly-Rosen, who is also the George D. Smith Professor in Translational Medicine. "They're responsible for cleaning toxins from your cells, recycling some of the cell's broken parts, fighting viruses, sending signals out about the status of your body — and that's just some of what they do," she said.

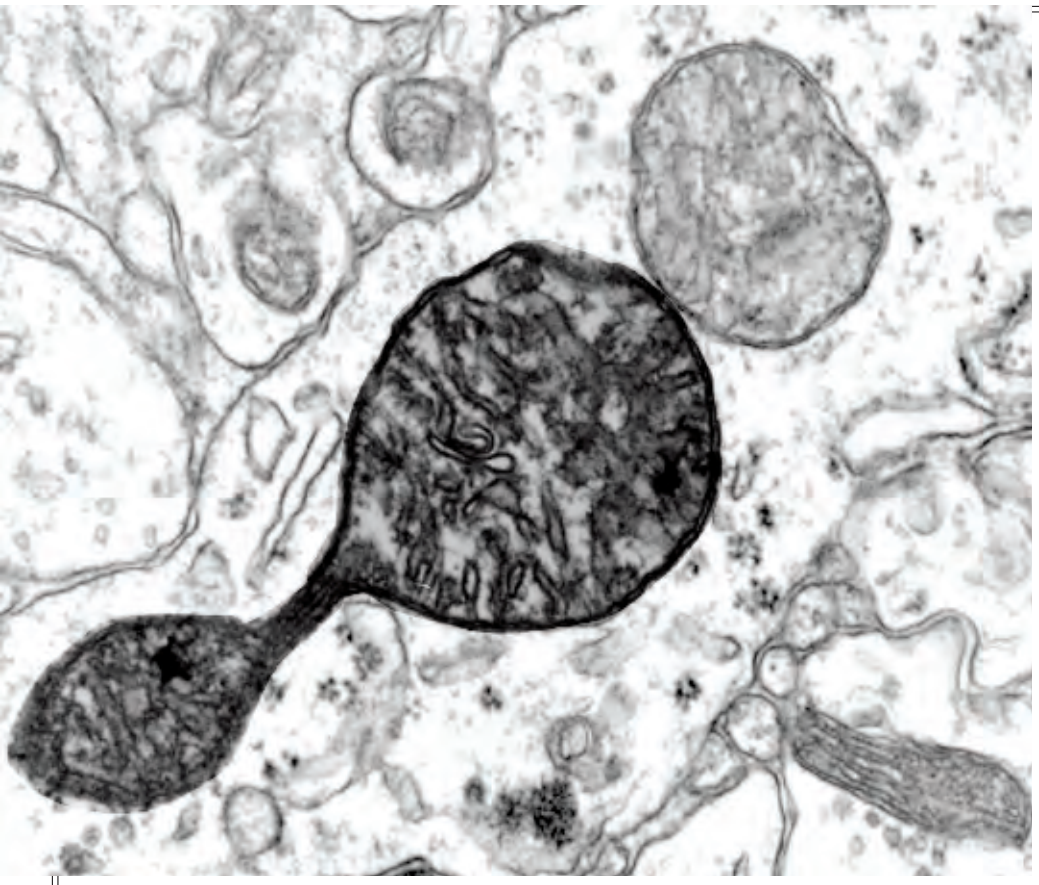
In their book, *The Life Machines*, published in October 2025, the couple explain how the hundreds (and in some cases thousands) of mitochondria in each of our cells pull off what they're best known for — converting what we eat into adenosine triphosphate, or ATP, a molecule that acts like the cell's fuel. The couple also spell out mitochondria's other roles and what we can do to help them out. That's important, because, as they write: "Our life and death are quite actually in the hands of these tiny nanomachines."

In this excerpt from the book, we gain a better view of how mitochondria constantly split and fuse — and how that choreography helps them repair damage, recycle faulty parts and keep them fit. And we learn why sleep is a mitochondrion's friend.

