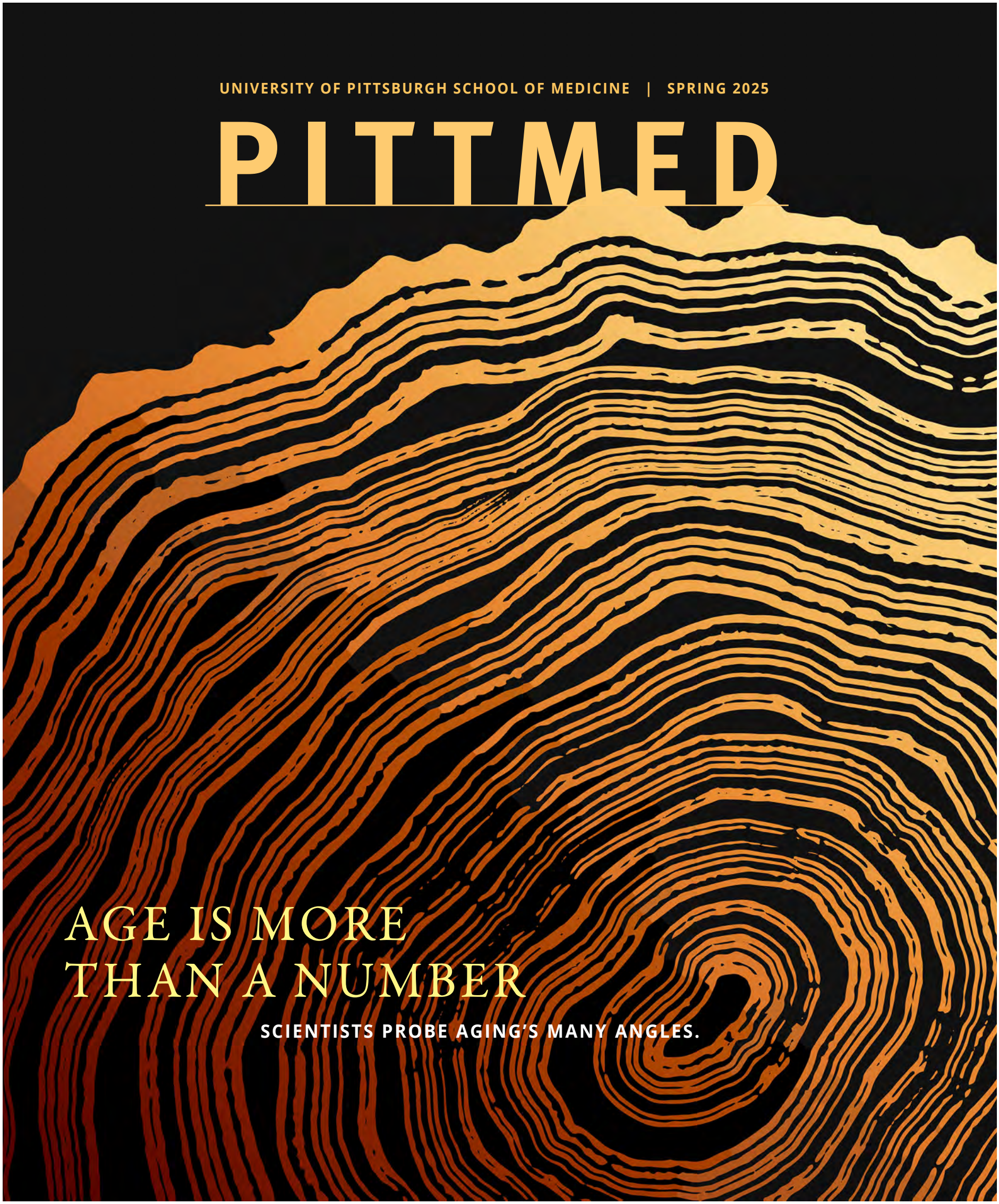
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SPRING 2025

PITTMED



AGE IS MORE THAN A NUMBER

SCIENTISTS PROBE AGING'S MANY ANGLES.

LUCKY TO HAVE COACHES

The new coaching program described in "Building whole doctors, and whole people" (Winter 2024/25) is an excellent idea. Dr. Julia Meade's description of the talent and qualities a student needs to reach medical school are spot on. Several issues back, the magazine ran an article about imposter syndrome ("Cultivating equanimity," Fall 2023). I think the phenomenon begins in the first two years of medical school when it feels like it's you against all these incredibly bright people. Those were two of the toughest years of my career. Thankfully, I had supportive classmates to get me through difficult times. In my clinical years I was fortunate to have met preceptors Drs. Judith Black from West Penn and Gerald Levey, then-chair of Pitt's Department of Medicine, who took me under their wings and guided me into appropriate fourth-year electives and picked residencies that fit me. These mentors (coaches) helped me launch a successful career. Today's students are lucky to have coaches such as Dr. Meade to support them during med school.

John M. Costello Jr., MD '85
Jacksonville, Florida

RECENT MAGAZINE HONORS

Winner, 2024 Graphic Design USA American Inhouse Design Award (Winter 2023/24 Issue)

Winner, 2024 Press Club of Western Pennsylvania Golden Quill, Excellence in Written Journalism, Medical/Health (E. Lloyd, "Cultivating equanimity")

Finalists, 2024 Press Club of Western Pennsylvania Golden Quill, Excellence in Written Journalism, Medical/Health (M. Aubele, "A moving story" and A. Doerfler, "Outside influences")

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Aging well

"It is not a question of how old you are, but a question of how you are old." —*Jules Renard*



AIMEE OBIDZINSKI/UNIVERSITY OF PITTSBURGH

Dear Pitt Med Readers,

The United States is getting older, as no doubt you're aware. Here's what the numbers amount to: The population age 65 and older grew nearly five times faster than the total population from 1920 to 2020. In 2022, 1 out of every 6 Americans was over 65.

Nearly 95% of older adults have at least one chronic condition, and nearly 80% have two or more. The question of whether we can extend people's lives should be asked with another: How can we extend the years lived without debilitating disease and disability?

At Pitt, we are working toward that goal, across disciplines and in a variety of settings. In this issue's cover story, you'll learn about advances from Pitt's Aging Institute. While each of us adds one year to our chronological age every birthday, the way biological aging plays out in our bodies varies drastically from person to person. We all know some people who are vibrant and sharp in their later years and others who aren't. Our researchers are gaining new insight into the biological processes that drive those differences and testing new approaches to slow and counteract the effects of aging.

For instance, Anne Newman, the Aging Institute's clinical director, is in the middle of the largest-ever study to uncover how muscles weaken and mobility declines with age. For people already dealing with mobility challenges, Pitt's Healthy Home Lab explores high- and low-tech solutions to allow older adults to "age in place," that is, at home—the preference for most of us. (You can read more on page 30.)

We are fortunate to have among our faculty some of the foremost experts in many age-related illnesses—scientists like Timothy Greenamyre, whose decades-long work on Parkinson's disease has untangled its underlying mysteries. You'll want to read the profile on him that starts on page 26.

Our students, too, have a hand in helping older adults. The comic journalism piece on page 32 tells the story of Anna Li, who's enrolled in our MD/PhD program. Anna won the $1 million Hult Prize to further develop a user-friendly device for heart and lung screenings that allows more routine care to take place at home. The device will be of great benefit to older adults who have difficulty getting to doctor's appointments.

These investigators, and others like them, will help more of us live through later years that truly are golden.

Anantha Shekhar, MD, PhD
Senior Vice Chancellor for the Health Sciences
John and Gertrude Petersen Dean, School of Medicine

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Should you scratch that itch? Pitt labs answer the question and uncover paths for relief.

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Editor's note: School of Medicine faculty with clinical duties often have joint appointments with UPMC or the VA Pittsburgh Healthcare System, the University's clinical partners.

ABOUT THE COVER Wisdom with age: By sharing a number of perspectives, and pursuing different research paths, Pitt scientists are finding clues to good health in advanced age. © Getty Images/ Alona Horkova, 2025.

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In 1982, a handful of patients appeared in emergency rooms across California. One day, they were healthy; the next, they were unable to walk or talk. Many had tremors. The symptoms were classic Parkinson's disease.



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Aging is complex, but Pitt scientists are coming to new understanding by combining their expertise. Their advances look to a future where people can live well for longer.

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We humans don't just have 24-hour biological rhythms. Traces of our marine ancestors live on in 12-hour biological rhythms. Could these alternative cadences play a role in metabolism and aging?

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Timothy Greenamyre has spent decades unraveling the mechanisms that cause Parkinson's disease. His work continues to be profound and has recently taken on personal relevance.

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There's no place like the Healthy Home Lab.

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A Pitt Med student wanted to help more people do heart and lung screenings from home. Her patient-friendly device has been awarded the $1 million Hult Prize.

COMIC WRITTEN BY KATY RANK LEV | ILLUSTRATED BY MAGGIE NEGRETE

CONTRIBUTORS

CARRIE ARNOLD ("The chemical connection") likes to write about "slow-burning disasters—not just what happens in the headlines, but what happens afterwards." Before her career as a freelance public health journalist, during which she's been published in outlets like Nature and National Geographic, she worked in tuberculosis control. Arnold has a master's in science writing from Johns Hopkins and first contributed to Pitt Med Magazine in 2018. In writing about Timothy Greenamyre, Arnold wanted to capture the emotional experience of his Parkinson's diagnosis without overshadowing his research: "His diagnosis is not more important than the decades of work he's contributed."

FRANK WALSH's ("The chemical connection" portrait) portfolio ranges from advertising to editorial, with clients such as ESPN and Campbell's, but much of his work centers on people. To best capture their experiences, he tries to "be the subject," as he puts it. "Remind yourself of what they're going through." When people feel self-conscious about being photographed, Walsh encourages them to think about what makes them happy, often family. He does much of his work in his studio, a converted former church in Lawrenceville.





UPMC/PITT HEALTH SCIENCES

Phillip McKenzie dominated at the Cybathlon, nabbing the gold for PittCrew.

Cyber team takes home gold

A team from Pitt's Rehab Neural Engineering Labs (RNEL) took home a gold at the 2024 Cybathlon, an international competition where technology developers and a competitor with a disability tackle everyday tasks using modern assistive technologies.

The team, called PittCrew, consisted of 11 researchers and a pilot, Phillip McKenzie, who is paralyzed from the neck down. McKenzie received a perfect score using RNEL brain-implant technology in the competition's Brain-Computer Interface (BCI) Race last October. McKenzie has four microelectrode arrays surgically implanted in his brain: two in the somatosensory cortex, which stimulate the brain to create a sense of touch, and two in the motor cortex areas of his brain.

"The implants are very small—the size of your fingertip—and each can contain up to 100 electrodes," says Ceci Verbaarschot, the team manager and a postdoctoral associate at RNEL.

In the BCI Race, McKenzie used the microelectrodes in his motor cortex, which record directly from the parts of the brain that would typically control his hand. When McKenzie attempts to move his hand, the implants in the motor cortex are activated, and brain signals then decode the direction and type of hand movement to control the BCI. For the race, he completed a series of virtual reality tasks.