The dance: They constantly split and merge

THERE'S A PHOTOGRAPH on the wall of Daria's office at Stanford that often stumps first-time visitors. It was taken with a powerful electron microscope that can magnify objects more than one hundred thousand times, and it features a figure-eight structure. When Daria asks guests what it is, they rarely identify it as a mitochondrion. They're not alone: When Daria was first shown this photo 15 years ago and was told this was a mitochondrion, she remembers her succinct reaction: "Huh?" Most of us remember that static picture of a mitochondrion in our biology textbook, but the life machines change their shape all the time. The photograph in Daria's office shows a mitochondrion going through fission, the process by which more mitochondria are generated. And mitochondria also merge with other mitochondria, a process known as fusion. Together, through this constant dance of fission and fusion — splitting and merging — the mitochondria's ability to function properly is maintained.

The dance of fission and fusion is a fascinating process. Consider, for example, how a single mitochondrion decides whether it should merge with another mitochondrion. It starts with a handshake, during which each mitochondrion seems to check out the other one, as in speed dating. If either of them senses that the other one is not good enough, they move on, looking for a better partner. On the other hand, if merging is beneficial, they connect, fuse and start to exchange components to complement each other.



MOCHLY-ROSEN LAB

THIS PHOTOGRAPH OF A MITOCHONDRION DURING DIVISION USUALLY FLUMMOXES VISITORS TO DARIA MOCHLY-ROSEN'S OFFICE, WHERE IT'S DISPLAYED.

Think about how this ingenious process helps the state of mitochondria in the cell and thus your health: A mitochondrion that is repeatedly rejected by others doesn't get the good stuff from other mitochondria and eventually will be removed through mitophagy, the recycling program of mitochondria. In contrast, good mitochondria get better.

THE PROCESS OF FISSION, the division of a single mitochondrion into two, is no less fascinating. Fission is the way more mitochondria are generated, which is needed, of course, when the cell itself divides, which happens for some cells every 24 hours. But even when the cell does not divide, mitochondria need to split to remove damaged parts, in the same way that a tree needs to be pruned for optimal growth. This happens through the mitochondria's recycling program — mitophagy.

Remarkably, before mitophagy can begin, our body separates between what needs to be recycled and what can still be used. Recall that mitochondria have their own small DNA (mtDNA). Unlike nuclear DNA, which has efficient machinery to prevent and correct mistakes, the mtDNA is much less efficient in taking care of such errors. This means that the mtDNA collects many mistakes throughout the life of each cell.

But here's the good news: Unlike nuclear DNA, each mitochondrion has several copies of mtDNA. Therefore, in the same mitochondrion, you may have some lucky mtDNA that are still in good shape, and less fortunate ones that were damaged.

The same is true for the proteins in a mitochondrion. How is it then that mainly damaged mtDNA and damaged proteins are removed from a mitochondrion? This is yet another extraordinary process that happens inside our mitochondria. Damaged components assemble at one end of a mitochondrion while the intact mtDNA and proteins stay on the other end. Next, in coordination with another organelle called endoplasmic reticulum (ER), something like a noose is formed around the mitochondrion and cuts the mitochondrion into two mitochondria. The part that was pinched off contains the bad stuff while the other part is a healthy fresh mitochondrion ready for action. The bad section is collected by autophagosomes, which we can think of as garbage trucks, and brought to lysosomes, which we can think of as recycling centers. There, the damaged parts are digested into their building blocks, and those are later used to build new cell components.

How is this fascinating process relevant to your health? Here's an example: During the day, mitochondria focus mainly on producing ATP and building blocks for all your daily activities; at night, while still generating ATP, they switch to a recovery mode — sorting the functional parts from the damaged ones and removing the damaged parts through mitophagy. So, when you get enough quality sleep at night, you give your mitochondria a chance to complete this pruning process.

Part of the "noose" that cleaves a mitochondrion into two mitochondria is a protein called Drp1, and researchers found that it receives signals from (and sends signals to) our body's circadian clock (the internal clock that tells us when it's time to sleep and when it's time to get up). We'll go into more details in chapter 9, but the key point is that getting enough quality sleep allows mitochondria to go through this deep cleanup. You should get enough sleep at night to let your mitochondria complete the job. **SM**

— *Excerpted from* The Life Machines.

Through their eyes

A student-led program giving pediatric patients a chance to tell their stories through photos goes global

BY LAURA FRASER

Niisoja Torto, a medical student and Knight-Hennessy scholar at Stanford University, has always been interested in storytelling and how the way we share our stories can change our perspectives. So, in 2021, when he was looking for a topic for a Knight-Hennessy project that would address a social issue, Torto thought about how children in hospitals often aren't able to tell the stories of their experiences there.

"Pediatric patients lose a lot of agency for storytelling in the hospital," Torto said. "Things that involve them are discussed with their parents or among the medical team. It's a struggle to tap into their perspectives about what they care about."

Torto pitched a project that would involve giving cameras to children and their parents at Lucile Packard Children's Hospital Stanford to document their experiences, empowering them to tell their stories through creative means. The Knight-Hennessy scholarship program for graduate students has three pillars — civic mindset, independence of thought and purposeful leadership — and encourages each of the scholarship recipients to complete a multidisciplinary collaboration that solves a pressing regional or global issue. The pediatric photography project was a good fit. "It could bring together interdisciplinary scholars to work on something that's important to the community," Torto said.

Launched in 2021, the resulting program, Through Their Eyes, has become a way for children and their parents who are cooped up in a hospital to express themselves. And now a new crop of scholars are taking the project in different directions.

"It's gone global," said Aaron Abai, a second-year medical student. "A scholar working on a project in Chile has given new mothers cameras to help document their experience with motherhood. Another scholar has taken cameras to the border to work with migrant children."

The pediatric photo project begins

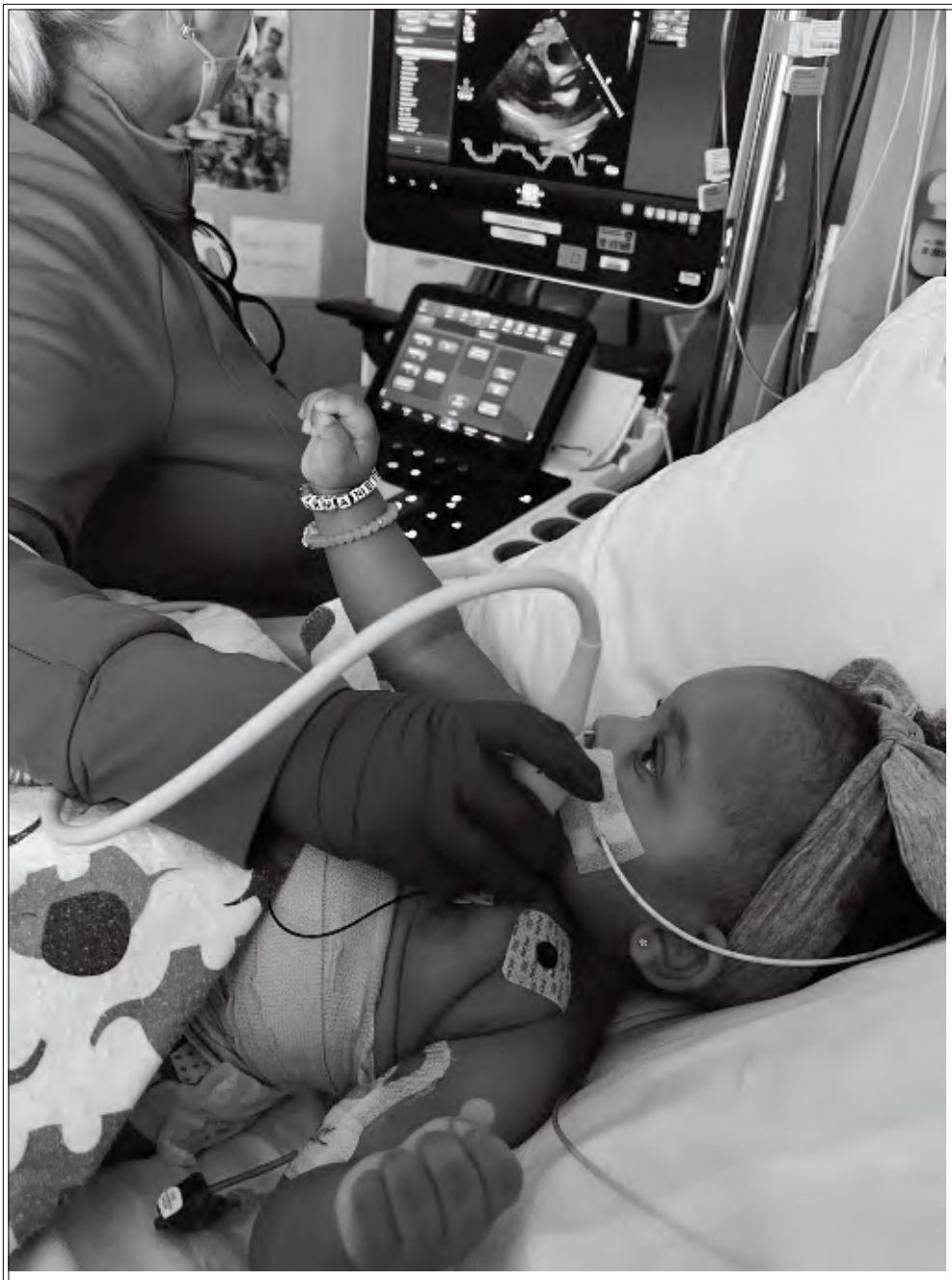
THAT FIRST YEAR, A TEAM OF 11 Knight-Hennessy scholars, in medicine and other fields as varied as arts and engineering, participated in the project, interviewing the photographers — parents of young children and pediatric patients older than 5 — about the significance of the images they took in the hospital. The project culminated in three gallery exhibits and a celebration for the patients, their families and the students on campus at Denning House, the hub for the scholars' program. The photos are still on display at Packard Children's.