"One task was navigating a wheelchair from one side of a room to another while avoiding obstacles, such as furniture or plants. At the more difficult level, there were little Roomba robots that he had to avoid," Verbaarschot says. Other tasks included navigating a key to a lock using digital menu selection and holding a cup steady underneath an ice machine.

The researchers worked with McKenzie to practice the game in his home and in their lab. McKenzie, one of three participants in RNEL's BCI research trial, had the electrodes implanted about a year and a half ago.

"What I like most about Cybathlon is that it gives an opportunity to focus on our research participants. They go to the lab two to three days a week for years on end, and nobody ever sees that," Verbaarschot says. "But they work very hard, and we wouldn't be able to do anything without them." *—Shannon Turgeon*

RAYNI SHIRING/UNIVERSITY OF PITTSBURGH

FOOTNOTE

Not one, but two medical drama series based in the Steel City premiered this winter: "The Pitt" (Max) and "Watson" (CBS). They're fictional, but Pittsburghers will catch plenty of real local references. For instance, "The Pitt" nods to Primanti Bros. and Frick Park, as well as an important piece of the city's history: Freedom House Enterprises Ambulance Service. Considered the first professional paramedic service, the Hill District–based program was staffed by Black paramedics trained by Pitt physicians Peter Safar and Nancy Caroline. The experiences of Sylvia Owusu-Ansah, an MD, MPH associate professor of pediatrics and emergency medicine, also inspired a plotline.

Luna and Phillips elected to National Academy of Medicine



Luna (left) and Phillips

Beatriz Luna and Mary L. Phillips, both of the Department of Psychiatry, have been elected to the National Academy of Medicine.

NAM's members are among the most accomplished professionals in their respective fields. The academy's work informs government policies, guides health care practices and fosters public health improvements.

Luna, a PhD, is the Staunton Distinguished Professor of Psychiatry and Pediatrics and a professor of psychology, bioengineering and radiology. The scientist is known for her transformative research in adolescent neurocognitive development; her work has uncovered neural mechanisms of plasticity that support the transition from adolescence to adulthood.

Phillips, an MD/MD (Cantab), holds the Pittsburgh Foundation-Emmerling Chair in Psychotic Disorders and is a Distinguished Professor of Psychiatry. She is also a professor of clinical and translational science and directs the Center for Neural Circuit-Based Technology Interventions in Psychiatry. Her research has identified biomarkers that improve early mood disorder diagnosis and risk identification in youth, opening new avenues for treatment.

NAM elected 100 members in 2024. Luna and Phillips join 22 other esteemed Pitt faculty who have been elected to the academy.

—Staff reports



Dean Anantha Shekhar and Chancellor Joan Gabel present plaques to Vishnu Vardhan and his mother, Vijaya Lakshmi Pogunulu, for whom a new center was named.

Advanced women's health center takes shape

In December, Pitt announced it was establishing the Vijayalakshmi Innovation Center in Women's Health Analytics and Research (VIHAR). Vanathi Gopalakrishnan, a PhD associate professor of biomedical informatics, bioengineering and clinical and translational science, is the center's director. Her work has involved using large datasets to improve women's health and find patterns in preventable causes of death in women.

VIHAR will be a global initiative that leverages advanced artificial intelligence tools and collaborations to address disparities in women's health. The center has taken shape through investments from Pitt's School of Medicine and the brother-sister team Vishnu Vardhan and Harsha Vardhini, cofounders of Vizzhy, a generative health care AI systems company that works to locate the root causes of metabolic diseases and develop personalized health management guidance.



Gopalakrishnan

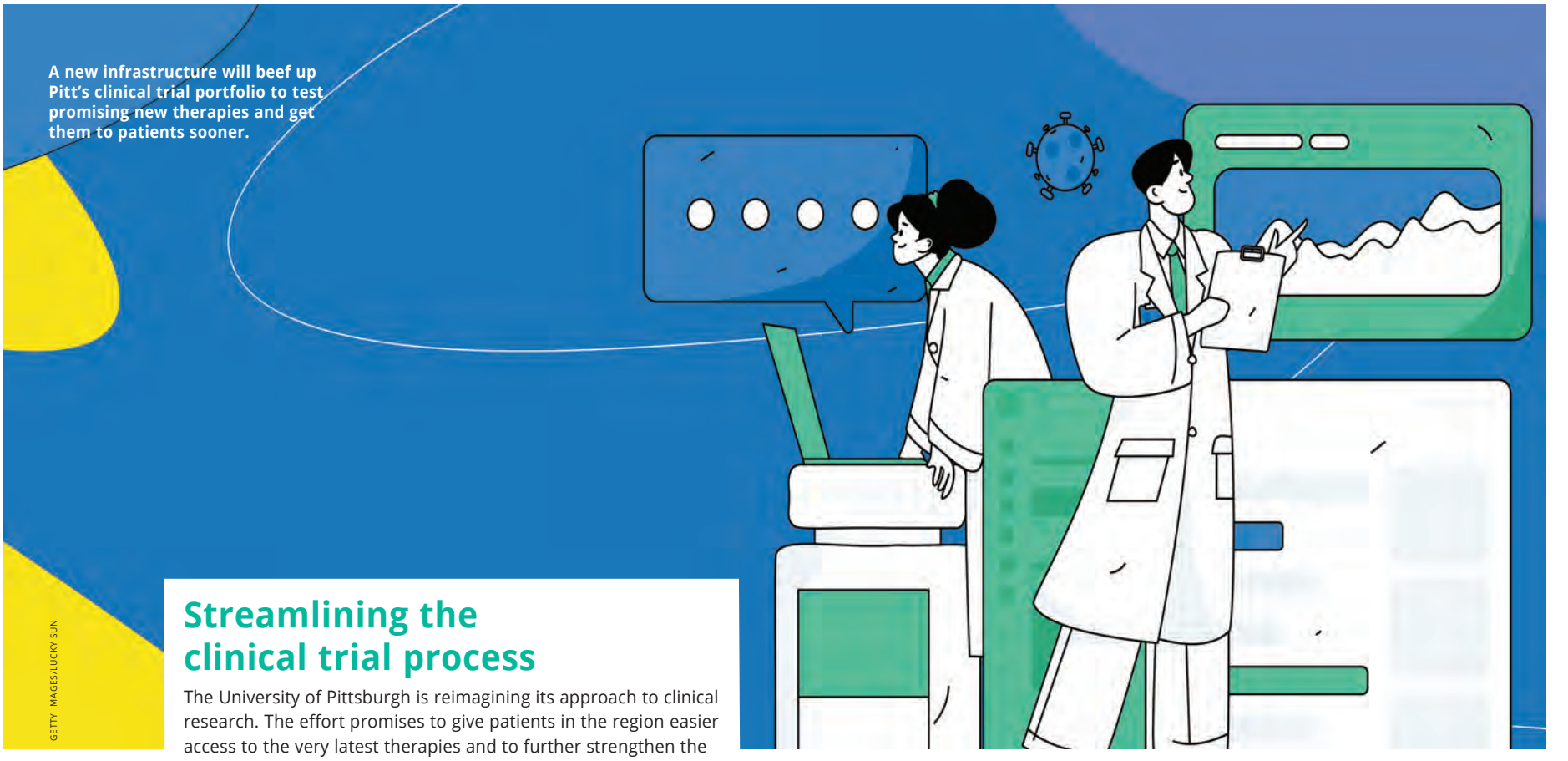
The center is named after the siblings' mother, who had pregnancy complications. The family believes future mothers could avoid such difficulties if doctors had a better understanding of women's health at every stage of the life cycle.

"Issues facing women and girls are underrepresented in medical research, which results in fewer treatments available for them," said Anantha Shekhar, senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine at Pitt. "VIHAR will directly address this issue by coalescing communities of researchers and developing innovative AI tools for efficient analyses."

Gopalakrishnan says VIHAR will focus on preventive health care by creating a massive database of health data of women and girls of all ages. That way, the center can monitor medical trends and find such things as the causes of disease and potential treatments. "We're talking starting with the placenta and going all the way."

Using the power of AI, Gopalakrishnan intends to one day build digital twins, which will simulate and optimize strategies for medical issues as they affect girls and women. "But building the female digital health twin isn't going to be an easy task," Gopalakrishnan cautions. She says it will take coordination at a global scale, millions of dollars and as many as 20 years to accomplish what she has in mind.

Her role, as she sees it, as the center takes shape is part researcher and part administrator. "It's 50-50," she says. Relationship building can't be lost in the mix as she outlines the vision for an effort with a global impact, she says. "We already know this will drive the science." *—Staff reports*



A new infrastructure will beef up Pitt's clinical trial portfolio to test promising new therapies and get them to patients sooner.

GETTY IMAGES/LUCKY SUN

Streamlining the clinical trial process

The University of Pittsburgh is reimagining its approach to clinical research. The effort promises to give patients in the region easier access to the very latest therapies and to further strengthen the health sciences at Pitt.

To ramp up clinical trials, leaders here are building a new infrastructure that streamlines the processes involved, which, until now, had been spread across different offices, departments and pathways at Pitt and UPMC, its clinical partner.

"The purpose is to help our investigators, our clinicians and clinical researchers conduct more clinical trials and conduct them more effectively and efficiently," says Anantha Shekhar, senior vice chancellor for the health sciences and the John and Gertrude Petersen Dean of the School of Medicine.

In January, the new Clinical Trials Office (CTO) launched, becoming the "front door" for clinical research at Pitt. For the first year, it will serve mainly to guide researchers through the current process as the team builds the new infrastructure.

By 2026, the office will act as a central hub for coordinating clinical trials activities, with the ability to handle all aspects of study startup. Another new office, Clinical Research Operations (CRO), will work in tandem with the CTO to offer operational support for studies throughout their life cycle.

Patricia Corby, Pitt's associate vice chancellor for clinical trials development and operations, will lead the CTO, while **Mark Geraci**, vice chancellor for research, health sciences, will lead the CRO. **Uduak Ndoh**, vice chancellor and deputy chief information officer for the health sciences, will lead the clinical technology office, and **Steve Wisniewski**, associate vice chancellor for clinical trials data coordination for the health sciences, will lead a data coordinating center program. The new infrastructure will pave the way toward more multisite, national clinical trials that Pitt's investigators can both design and implement.

The new offices will also help the University to take on more industry-funded clinical trials. In a recent town hall, Shekhar pointed out that of the over $800 million in research funding in the health sciences, only roughly $40 million comes from industry and other nonfederal sources.

"Together, we will create an environment where our faculty and researchers thrive and, ultimately, patients benefit," says Shekhar.

—Staff reports

Next gen

Medical school's packed schedule didn't keep fourth-year student Ashti Shah from reaching the top 2% for research activity among all systems biologists over three years.

Shah received the Foundation of Systems Biology in Engineering (FOSBE) Young Investigator Award in 2024 for her research in computational immunology. She flew to Corfu, Greece, in September to accept the award and give a presentation on the future of systems biology at the 2024 FOSBE conference.