"Everyone was excited and even a little surprised at how quickly the patients and families grabbed onto this project and how eager people were to participate and share with others," said Sam Rodriguez, MD, the project adviser, who is a pediatric anesthesiologist at the children's hospital and a founder and co-director of the Stanford Chariot Program, which creates and studies innovative ways to treat pediatric pain and stress through technology.

"It's an outlet for the patients and their families — many who are in the hospital for long periods of time," he said. "Although they're here and not participating in usual activities, there still are stories that are happening in the hospital, and it's human nature to tell stories."

Rodriguez said that because children tend to be very visual, the cameras — which pop out instant photos as well as keep digital copies — were well-suited for documenting their experiences.

The first year of the project, Tianna Williams' daughter, Armaneigh, was just over a year old when she entered the hospital for a stay that lasted 341 days. She had a condition called dilated cardiomyopathy, in which the heart becomes weakened and enlarged, and



PHOTOGRAPHS taken for the project and the photographers' words about them have been displayed in several galleries. Here's what the photographer said about this one: I'm in college, so now I have to do online courses, which kind of sucks a little bit because it's a lot — and then just seeing my daughter go through all these drastic changes, like having to get a heart transplant. Like we were at home, you know, living normal lives. And then now we're here in the hospital and don't know when we're gonna go home.

–TIANNA WILLIAMS,
MOTHER OF ARMANEIGH, 17 MONTHS

had a long wait for a donor heart. In the meantime, a cardiac pump helped her heart circulate blood and keep her alive. A certified child life specialist at the hospital, Christine Tao, told Williams about the photo project. Williams, who liked to take pictures for her blog and TikTok, was eager to join.

"I took pictures all day in the hospital, documenting our journey — her dressing changes, baths, walks, medicine, the nurses, any interaction that was going on," Williams said. "Taking pictures helped me capture moments, and it also helped me get through the experience. Every day waking up and taking pictures, my daughter was still there. Every day of fighting for her heart transplant was another day of hope."