Mentored by Yoram Vodovotz, a PhD professor of surgery now with the Advanced Research Projects Agency for Health, Shah developed software during her research year to model how inflammation, which can be sparked by anything from illness to trauma, spreads throughout body tissue.



Shah



Kudaravalli



Pan

Third-year medical student Sriya Kudaravalli wants more states to expand Medicaid coverage—and save lives.

The Affordable Care Act allowed states to expand Medicaid insurance coverage to reach more people, but some states have declined federal funding for the program. Kudaravalli's research analyzed treatment patterns before and after expansion for more than 3,000 Pennsylvania patients with stage 3 colon cancer. She found that more patients from underserved groups received higher-quality care following the expansion, underscoring how Medicaid can make better cancer care more accessible. Kudaravalli presented her research at the 17th American Association for Cancer Research Conference on Cancer Health Disparities last September.

Fourth-year medical student Daniel Pan received the 2024 West Virginia Governor's Service award for his commitment to STEM education in the state. Pan mentored students at Morgantown High School, where he founded and led a Science Olympiad team to the national competition in 2023 and 2024. Pan also secured funding for students to ensure cost would not be a barrier to participation in future science, technology, engineering and math competitions. *—Staff reports*



AIMEE OBIDZINSKI/UNIVERSITY OF PITTSBURGH

Vaughn Cooper

Overheard The risks of 'mirror bacteria'

The molecules that make up life, like DNA and RNA, have "handedness," just like most people are either right- or left-handed. Over the course of billions of years, all life has evolved standard left-handed proteins.

But what if those proteins were on the right? "Mirror life"—a synthetic organism with reversed "chirality," or handedness, compared to its natural counterpart—is still a hypothetical.

Some scientists have been intrigued by what mirror life could tell us about how life first arose and the idea that it might lead to potent future therapeutics. If developed, however, mirror life could potentially mean a disastrous outcome for existing life, warned a group of 38 multidisciplinary researchers, including the University of Pittsburgh's **Vaughn Cooper**, a PhD professor of microbiology and molecular genetics, and **Timothy Hand**, a PhD associate professor of pediatrics and of immunology, in a paper published by Science in December 2024.

The authors urged a halt to the research and called for a global discussion among scientists, policymakers and stakeholders to examine these risks and determine how to avoid them. They also produced a 300-page technical report supporting their conclusions. In a Q&A, Cooper explains the team's reasoning.

What exactly are mirror bacteria?

Mirror bacteria would be synthesized organisms in which all their molecules are reversed. These organisms don't exist and have never existed. There's been significant movement in this area of research in the last few years, but the actual creation of mirror bacteria would be at least a decade, possibly several, away.

The notion of mirrored life goes back decades, but only a few have been able to make progress on the foundational technology needed to develop mirror bacteria. Many of them now welcome a new path forward to understanding mirror life without incurring the vast risks it could pose.

What are the risks if they're created?

Before digging further, our team of scientists was skeptical—myself included—of the risks that these synthetic organisms could pose. We learned that if they're successfully created—which would require an enormous effort—mirror bacteria would likely be able to evade many human, plant and animal immune system responses, possibly leading to widespread, lethal infections in multiple species.

In the natural world, viruses, other microbes and predators limit microbial populations. But mirror bacteria, because of their reversed structure, would likely be able to evade these predators and establish themselves, with catastrophic consequences.

When my coauthors and I came to this conclusion, we reached out to other experts and challenged them to find fault with our hypothesis and concerns, which is a great example of how science should work. None of us were able to find a critical flaw in what we discovered.

What are the consequences of stopping this research?

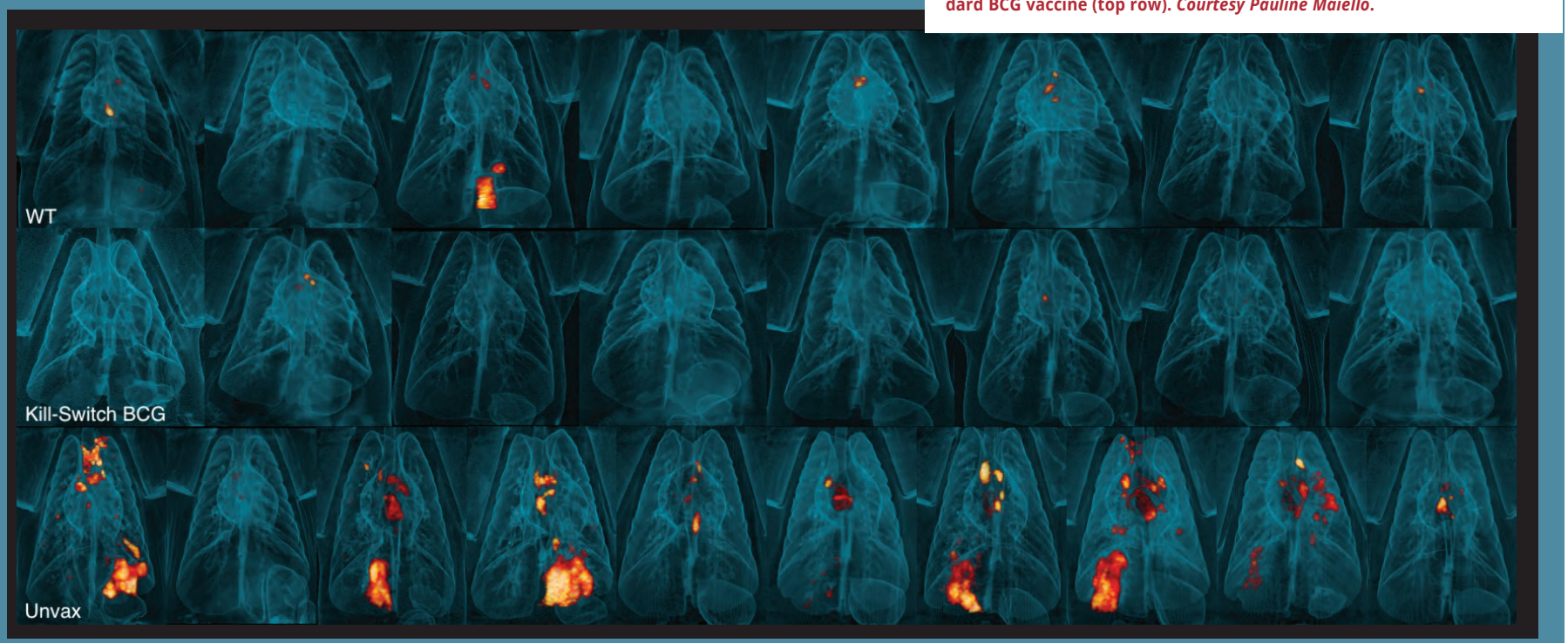
From my perspective, there aren't really any practical benefits to mirror bacteria, so ceasing this work would have very little effect on other research. Research on mirror-image nucleic acids and proteins that could help targeted therapies or new drug delivery systems will be able to continue.

Now that we know that this problem exists, how do we navigate it?

There's an opportunity here that we didn't have before. Discussing it now allows us to consider and prevent the risks of mirror bacteria long before they're realized.

At this moment, we are urging the scientific community to no longer pursue research with the goal of creating mirror bacteria, as well as encouraging funders to make clear they won't support this work. We're inviting the global scientific community to attend a series of events to further examine the risks and explore promising ways to avoid them. By making this a global effort, we're far ahead of this ever becoming a problem.

—Interview by Kat Procyk. The conversation has been condensed and edited for clarity.



PET-CT scans of monkey lungs. While unvaccinated macaque monkeys exhibited signs of severe lung inflammation and disease following Mycobacterium tuberculosis infection (warm colors indicate inflammation and disease, bottom row), monkeys that received the intravenously administered kill-switch BCG vaccine (middle row) were equally or better protected against the infection as those immunized with the standard BCG vaccine (top row). *Courtesy Pauline Maiello*.

TB breakthrough

Tuberculosis was named the deadliest infectious disease of 2024 by the World Health Organization, and safe and effective protection strategies against the infection are lacking.



Flynn

New Pitt research points to a promising way to combat it: a self-destructing, intravenously administered vaccine. A study published in Nature Microbiology in January found it provided additional protection against the disease in macaque monkeys, and its built-in safety mechanisms circumvent the possibility of an accidental self-infection with weakened mycobacteria.

"To our surprise, it was equally good, or even slightly better, than the regular TB vaccine in protecting monkeys against infection, providing sterilizing immunity in almost all animals," says JoAnne Flynn, a senior author of the study, a PhD Distinguished Professor of Microbiology and Molecular Genetics at Pitt and chair of that department. "The live-attenuated form of the mycobacteria does not need to be alive for very long to provide outstanding protection, and with this strain there is essentially no chance for a vaccine-derived infection, even in an immunocompromised host."

The standard TB vaccine contains inactivated mycobacteria that naturally infect cattle and remains the only vaccination strategy against the infection in humans. Injected into the skin, it provides only partial protection against TB in young children and no protection in adults.

To develop a more universally effective vaccination approach, Flynn partnered with colleagues at Cornell University. In Flynn's earlier work in macaque monkeys with collaborators at the National Institutes of Health, the researchers saw a 100,000-fold reduction in bacterial burden in the lungs of animals that were given the BCG (Bacille Calmette-Guérin) vaccine intravenously compared with the standard route of delivering it through the skin with a needle. Nine out of 10 animals showed no inflammation in their lungs in that study.

To improve the safety of the IV vaccination, researchers engineered two built-in mechanisms that instruct the BCG particles to dissolve either upon exposure to the antibiotic doxycycline or when chronic doxycycline treatment is stopped.

In macaque monkeys, the updated self-destructing BCG vaccine caused an even stronger immune response and better protection against TB than a standard IV BCG injection.

Says Flynn: "We hope that this 'kill-switch' BCG strain could limit safety concerns over intravenous vaccine administration and provide an option for a safer and more effective vaccination route for individuals who are immunocompromised." *—Anastasia Gorelova*

A model of mentorship



Bondi

Corina Bondi, a PhD associate professor of physical medicine and rehabilitation and associate director of the Safar Center for Resuscitation Research, received two awards for her outstanding work as a mentor.

Bondi first received the 2024 Landis Award for Outstanding Mentorship from the National Institute of Neurological Disorders and Stroke. She was one of five recipients and the first from Pitt to earn the award.

Then, at the annual meeting of the Society for Neuroscience in Chicago, she received the society's Faculty for Undergraduate Neuroscience Mentor Award.

Among Bondi's many activities, she also trains undergraduates and encourages her team to take part in community outreach initiatives, including one in which her mentees present topics related to traumatic brain injury prevention at local elementary schools. *—Staff reports*



GETTY IMAGES/AGUS SUBIANTO

Vulnerable and stronger for it

A MED SCHOOL STORY SLAM DEMONSTRATES IMPORTANCE OF REFLECTION.

A soft hum of anticipation fell over the auditorium as the first medical student stepped up to the microphone. Clutching a small tablet, she paused, took a deep breath and began. Her voice wavered at first, yet as she recounted the moment she had become a patient, the room fell silent.

"Throughout the 40 days and 40 nights I spent as a patient in a psychiatric hospital, the biggest loss I experienced was trust—the trust I had in my mind's ability to consistently function lucidly. However, what I gained was far greater: immense gratitude for every single day that I wake up and remember my own name."

For one night in September, the sterile walls of a lecture hall transformed into a haven for connection, where the weight of white coats gave way to vulnerability and emotion. It was the University of Pittsburgh School of Medicine's story slam, a celebration of humanity and the transformative power of storytelling. Second-year medical students Elise Barberis, Eugene Kim, Maya Singh and Ivy Yip, who share a passion for the intersection of writing and medicine, hosted the event as part of the Pitt Med student group In Your Own Words. The story slam, called "Lost and Found: Stories of Gains, Losses and Growth," invited students and faculty from the School of Medicine and across the University to share their personal journeys in health care.

The slam was designed to nudge participants out of their comfort zones, creating a space where people at various stages of their health care journeys could share their experiences, as well as their vulnerabilities. Watching participants embrace the challenge and support each other, even in moments of nervous anticipation backstage, was both inspiring and rewarding, say the organizers. For some, storytelling became a way to process moments that had lingered unresolved in their minds. Gaetan Sgro, an MD clinical associate professor of medicine, shared a story he had been grappling with for almost 12 years.

"Throughout my career, I have revisited this irony—that I had missed my Granny's passing so that I could be there for someone else's Granny. Even in the moment, I remember being attuned to this cosmic symmetry." As Sgro, an accomplished poet, contemplated the complexity of our spirit, the audience joined him on his journey. The story slam reminded participants that they are not alone in their struggles or triumphs.

The event also highlighted the role storytelling can play in bridging the gap between clinical detachment and genuine connection. The hospital environment and all its quality and efficiency protocols, for instance, can be humanized through moments of reflection, reminding us that medicine is as much about understanding people as it is about treating conditions.

As Robin Maier, an MD, MA associate professor of family medicine and story slam participant, put it, "You don't really understand what just happened until you tell a story about it." *—Anvi Jain*

Itching and scratching: the skin-ny

You heard it plenty as a kid: Stop scratching, or you'll make the bug bite worse. But why does scratching feel so good? Other animals itch, too, from squirrels to fish. Scratching helps us detect and remove parasites like fleas, and it also activates an immune response in the skin. Plus, the annoyance of itching teaches us to avoid the trigger in the future. New findings from University of Pittsburgh researchers, including Dan Kaplan, an MD, PhD professor of dermatology and immunology, reveal there's more to the story. And Sarah Ross, a PhD professor of neurobiology, has detailed exactly how the sensation makes it through the spinal cord to the brain. *—Livia Daggett and Erica Lloyd*



GO AHEAD AND SCRATCH, A LITTLE.

When mice infected with Staphylococcus aureus, bacteria commonly found on humans, were allowed to scratch, they had significantly less bacteria on their skin after 24 hours than mice that weren't able to scratch, observed Marlies Meisel, a PhD assistant professor of immunology and coauthor with Kaplan on a recent paper in Science. That means a scratch's bacteria-fighting potential could be an evolutionary benefit in certain cases—though damage to the skin can outweigh it if you scratch long enough, says Kaplan.

BUT DON'T SCRATCH THAT!

If you rub up against poison ivy or something else you're allergic to, the allergens activate mast cells in your skin, leading to itchiness. With the Kaplan team, Andrew Liu, an MD, PhD student who is first author on the Science paper, found that scratching the itch causes pain-sensing neurons to release substance P, a molecule that further activates mast cells, aggravating the inflammation. In other words, in this case, your parents were right. Scratching makes allergic reactions worse.

RELIEF IN REACH

Within those first protective layers of the skin, certain neurons release glutamate, which suppresses inflammation-causing mast cells. Ramping up glutamate production by these neurons can prevent inflammation and subsequent pain or itch. A small molecule called beta alanine activates these neurons and is being explored as a therapy for mast cell–mediated diseases, says Kaplan. This could mean sweet relief for people with certain chronic skin conditions or hives.

PHOTO: SONY MOON/GETTY IMAGES

HOW DOES THE BRAIN GET THE SIGNAL THAT WE HAVE AN ITCH?

Once skin cells sense the need to itch, the immune system responds, as do the neurons that reach from our skin to the spinal cord. Then a network of spinal cord neurons, with its chemical messengers, takes over. Sarah Ross provided insight into this network when she was a postdoc at Harvard. In 2010, she reported that a loss of certain neurons in mutated mice made itch a lot worse, abnormally elevated in fact. She labeled that group B5-I and later identified them as spinal neurons that make the opioid peptide dynorphine. (Don't forget that our bodies naturally make some opiates.) In 2011, Ross established her own lab at Pitt, where throughout the next several years her team went on to figure out the rest of the odyssey of an itch. Former Ross lab team members Adam Kardon, now a DO neurologist, and Tayler Sheahan, a PhD, were lead authors on key papers.

An itch signal travels through spinal neurons that make dynorphine to dampen the itch urge or, if they're disrupted, make it worse. Opioid peptides and their receptors play a big role, the Ross lab has found. These discoveries "made sense because drugs that activate the kappa opioid receptor were known to inhibit itch" in certain conditions, says Ross. She says that her lab's findings suggest that drugs that work on the same receptor could be used to treat all kinds of itch.

NO SKIN IN THE GAME

We can feel an urge to itch even without a skin irritant. It's not unusual for patients who receive epidurals or spinal opiates to experience itch. Eileen Nguyen (MD '22, PhD '21), who worked in Ross's lab as a student and is now an anesthesiologist at UCLA, figured out why. It turns out that spinal morphine inhibits the neurons that tamp down itch, sort of a double-negative in the nervous system.

WHY DO WE RANDOMLY ITCH SOMETIMES?

"I don't think anyone knows," says Ross.

PHOTO: SONY MOON/GETTY IMAGES



SUPER

NEUROSTIMULATION STRENGTHENS WEAKENING LEGS.

BY MICHAEL AUBELE AND ANASTASIA GORELOVA

A degenerative illness has zapped the strength in Doug McCullough's legs, though spinal cord stimulation substantially restored it when applied during clinical testing. ABOVE: McCullough walks with assistance during a 2023 clinical trial at Pitt.

NATE LANGER/UPMC AND PITT HEALTH SCIENCES

When he started to do the math, Doug McCullough thought, "Wow! What if I had this stimulation on continuously?" McCullough was one of three patients with spinal muscular atrophy (SMA) who participated in a clinical trial in 2023 to test the benefits of electrical stimulation of the sensory spinal nerves; his leg strength improved—so much so that he would return to his hotel room at night feeling like his legs were "supercharged." He wore a device that would stimulate his spinal cord for about two hours a day for a month and would enhance his ability to walk.

It got him to consider the possibilities. "We were on an upward trajectory as far as the benefits we were seeing. So I wonder, if I had this on for longer, what would the results be? It's not like the results plateaued."

SMA is an inherited neurodegenerative disease that manifests in progressive death and functional decline of motor neurons, nerve cells that control movement by transmitting signals from the brain and the spinal cord to the muscles.

Through time, the loss of motor neurons causes gradual muscle weakness and leads to a variety of motor deficits. The participants in this trial had difficulty walking, climbing stairs and standing up from chairs.

CHARGED

McCullough first noticed symptoms when he was 11 and was losing his ability to run as fast as everyone else his age, though it took a while to be properly diagnosed. He's 57 now, and around 2018, he started using a cane full time. At the time of the study, he was able to walk short distances using two canes, though longer distances required a power wheelchair. He's currently dependent on the wheelchair after breaking his femur in 2024. A major goal once his leg heals, he says, is to be able to move about his house freely, even without the use of a wheelchair.

Early results of the study show that one month of regular neurostimulation sessions improved motoneuron function, reduced fatigue and improved strength and walking in all three participants, regardless of the severity of their symptoms. The study is the first to show that a neurotechnology can be engineered to reverse degeneration of neural circuits and rescue cell function in a human neurodegenerative disease.

"To counteract neurodegeneration, we need [to do] two things: stop neuron death and restore function of surviving neurons," says Marco Capogrosso, a University of Pittsburgh PhD assistant professor of neurological surgery who was co-corresponding author on a February 2025 Nature Medicine paper reporting on the study. "In this study, we proposed an approach to treat the root cause of neural dysfunction, complementing existing neuroprotective treatments with a new approach that reverses nerve cell dysfunction."

While there is no cure for SMA, several promising neuroprotective treatments have become available in the last decade. These include gene replacement therapies and medications, both of which stimulate the production of motoneuron-supporting proteins that prevent neuronal death and that slow down—but do not reverse—disease progression. But studies show that movement deficits in SMA emerge before widespread motoneuron death, suggesting that underlying dysfunction in spinal nerve circuitry may contribute to disease onset and symptom development. According to earlier research on animal models of SMA by paper coauthor George Mentis, a PhD professor of pathology and cell biology at Columbia University, surviving motor neurons receive fewer stimulation inputs from sensory nerves, fibers that return the information from skin and muscles back to the central nervous system. Compensating for this deficit in neural feedback could, therefore, improve communication between the nervous system and the muscles, aid muscle movement and combat muscle wasting.

Pitt researchers hypothesized that a targeted epidural electrical stimulation therapy could rescue lost nerve cell function by amplifying sensory inputs to the motor neurons and engaging the degenerated neural circuits. These cellular changes could, in turn, translate into functional improvements in movement capacity.

A pilot clinical trial included McCullough and two other men with milder forms of SMA. During the 29-day trial, a surgical team implanted the men with two electrodes in the lower back on each side of the spinal cord, directing the stimulation exclusively to sensory nerve roots. The men took part in testing sessions that lasted four hours each, five times a week, for a total of 19 sessions, until the device was removed.

After confirming that the stimulation worked and engaged spinal motor neurons, researchers performed a battery of tests to measure muscle strength and fatigue, changes in gait, range of motion and walking distance, as well as motoneuron function.

"Because SMA is a progressive disease, patients do not expect to get better as time goes on. But that is not what we saw in our study," says co-corresponding author Elvira Pirondini, a PhD assistant professor of physical medicine and rehabilitation at Pitt. "Over the four weeks of treatment, our study participants improved in several clinical outcomes with improvements in activities of daily living. For instance, toward the end of the study, one patient reported being able to walk from their home to the lab without becoming tired."

The team captured footage of McCullough at various points during the trial to monitor his progress.