One of the photos picked for the gallery showed Armaneigh's scars. "Each scar was a different procedure, a different battle she had to fight," Williams said. "When people look at families in the hospital, they just hope they get better. This project was able to look through a wider lens to see what families are really going through to get to the other side, whether they have problems with their heart or liver, or have cancer or other diseases."

Surprising explanations

WHEN THE KNIGHT-HENNESSY SCHOLARS INTERVIEWED older kids who could take their own photos, they were often surprised by the stories behind the images. Torto was struck by an image of a flight of stairs, taken from the top, with a wheelchair at the bottom. When Torto asked the 11-year-old girl who took the photo what it meant to her, she said: "You can achieve your goals." Torto said, "The fact that she took the photo from the top of the stairs meant that she could climb the stairs on her own, which, after her illness, was amazing."

Torto interviewed a 15-year-old girl about a photo that seemed to show just an empty wall. When she was interviewed about what it meant, the girl said, "After surgery, that pole was filled with machines and all the things I needed to keep me alive. Well, as you can see, there is nothing there anymore. It's a huge reminder of how it was before and how it is now, because that means I made it."

Often, the stories behind the photos were different from what the scholars expected. "My hypothesis was that a lot of the stories or what was meaningful to patients would be more somber," Torto said. "Like, 'My childhood doesn't look

The photographer's words about this shot:
When I got discharged, it was kinda hard to walk from my room to the stairs, so I wheelchaired over there, and I climbed the stairs.

What does this photo tell us about your life?
You can always achieve your goals.
– PATIENT, 11

like an ordinary kid's, and X, Y and Z suck about this experience.' There was definitely some of that, but a lot of kids talked about the positive things — the progress they had made, being able to play and the nice relationships they had with staff at the hospital."

Indeed, when the team analyzed their findings, published in January 2026 in *BMC Pediatrics*, five themes emerged from the interviews: resilience and mental health; environment; playing and being a normal kid; joy, gratitude and appreciating small things; and life before, current and future. Parents and children, they found, valued taking photos as reminders of strength, growth and progress. Parents and children also emphasized the value of play and normal routines as fun distractions for patients and evidence of healing for caregivers.

Tao, who mainly worked with children with cardiac illnesses at the time, said the project helped her make the kids' lives seem as normal as possible when they are hospitalized for long periods.

"It was an amazing collaboration because these patients and families had a creative outlet for expressing their journeys and sharing them with others," she said. "A lot of times kids don't get a sense of control in the hospital. With this project, they were able to use the camera as their voice — they could control and manipulate it and tell their story through their eyes and their lens, the way they wanted, rather than through an adult perspective."

She saw parents similarly benefit from documenting their journeys. "I had a mom who was here with her baby for a long time, and the project helped her capture important milestones," Tao said. "During rehab, she was able to document her daughter's progress in getting stronger and playing with the toys we brought her. That gave mom a sense of stability and routine and a way to be creative during what was, for her as well, a very long stay."

"In many ways, it's opened up my perspective about what may be meaningful to patients, which may not always be what we as providers might guess is meaningful," Torto said. "Kids are often far wiser than we give them credit for. When we work with kids, we lean into talking with the parents more often. But even with our young kids, our 4- to 6-year-olds, we should ask them as well."

This doesn't apply only to working with children, he said. He expects it will serve him if he goes on to become an emergency medicine doctor, as he plans. "Instead of me serving patients or working for patients, I'm thinking about it more as a collaboration. That's an important frame shift — patients as collaborators, as opposed to people who are just at the whim of our health care expertise."

Kathy Hu, a Knight-Hennessy scholar in her fourth year of the MD/MBA program, has been translating documents from the project, such as recruitment materials, instructions and participation forms and is introducing it to Spanish-speaking patients at Packard Children's. She has also brought Through Their Eyes to Santiago, Chile, where she is doing unrelated medical schoolwork, and created a community-based photo program at a local public library there.