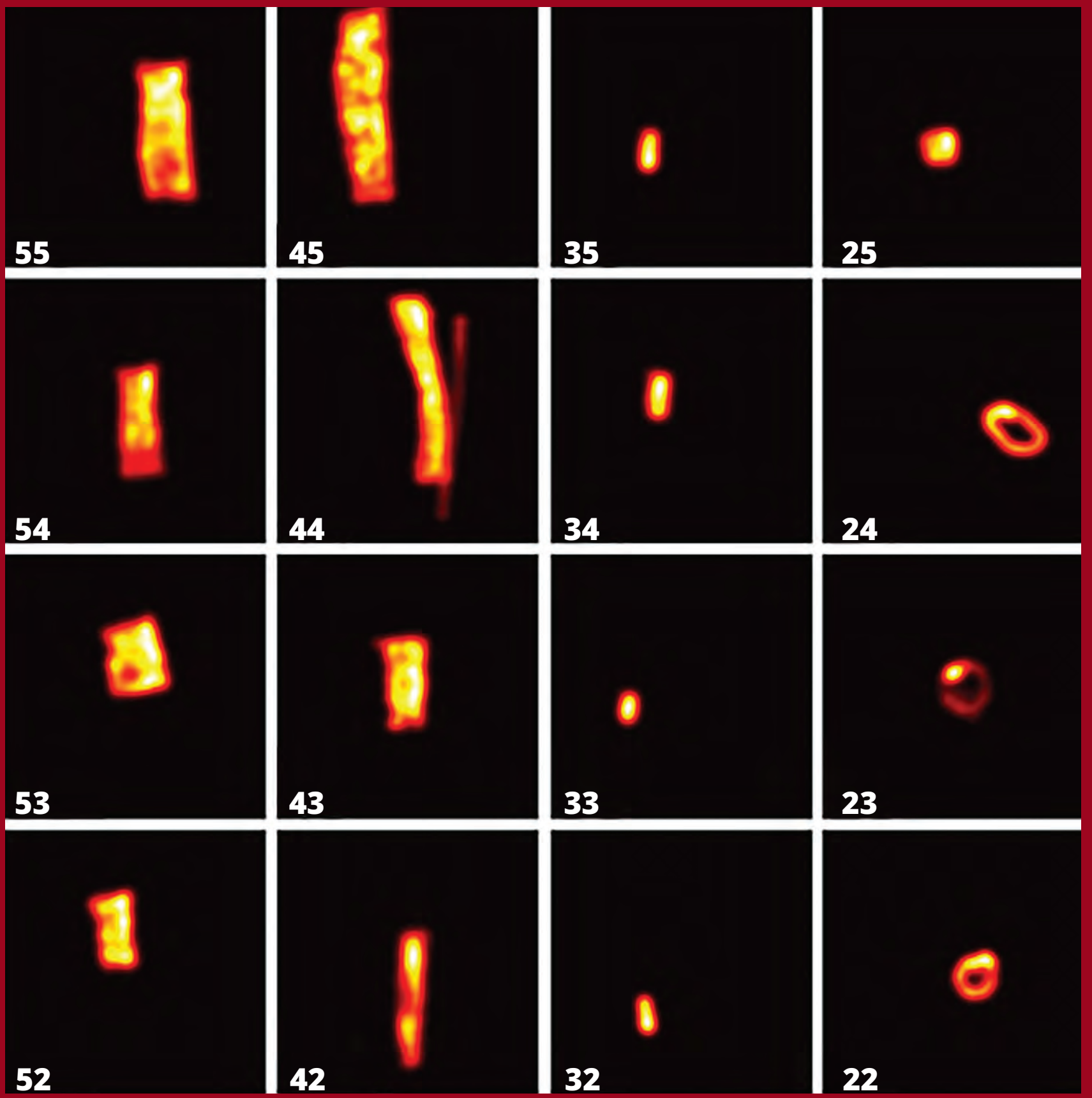
"Because my hip flexors are so weak," McCullough says, "I basically have this waddling gait where my hips sway back and forth, and I swing my legs out to the side because I can't pick them straight up. You could clearly see from the video that my walk was improved and that I was walking faster. I had a little more natural gait. It still wasn't completely normal, but it was better than what it was before the study."

All participants increased their 6-Minute Walk Test score—a measure of muscle endurance and fatigue—by at least 20 meters, compared to a mean improvement of 1.4 meters over three months of comparable exercise regimen unaided by spinal cord stimulation and a median increase of 20 meters after 15 months of SMA-specific neuroprotective pharmacologic therapy.

These functional gains were mirrored by improved neural function, including a boost in motoneuron capacity to generate electrical impulses and transmit them to muscle.

Capogrosso, Pirondini and other Pitt researchers who collaborate through Pitt's Rehab Neural Engineering Labs have been testing the usefulness of spinal cord stimulation to treat other neurological conditions, including stroke and phantom limb pain, with success. (The technology has been used for decades to treat persistent pain.) Based on the results of this study, there is hope the therapy can be used to treat other neurodegenerative diseases.

"Our results suggest that this neurostimulation approach could be broadly applied to treat other neurodegenerative diseases beyond SMA, such as ALS or Huntington's disease, as long as appropriate cell targets are identified in the course of future research," says co-corresponding author Robert Friedlander, an MD, MA Distinguished Professor of Neurological Surgery and chair of the department at Pitt. "We are hoping to continue working with SMA patients and launch another clinical trial to test the long-term efficacy and safety of electrical spinal cord stimulation." ■



Stimulating neurons in the visual cortex can produce perceived spots of light called phosphenes. These are drawings of phosphenes made by a blind patient. Each panel depicts a phosphene created by stimulation from one electrode.

PROGRESS IN ARTIFICIAL VISION

CHEN'S WORK DESIGNED TO PREVENT MERGING IMAGES

BY MICHAEL AUBELE

Maybe you're familiar with the toy Lite-Brite. Picture a kid at the kitchen table plugging backlit yellow pegs into a board to make the outline of a sun with a smiley face. At age 4, she's proud of her art, and her parents probably think she's a genius. But then she haphazardly fills in most of the holes inside and around the sun with more yellow pegs. Now it looks like a bright yellow blob.

That blob could represent phosphene fusion, which happens when perceived dots of light, called phosphenes, merge in the visual field. Scientists for decades have been trying to use phosphenes to let people "see" without their eyes but have found that the discernable images of objects they can create often blend to form a single unit of light.

Xing Chen, a PhD assistant professor of ophthalmology at the University of Pittsburgh, wants to better understand how phosphene fusion occurs—and how to circumvent it to improve artificial vision using a brain-computer interface. A recipient of a National Institutes of Health Director's New Innovator Award, Chen is pursuing these questions with a $1.5 million grant from the NIH's High-Risk, High-Reward Research Program. She hopes her research will eventually assist those with blindness resulting from damage to the eye, optical nerve or both.

Stimulating neurons in the visual cortex produces phosphenes. Chen says that, typically, placing a small number of electrodes not too close together on the surface of or in the brain can create phosphenes in recognizable shapes. Research like this in nonhuman primate studies and human clinical trials dates to the 1960s and has included both those who are sighted and those who are blind. (Her current study involves macaque monkeys that can see.)

Chen and her team are using 16 arrays of 64 electrodes each, for a total of 1,024 silicon electrodes, and implanting those into the brains of the macaques. That's more than 10 times the number used in a recent human trial that helped a woman blind for 16 years recognize various shapes.

The high count not only allows the monkeys to perceive phosphenes in the shapes of letters but also to determine horizontal versus vertical orientation and even sense motion. To confirm that the monkeys recognize the phosphenes, the scientists use methods such as tracking eye movements. A brain-computer interface also allows the researchers to send signals to the brain and receive signals back so they can track neuronal activity.

Eduardo Fernandez, an MD, PhD professor of cellular biology at Miguel Hernández University in Spain, who is working with Chen as a clinical collaborator, led the clinical trial that helped the woman "see." He says while Chen's study is ambitious, the technology still has a way to go.

"Although 1,024 electrodes are a significant achievement with current technology, this is still a low number in comparison to the more than one million axons each human eye [uses to send information] to the brain," Fernandez says. "This vast difference likely underlies the current limitations of cortical visual prostheses: low visual acuity, poor spatial and temporal resolution and limited control over phosphene perception." Innovative approaches like Chen's are needed to move the field forward, he says.



Chen

Throughout five years, Chen will implement her technique bilaterally in the brain and elicit phosphenes across a larger area of the visual field. It's uncharted territory in this type of research.

"Creating bilateral cortical visual implants presents significant challenges," Fernandez says. The surgical complexity is doubled, requiring precise implantation in two brain regions. And the bilateral approach requires the researchers to manage the interaction and coordination of both implants to create coherent visual percepts.

"This raises many scientific and technological questions, which is probably why we haven't seen successful bilateral implants yet," he says.

Chen is intent on advancing this field, and not through baby steps: "So, the main goals are to be able to investigate how phosphene fusion occurs—how many electrodes could potentially be inserted, while we stimulate in a way that prevents [the fusion] from occurring, which will give us an overview of how far we can push the technology." ■

EDUARDO FERNANDEZ, MIGUEL HERNÁNDEZ UNIVERSITY



Antibiotics aren't effective against biofilms, which form when communities of bacteria (blue) cluster and embed in an extracellular matrix (red).

JESSICA GILBERTIE

JOINT VENTURES

NEW WAYS TO BATTLE INFECTIONS IN KNEE AND HIP REPLACEMENTS

BY KIRA GOLDENBERG

Total hip and knee replacements are the most common major surgical procedures in the United States; about 1.3 million people undergo one of them annually. When the procedures work without complications—which they do the vast majority of the time—they can transform lives, making chronic pain vanish and increasing mobility.



Urish

"Patients would do anything to be able to get from point A to point B and not have it hurt them," says Ken Urish, associate professor of orthopaedic surgery at Pitt. He's also the associate medical director of the Bone and Joint Center at Magee-Womens Hospital and director of the Arthritis and Arthroplasty Design Group at Pitt.

After graduating from the Medical Scientist Training Program here, Urish (MD '08, PhD '06) became fascinated with prosthetic joint infection during residency. He researched biofilms, the protective clusters of largely dormant bacteria that can form—and then wreak havoc—in prosthetic joints. Biofilms don't typically respond to antibiotics, the longtime standard treatment for eradicating infection, for a number of reasons. They are difficult to penetrate, and the dormant bacteria within can survive even under extreme conditions.

Infection happens in just 1–2% of hip and knee replacement cases, Urish says, but the popularity of the surgery means infection affects more than 26,000 patients in this country each year.

"It's such a big problem, and there aren't many good solutions," Urish says, especially since it's virtually impossible to discern whether an infection has been completely vanquished. "Because you're trying to save the implants, and you're not removing them, a certain amount of that biofilm is still stuck somewhere around the implant."

Thanks to research coming out of his lab, however, good solutions are en route. Ideas that originated with Urish and colleagues form critical parts of current FDA-funded clinical studies with the potential to help heal joint replacement biofilm infections. Urish is leading work on using a potential new class of antibiotics on these infections, applying antibiotics in addition to a standard joint-washing procedure to decrease recurrence, and employing bacteriophages—viruses that "eat" bacteria—to manage chronic conditions.

The new antibiotics class, which uses molecules called antimicrobial peptides (AMPs), was developed to disrupt bacterial membranes, so it includes good candidates for attacking biofilm and other normally antibiotic-resistant microbes. (Peptides are chains of amino acids.)

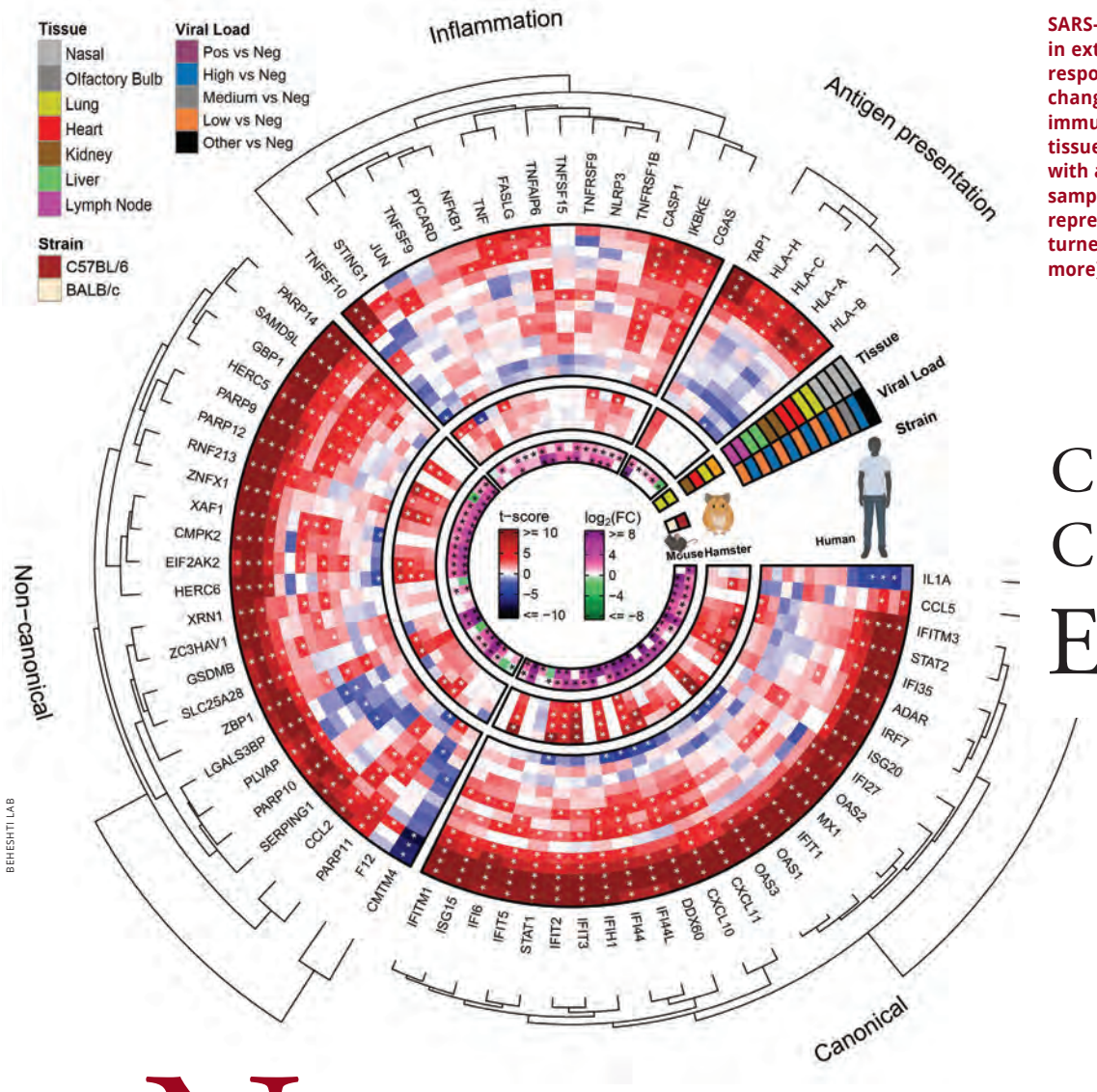
"It worked independently on biofilm, which no other compound had ever been demonstrated to do," Urish says. In an early phase clinical trial, a majority of joint replacement patients with infection showed no recurrence. (The early data were shared in 2023 by Peptilogics, a Pitt startup that Urish works with and has equity in.)

Another infection-control method Urish studies is what he calls a "rapid two stage." Currently, the standard approach for fighting stubborn, antibiotic-resistant infections in implants is surgery to perform joint washing and replacement accompanied by a long, sedentary course of IV antibiotics. In a phase 2 clinical trial, which includes a Pitt site, doctors are instead following the joint washing with localized antibiotics to see if the combination eradicates biofilms. "Our laboratory data was very strong support for their approach," Urish says.

Urish and collaborators are also attacking biofilm infections through the use of bacteriophages, viruses that destroy bacteria by inserting their genetic material into them and replicating. In a preprint paper currently under review for publication, with Urish as senior author, his team documents treating a man with chronic, multidrug-resistant infection in his knee joint replacement who was otherwise set to begin palliative care.

Although the technique, authorized by the FDA for compassionate use in this case, did not completely eliminate the infection, it was controlled, and the patient achieved greater mobility.

"As a physician or a surgeon, you just want to take good care of your patients," Urish says. "These are tools that help me take good care of my patients." ■



BEHESHTI LAB

SARS-CoV-2 impacts genes involved in extracellular-mediated immune responses. This heatmap shows changes in gene activity related to immune defense in different samples: tissue from infected hamsters, patients with and without the virus, and lung samples from infected mice. The colors represent how much these genes are turned up (deep red and purple indicate more) or down in response to infection.

COVID COMPLICATIONS EXPLAINED

DAMAGE TO LYMPH NODES AMONG FINDINGS

BY ASHER JONES

New findings shed light on the pathways that drive organ damage and death in severe COVID-19 and help explain why survivors of the disease can experience long-term complications.

"Our study resolves some of the long-standing unanswered questions about how the SARS-CoV-2 virus impacts the body," says cosenior author Afshin Beheshti, a PhD professor of surgery and of computational and systems biology at the University of Pittsburgh and associate director of the McGowan Institute for Regenerative Medicine. The team's results were published in the Proceedings of the National Academy of Sciences in November 2024.

For the study, Beheshti, president of the COVID-19 International Research Team, brought together a multi-institutional group that included researchers from Johns Hopkins University, Children's Hospital of Philadelphia and Weill Cornell Medicine.

By analyzing the expression of genes in nasal swab samples from patients with severe COVID-19 compared to those from healthy people, the researchers found that SARS-CoV-2 disrupts essential reactions in the mitochondria, the cell's energy-producing factories. Mitochondrial stress leads to the release of compounds that act as danger signals, which in turn trigger immune sensors that activate what's known as the renin-angiotensin-aldosterone system (RAAS).

RAAS is a network of hormones, proteins and enzymes that's essential for regulating blood pressure but can trigger a cascade of organ-damaging events when overactivated. In severe COVID-19, overactivation of RAAS and mitochondrial stress intensify the out-of-control immune reaction, or cytokine storm, often seen in patients with severe COVID-19.

Unique among COVID-19 studies, this research used a comprehensive analysis of autopsy samples to analyze organs of patients who died from the disease.

The team found that overactivation of RAAS and a cytokine storm combine to create a hurricane of inflammation that's damaging to multiple organ systems, leading to heart failure, myocardial injury, pulmonary fibrosis and chronic kidney disease, all conditions often seen in long COVID patients.



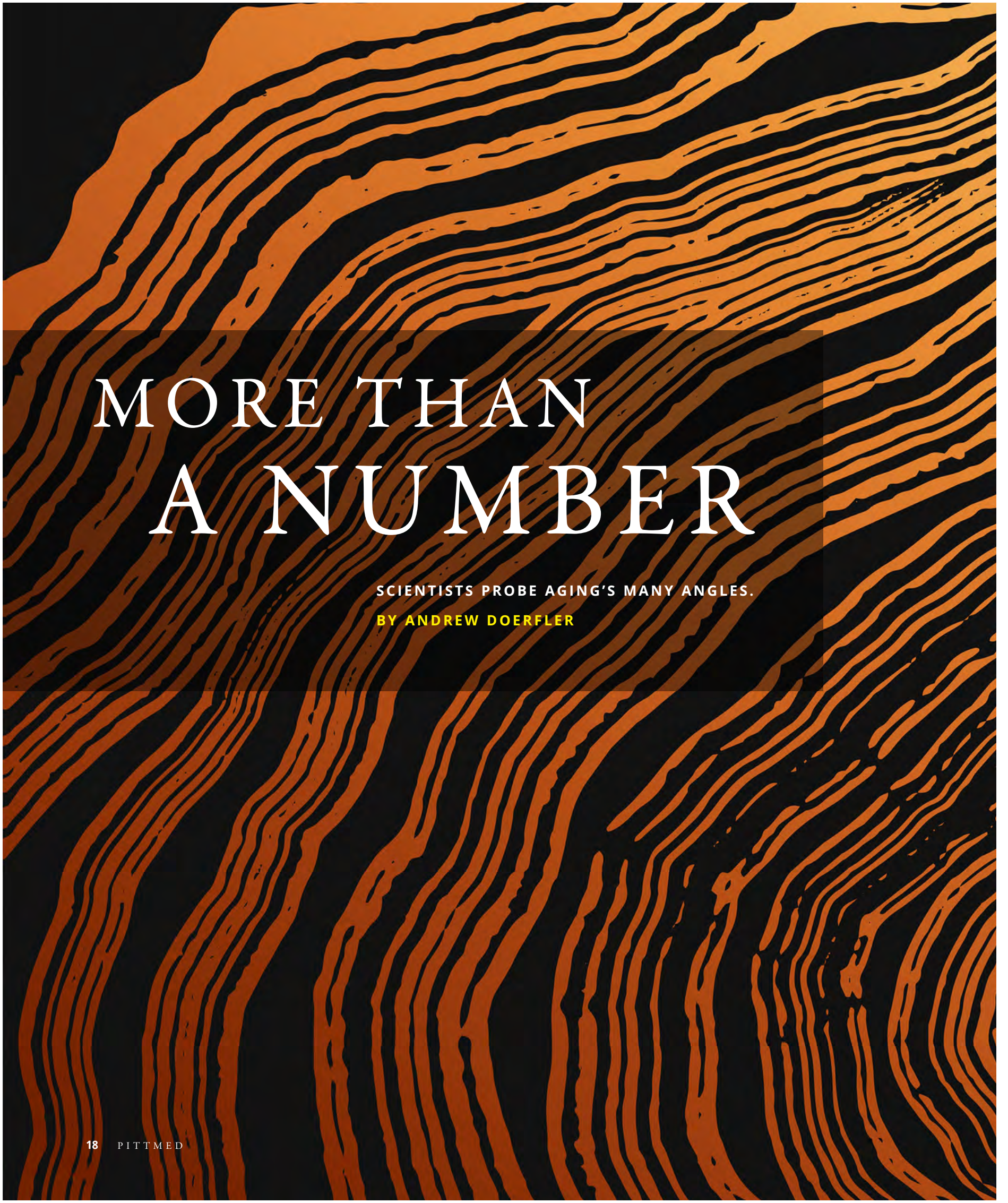
Beheshti

"Notably, we also found that activation of RAAS caused substantial damage to the lymph nodes, which hasn't been shown in COVID-19 before," says Beheshti, who is also director of Pitt's Center for Space Biomedicine. "This could explain the long-lasting immune dysregulation seen in survivors of COVID-19 and may contribute to long COVID."