"A lot of the families going to the library are in a vulnerable situation," she said. "They're migrants or refugees, and we thought that a photo project would similarly help highlight stories and experiences we don't often hear."

At a workshop with the theme of tenderness, about 20 families gathered to draw and create photographs that showed what tenderness meant for them.

"Many have pretty tumultuous lives, and to have the opportunity to slow down, reflect on the connection between themselves and their kids, and take pictures was special."

Each family left the workshop with a book of images.

"When people feel powerless and out of control and you give them a camera, you give them the power to shape their own story. The photo project has been dear to all our hearts, being able to connect with children and families not only at Stanford," Hu said.

"Whether it's in the hospital or across the border, kids need to be able to express themselves." **SM**

— Contact Laura Fraser at medmag@stanford.edu

FEATURE

'We need a breakthrough'

CONTINUED FROM PAGE 37

She believes the trial is a good starting point for treating a disease with an urgent need for new approaches.

"I think it's an exciting target in a disease that doesn't have a lot of options," she said. "This is something we can offer to the field that has yet to be available. One of the advantages is that we have a great team focused on women's cancers. I can't emphasize that enough. It allows us to learn a lot from our patients. I think this is step one. We are in it for the long haul."

Because this trial was initiated by Stanford Medicine, using a $5 million gift from a donor,

the researchers have full control over how it's conducted.

"We are the ones who can modify the treatment on our study protocol," Dorigo said. "We can therefore be very flexible and react to clinical observations quickly. It's very different when a company sponsors a trial, where we are subject to their strategies and thinking."

In a separate effort, Dorigo is testing an antibody discovered in the laboratory of Irving Weissman, MD, the Virginia & D.K. Ludwig Professor in Clinical Investigation in Cancer Research at Stanford Medicine, and his colleagues. He's participating in a multicenter trial sponsored by Pheast Therapeutics Inc., which was co-founded by scientists who trained in Weissman's lab.

Weissman's team identified a protein on the surface of cancer cells, called CD24, that allows them to escape destruction by immune cells called macrophages. The researchers devised an anti-CD24 antibody that removes this obstacle, allowing the macrophages to gobble up and destroy the cells.

Ovarian cancer is a good target for this therapy, Dorigo said, as these tumors express high levels of CD24 and contain a lot of macrophages. So far, five patients have been treated with the anti-CD24 antibody at the Stanford Women's Cancer Center. The goal is to determine if the drug is safe and shows any anti-tumor activity. The trial began in July 2025 so it's too early to draw conclusions. Patients treated at Stanford and other institutions have tolerated the treatment well so far, Dorigo said.

These two Stanford Medicine trials are encouraging, as they represent a whole new direction for immune-based therapies, said Anne Mette Buhl, PhD, senior director for treatment access and scientific education with Ovarian Cancer Research Alliance.

"This is a particularly hopeful time for the ovarian cancer community, as substantial efforts are underway to develop more effective and precise treatment options," she said. **SM**

— Contact Ruthann Richter at medmag@stanford.edu. More information about the CAR-T clinical trial is at stan.md/OvarianTrial

FEATURE

Catalyst

CONTINUED FROM PAGE 41

Catalyst transformed how Ferrara thought about innovation, collaboration and what was possible for her project. "It's an opportunity to open up your project and your thinking about the impact you could have on a broader scale," she said.

Innovation is a discipline

Five years is not a long time in health care innovations. In five years, Catalyst has reviewed more than 500 applications, awarded more than 30 projects, worked with more than 200 Stanford innovators, completed 12 clinical pilots and translated 13 projects into companies, licenses and partnerships that have made a difference in patients' lives.

"These results prove that innovation — actively cultivating good ideas — is alive and well at Stanford," Minor said.

"Now, with Catalyst, innovation isn't just a buzzword but, frankly, a discipline," Siegel said. "The structures that Catalyst has brought to bear are so important to disseminate across the board, so everybody understands that innovation is not just idea creation. There's truly a process, a discipline, and rigor that allows innovation to be translated into actual impact." **SM**

— Contact Nina Bai at nina.bai@stanford.edu

FEATURE

Cells that heal

CONTINUED FROM PAGE 79

Mulgado was fortunate that one of her brothers, Dillon, was a close immunological match, able to serve as her blood stem cell donor, and he readily agreed. "I thank him for literally giving me a part of himself," the 21-year-old resident of Turlock, California, said at the reunion event.