It's also possible that this damage to lymph nodes could impair the immune system's ability to detect and destroy cancerous cells, which might help explain the postpandemic increase in cancer cases.

According to Beheshti, the new findings suggest that targeting RAAS overactivation and supporting mitochondrial function could be new approaches for developing therapeutics to prevent or mitigate severe COVID-19 outcomes and potentially reduce the risk of long COVID. ■

Online only: In other COVID news, Pitt researchers have developed a powerful tool that can detect variants of the virus with high transmission potential before they become widespread. See **pi.tt/spreadCOVID**



MORE THAN A NUMBER

SCIENTISTS PROBE AGING'S MANY ANGLES.

BY ANDREW DOERFLER



In January, Netflix released the documentary "Don't Die: The Man Who Wants to Live Forever." Even if you haven't watched it, you may have heard about its subject: Bryan Johnson, the 47-year-old tech millionaire with pasty skin and statuesque muscles who dedicates every waking and sleeping hour to the extension of his lifespan.

His mission, which has been met with both admiration and derision, involves millions of dollars; strict sleeping, eating and exercise regimens; scores of pills a day and dozens of other medical interventions with wildly varying levels of efficacy and safety established by scientific literature. They range from mildly unorthodox to unnerving, even among his inner circle. (He's tried red-light therapy, penis shockwave treatment and an experimental gene therapy he received on a legally permissive island off the coast of Honduras.)

As the movie concludes, text on screen shares that Johnson says he has achieved a "personal best" biological aging rate of .64 years for every one chronological year.

If only aging rates were that clear.

While a wall calendar and a birth certificate do the trick for determining a person's chronological age, pinning down biological aging remains complex, even for top experts—and beyond the grasp, at this point, of a simple test spitting out a conclusive number that captures all its facets.



Newman



Finkel

"There's a lot of discussion about what's the best way to measure aging, and we don't have a best way yet, basically," says Anne Newman, an MD, MPH, the clinical director of the University of Pittsburgh Aging Institute who holds the UPMC Chair in Geroscience. "We have lots of interesting ways that are promising."

Appreciation for that complexity is built into the foundation of the Aging Institute, and it drives the way its scientists search for answers. While Johnson's constantly changing smorgasbord of interventions makes it impossible to parse out which are helping and how much, Pitt researchers are probing the many angles of aging in rigorous, interdisciplinary fashion. They're reaching new insights that paint a clearer picture of what it means for the human body to get older—and how to make that process a healthier one.

The need for answers is urgent as the world shifts toward an older population because of falling birth rates and interventions that extend life. The total number of people 65 and older is expected to more than double from 2020 to 2050, rising from around 730 million to 1.57 billion. But longer lives don't necessarily mean healthier aging, and age remains the single greatest risk factor for disease.

Still, interest in the science of aging is fairly recent, as is robust funding to tackle these questions. Toren Finkel joined Pitt and UPMC, Pitt's clinical partner, in 2017 to lead the Aging Institute after nearly 25 years at the National Institutes of Health.

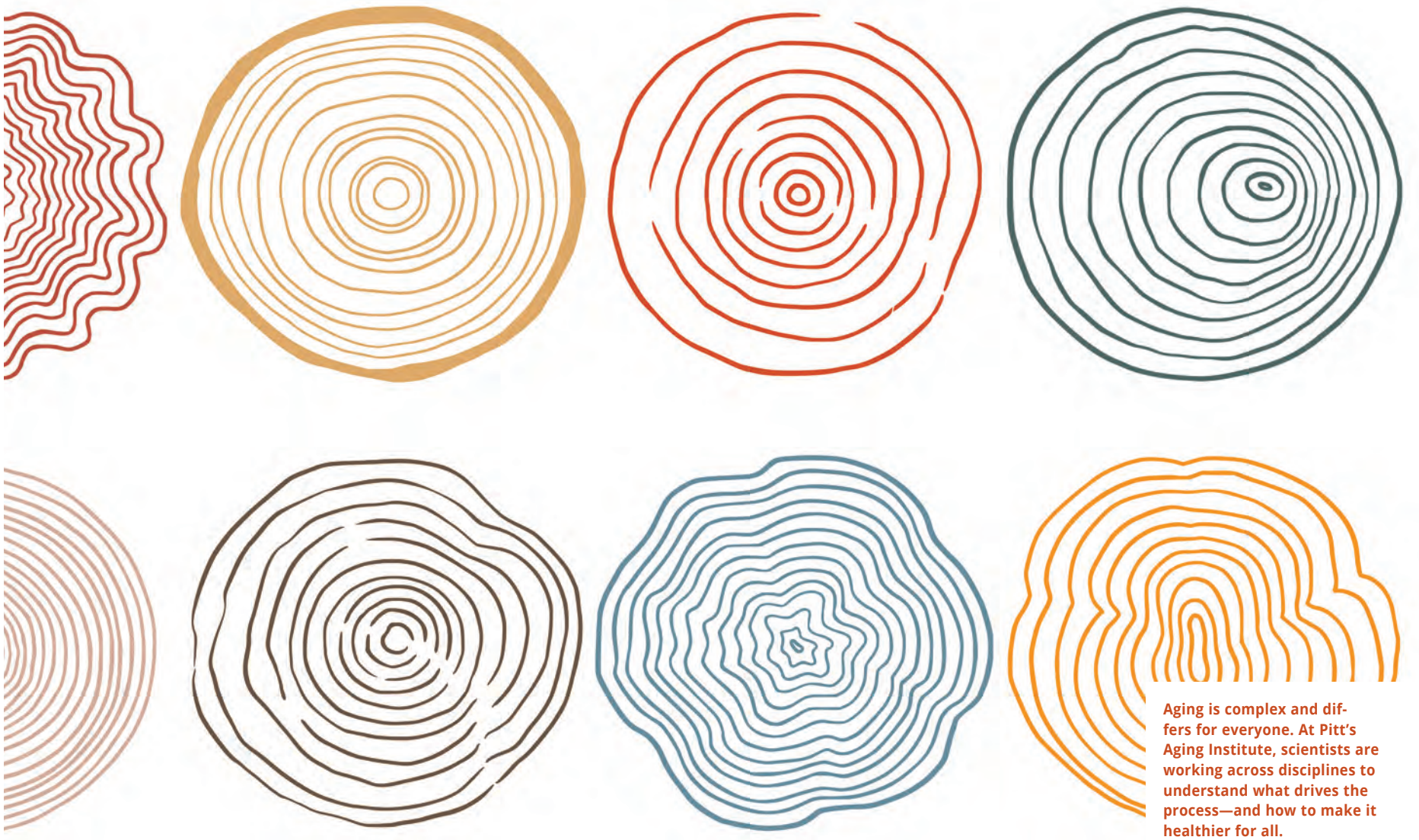
"When I was in medical school, [the science of aging] wasn't even in the curriculum," says Finkel, an MD, PhD who is a Distinguished Professor of Medicine as well as the G. Nicholas Beckwith III and Dorothy B. Beckwith Professor of Translational Medicine. "No one used to talk to me at cocktail parties when I told them what I worked on. And now, it's like everybody corners me to understand what they can do to slow aging down."

What changed? Besides the shifting global demographics, research began to suggest that something could be done about aging itself, not just the diseases that often accompany it. In the 1980s and 1990s, studies began to show that single gene mutations could significantly extend the lifespans of simple organisms like worms and flies. Further research found some of these pathways were conserved in mammals, including humans.

"It became less of a correlative science and more of a mechanistic science," Finkel says. "And that gave way to this idea that, hey, what is the biggest risk factor for all diseases? It's aging. So maybe we should pay attention to this."

PREDICTING RAPID AGERS

While various "epigenetic clocks" try different methods to pinpoint people's biological age, Aditi Gurkar is working on an approach of her own. A PhD assistant professor of medicine in the Division of Geriatric Medicine and a member of the Aging Institute, she often shares her origin story as a researcher who studies aging: Growing up in India, she watched two of her grandparents, roughly the same age, spend the final years of their lives very differently. Her grandmother lost physical and mental faculties, while her grandfather remained active and healthy. She wanted to know what was



Aging is complex and differs for everyone. At Pitt's Aging Institute, scientists are working across disciplines to understand what drives the process—and how to make it healthier for all.

behind the differences.

In March 2024, she and her collaborators took a step toward that goal. In a paper published in Aging Cell, they described a new way to predict how fast a person's cells and organs are aging using blood-based molecular markers.

Instead of focusing on genetics, which Gurkar says account for only about 20 percent of how a person ages, their work looked to factors that are influenced by a person's life and environment. It combines an analysis of metabolites—substances released into the body as it breaks down food, chemicals and tissue—with markers of senescent cells, so-called "zombie cells" that no longer divide. As they build up in the body, they are strongly associated with aging and inflammation.

The team compared 196 older adults whom they classified as "healthy agers" or "rapid agers" by how easily they completed walking challenges. "It's a great way to assess aging because it tells you about your pain levels, about your bones, about your motor coordination, about cardiopulmonary function," Gurkar says. "You need all of these in an integrated manner to work for you to do a walk test [comfortably]."

They found clear differences in metabolites between the two groups and created an index of markers that was 95% accurate in distinguishing them. The rapid agers they'd recruited were chronologically younger (ranging from age 65 to 75) than the healthy agers (who were 75 and up), allowing the researchers to home in on markers of biological—not chronological—aging, unlike other studies that have compared young adults with older people. Their approach strengthened the idea that metabolic changes aren't just a result of the march of time.

They validated their index by analyzing a group from a separate, Wisconsin-based study. With accuracy of about 68%, they could correctly predict whether someone could walk outside for 10 minutes without stopping.

Although her study focused on older adults, Gurkar hopes someday that they can use the index to find out whether someone is aging rapidly during or even before middle age. Beyond the usual recommendations for healthy sleep, exercise and eating relevant to all, early rapid agers might be candidates for other interventions that tackle aspects of aging like inflammation.

A widely available test, though, could require a decade or more of longitudinal studies to confirm its accuracy, Gurkar says. And it could face added hurdles because it doesn't present a specific disease to cure.

"It's not a biomarker for disease, so it's not something that companies or even other institutions want to jump into quickly," she says. "Aging is complex, right? It's easier to get funding when you think about a disease process." Our society, Gurkar thinks, tends to focus on looking for pills to cure a disease, rather than investing in health more holistically.

WHAT IS AGING?