After the transplant in June 2024, Mulgado had to take as many as 30 pills a day, including medications to help prevent rejection of the new cells, which have since repopulated her immune system. She is down to only two pills a day.

Now, Mulgado is a sophomore in college, majoring in biology, and spending her free time walking her English bulldog, cooking and hanging out with her boyfriend, she said.

"These days I feel normal, actually. I'm doing the things I did before. The only reminder of what I went through is that my hair feels different," she said, explaining that it has turned dark and curly. "I look at the experience as something that is going to help me in the future."

Mulgado's goal is to become an oncologist — the kind of physician who understands all too well the challenges of being a cancer patient.

At her brother's wedding in the summer of 2025, Mulgado publicly expressed her gratitude for his support.

"I thanked him for being my donor and saving my life," she recalled. "I said he was a true older brother, a superhero. A lot of tears were shed that night."

She now plans a trip in 2026 to the Basilica of Our Lady of Guadalupe in Mexico City, a major Catholic pilgrimage site, following through on a vow she made early on in her treatment.

"I decided that when I was healthy, I would have to thank God the right way," she said. **SM**

— Contact Ruthann Richter at medmag@stanford.edu

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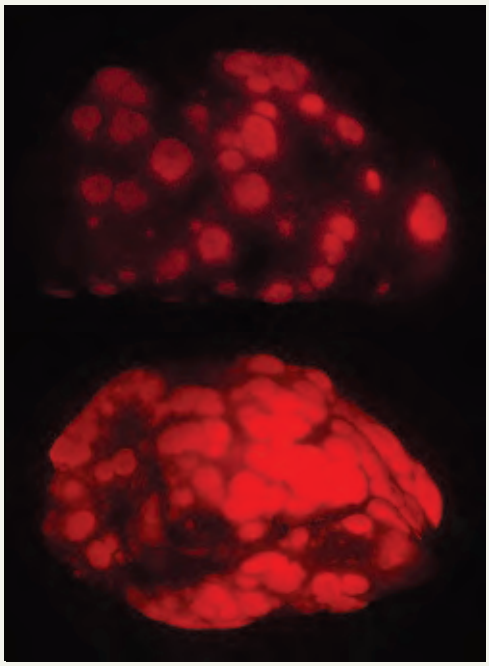
HOW AGING MIGHT LOWER CANCER RISK

YOUNG ADULT MICE HAD MORE, LARGER LUNG TUMORS THAN ELDERS

While our chances of getting cancer increase as we age, a recent Stanford Medicine-led study shows that changes related to aging might also suppress cancer.

In the study, researchers found that aged laboratory mice develop substantially fewer and less aggressive lung tumors than young adult animals.

"It's a striking finding," said Monte Winslow, PhD, an associate professor of genetics and of pathology and a co-senior author of the research with Dmitri Petrov, PhD, a professor of biology. "We would expect that older animals would get more and worse cancers, but that's not at all what the study found. So, what is it about the molecular changes associated with aging that suppress cancer?"



Lungs of old adult mice in a cancer model (top) developed fewer tumors (stained red) than lungs of younger adults (below). The findings suggest that in very old animals or humans the aging process suppresses cancer formation.

EMILY SHULDINER

To figure that out, the researchers examined the role aging plays in the biological mechanisms that transform healthy cells into proliferating cancer cells.

Studies in humans have shown that cancer incidence rises sharply beginning around age 50 and peaks around ages 70 to 80. This is because each time our cells divide, there's a chance that mutations will be introduced into the DNA. This leads to mistakes in how genes are expressed and function, and that can cause cancer. However, the curve plateaus or drops at age 85. While this could be due to decreased screening and diagnoses or because of a kind of natural selection — maybe people who live to a ripe old age tend to have immune systems better equipped to eliminate developing cancers — another possibility is that aging itself suppresses cancer development.

For the study, published in November 2025 in *Nature Aging*, former graduate student Emily Shuldiner, PhD, genetically engineered mice such that she could initiate fluorescently tagged lung cancers. Because she compared tumor formation in young adult (4 to 6 months) to old (20 to 21 months) mice, she had to wait nearly two years for the animals to age.

When they had, she induced lung cancer formation in the animals. Fifteen weeks later, the amount of cancer in the lungs of the younger mice — measured by lung weight and fluorescent imaging — was about three times as high as in the old mice. The younger mice also had about three times as many tumors than the old animals.

"In every way we could measure, the younger animals had worse cancers," Shuldiner said.

To understand what was protecting the older animals, she investigated the effect of inactivating 25 tumor-suppressor genes in the lung tumors. These genes make proteins that normally block the development of cancers.

Although tumor growth increased when these tumors suppressors were inactivated regardless of age, the effect was greater in younger mice. Inactivating one tumor suppressor gene in particular, PTEN, had greater differential impact than the others.

"It suggests that the effect of any given mutation, or the efficacy of cancer therapies targeted at specific pathways, might be different in young versus old people," Shuldiner said.

The findings illustrate the importance of developing new models of cancer that incorporate the effects of aging to develop new therapies.

"We develop animal models of cancer with an eye to developing new treatments for patients," Winslow said. "But for this to work, the models have to be correct. And this study suggests that models using young animals might miss important aging-related changes." BY KRISTA CONGER

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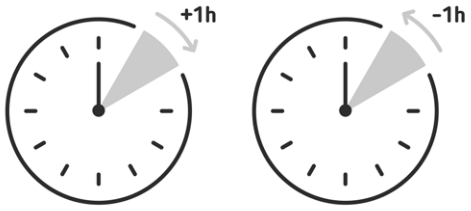
MOST AMERICANS WOULD BE HEALTHIER WITHOUT DAYLIGHT SAVING TIME, STUDY SUGGESTS

All but two U.S. states, Hawaii and Arizona, set clocks forward an hour just before spring and back again in the fall. These biannual time shifts are not only inconvenient but also, research shows, unhealthy: The second Sunday in March, when daylight saving time begins, has been linked to more heart attacks and fatal traffic accidents in the ensuing days.

A study by Stanford Medicine researchers found there are longer-term hazards — and better alternatives.

In a national study, the researchers compared how three different time policies — permanent standard time, permanent daylight saving time and biannual shifting — could affect people's circadian rhythms and, in turn, their health.

The team found that, from a circadian perspective, we've made the worst choice. Either permanent standard time or permanent daylight saving time would be healthier than our seasonal waffling, with permanent standard time benefiting the most people.



Indeed, by modeling light exposure, circadian impacts and health characteristics county by county, the researchers estimate that permanent standard time would prevent some 300,000 cases of stroke per year and result in 2.6 million fewer people having obesity. Permanent daylight saving time would achieve about two-thirds of the same effect.

"We found that staying in standard time or staying in daylight saving time is definitely better than switching twice a year," said Jamie Zeitzer, PhD, a professor of psychiatry and behavioral sciences and senior author of the study, which was published Sept. 15, 2025, in *Proceedings of the National Academy of Sciences*.

The human circadian cycle is not exactly 24 hours — for most people, it's about 12 minutes longer — but it can be modulated by light.

"When you get light in the morning, it speeds up the circadian cycle. When you get light in the evening, it slows things down," Zeitzer said. "You generally need more morning light and less evening light to keep well synchronized to a 24-hour day."

The researchers used a mathematical model to translate light exposure under each time policy, based on local sunrise and sunset times, to circadian burden — essentially, how much a person's innate clock has to shift to keep up with the 24-hour day.

They found that over a year, most people would experience the least circadian burden under permanent standard time, which prioritizes morning light. — BY NINA BAI

SUBKONTR/ADOBE STOCK

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