The aging research community, too, is still wrestling with the multifaceted nature of the subject. In 2013, a landmark paper in the journal Cell described nine "hallmarks of aging," including genomic instability, cellular senescence and mitochondrial dysfunction, each presenting a possible target to slow or reverse aging. But the hallmarks are intercon-



Gurkar



Rizzo



Chen



Steinhauser

nected, and aging research often takes aim at a few at once. In 2023, the same authors published an update adding three more hallmarks.

The complexity isn't just about the interlocking mechanisms—it extends even to the concept of aging itself. In December 2024, PNAS Nexus published a survey of 100 researchers focused on aging that found widely disparate perspectives on what aging is, whether it's a disease and when it begins.

"One of the challenges in the field is, how does the biology of the aging process differ from the biology of life itself?" says Newman, a Distinguished Professor of Epidemiology.

For her part, she describes aging in terms of damage and repair in the body, where through time the former eventually overcomes the latter.

"We're biologically able to repair damage. But what's damaged is never what it used to be. It's not as functional as it was before," she says. "It's an essential process to continue to maintain life, but it's imperfect and eventually catches up with us."

For many people, the accumulating damage plays out most visibly in the muscles, one of Newman's areas of focus. Through time, our muscles weaken, and we lose mobility. "Diseases of the muscle are quite rare, yet [people's] muscles will age and their function goes with it," she says.

Newman and her collaborators are conducting the largest-ever study (the Study of Muscle, Mobility and Aging, or SOMMA) to understand what drives this decline. They've recruited 879 people older than 70 at two sites at Pitt and Wake Forest University, with more volunteers to come. The team is measuring the participants' physical functioning along with biological factors that could be at play in the muscle tissue: mitochondrial function, genetic expression and muscle innervation.

In the first five years of the study, they collected data indicating that mitochondrial function was strongly related to walking ability and peak oxygen consumption on a treadmill test. The findings support past research suggesting that muscle quality, not just muscle mass, is essential to mobility as people age.

The importance of mitochondria is no surprise—their dysfunction is one of the dozen hallmarks of aging, after all. Newman is also working to better understand and address another: chronic inflammation, which is linked to all the other hallmarks and contributes to declines in physical, cognitive, vascular and immune function in older adults.

Her team is pioneering the use of clazakizumab, a monoclonal antibody that binds to and inhibits IL-6, a small protein that is a key mediator of chronic inflammation. They are conducting a trial to test the drug's ability to improve physical, cognitive and immune function for older people.

"IL-6, of all the inflammatory markers, is the most robustly related to multiple poor outcomes," she says. "We looked at it for heart attack, hip fracture and dementia, and it's the one that seemed to be most consistent across them."

A BIG TENT

Newman compares studying aging to the parable of the blind men and the elephant, where each touches a part of the large animal and imagines a very different beast. Only when the portraits are combined does the elephant start to come into focus.

The Aging Institute counts among its ranks people with expertise in neurobiology, cardiology, pulmonology, cell biology and more; by sharing an institute, they're working together to gain a fuller understanding of aging.

The scientists' work ranges from Newman's clinical research to advances in basic science, like the cellular pathways identified by Jay Xiaojun Tan, a PhD assistant professor of cell biology. (Read more about his work in the sidebar on page 23.) Just as important is bridging the gap between the bench and the bedside. That's the charge of Matthew Steinhauser, the MD associate professor of medicine who directs the Aging Institute's Center for Human Integrative Physiology.

"Whether it's testing hypotheses that emerge from model organisms in humans or thinking about ways to get proof of concept around therapies or therapeutic approaches for aging, all of this is sort of broadly under what we're trying to do," Steinhauser says. (Read about one example of the center's work on page 24.)

Steinhauser sees the variety of perspectives on aging as a major strength of the institute—one that even brings in people like himself who are skeptical that aging has distinct mechanisms separate from those involved in diseases and exposure to stressors.

"When [Toren Finkel] put together the institute, he didn't focus on recruiting just people who came out of the aging community," Steinhauser says. "I'm someone who came in through this big-tent approach."

Finkel has looked for people who approach science with creativity, rather than having a particular background. "Questions change over time but the ability to approach problems creatively, to me, is the most important trait for long-term success," he says.

That has led him to look outside of academia. Stacey Rizzo, a PhD associate professor of neurobiology and medicine, came to Pitt and the Aging Institute after 20 years working in drug discovery at pharmaceutical companies.

She is collaborating with Bill Chen, a PhD professor of medicine in the Aging Institute with a background in biochemistry, to find interventions for conditions that loom large for many older adults: Alzheimer's disease and neurodegeneration. (You can read more about the promising Alzheimer's work happening at Pitt in our Spring 2023 issue.)

Rizzo and Chen are trying to use small molecules to activate an enzyme in the brain called nicotinamide phosphoribosyltransferase (NAMPT). It regulates levels of another enzyme involved in energy metabolism called NAD+, which declines in aging brains and is associated with cell death and cognitive impairment.

NAD+ supplements are widely available, and in certain countries people even receive IV injections of it. But in supplement form, it metabolizes quickly and doesn't actually reach the brain. "That's just completely nonsense because it's so unstable. It doesn't make a lot of sense, but the market is increasing," Chen says.

By instead activating the enzyme that regulates NAD+, they think they can achieve sustained

levels through molecules that can be taken orally.

Rizzo says her lab is largely "translational," meaning she's focused on getting breakthroughs from the lab to the clinic. "[With] Bill being a chemist, we're great partners in looking at drug discovery together," says Rizzo. "Most of the people I collaborate with outside of this are neurobiologists. That work is very focused on the brain, and this collaboration really helps us look at aging holistically, beyond brain aging and neurodegeneration."

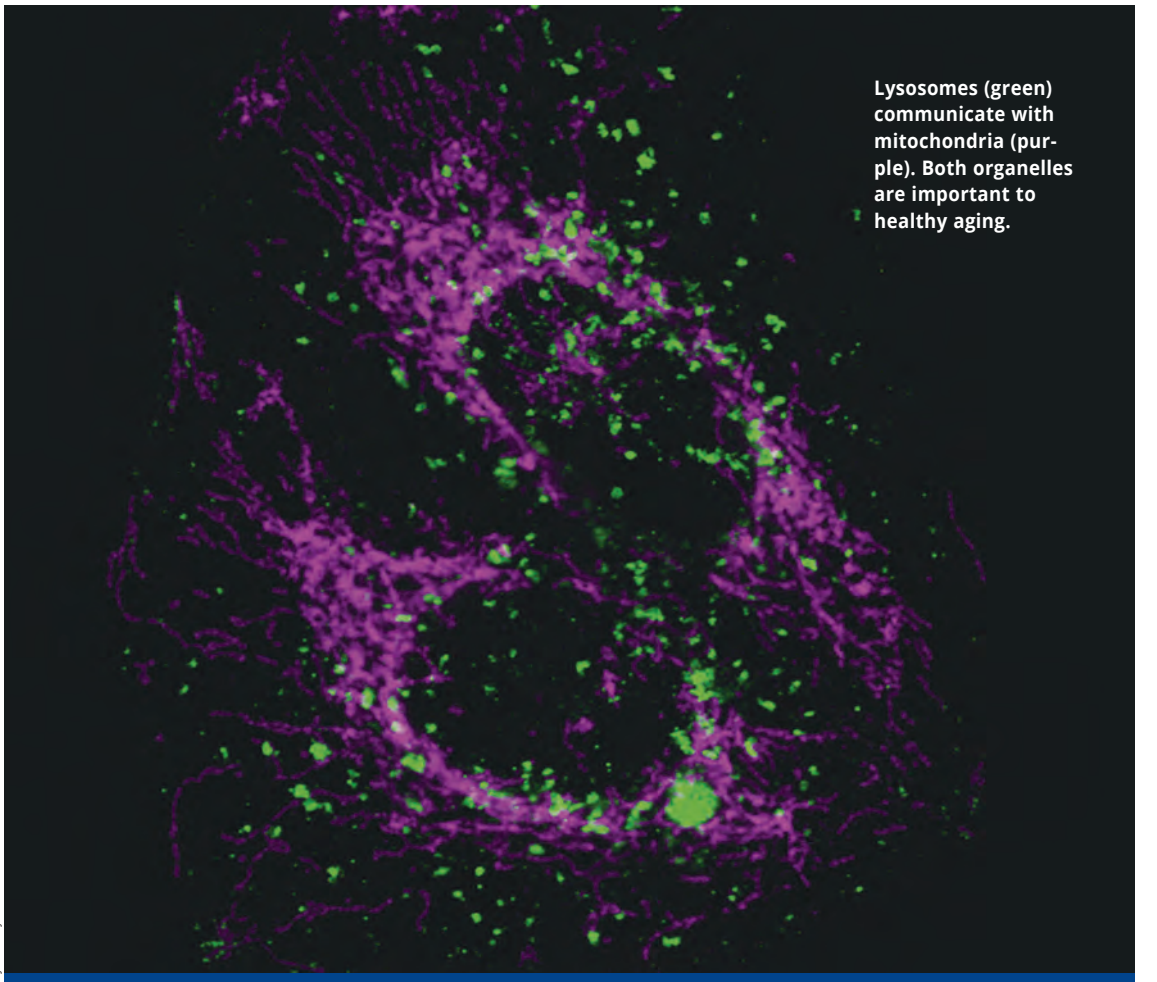
Other collaborations seek to get around hurdles that the aging field has run into. Remember those zombie cells—the ones that stop dividing with age but refuse to die? There's strong evidence in animal models that senescent cells play a causal role in aging, and Pitt is the lead institution of a consortium mapping senescence in the body. (The work is led by Finkel with fellow Department of Medicine faculty Melanie Königshoff, an MD, PhD, and Oliver Eickelberg, an MD.) But there remains no decisive biomarker to identify senescent cells. Gurkar is taking a different approach. She's working with Pitt physicist Rama Bala, a PhD, to see if nanoparticles can suss out senescent cells by finding a magnetic signature.

"We're thinking outside the box with cross-disciplinary approaches," she says. "We may not get a magnetic signature. On the other hand, I don't think I would ever regret trying something new. That's the fun of science."

Pitt's expertise in aging and its effects extends well beyond the Aging Institute. For instance, advances are under way in Geriatric Medicine, Psychiatry, Neurobiology, Physical Medicine and Rehabilitation, Orthopaedic Surgery and throughout the health sciences.

For Gurkar, who is not a clinician, the chance to work with geriatricians at Pitt who see patients has been particularly rewarding. And Newman says that her own work with clinical research volunteers, many of whom have remained healthy into old age, reminds her what the focus of aging research should be.

"I'm always surprised when they tell me how old they are, because being a clinical geriatrician, you tend to see people at their worst, not at their best," Newman says. "That's been very inspiring to me, to see that many of these folks who are volunteering for our study are thriving. They tell us what's possible." ■



JAY XIAOJUN TAN

Lysosomes (green) communicate with mitochondria (purple). Both organelles are important to healthy aging.

SOME ORGANELLES MIGHT NEED TO HIT THE GYM



Tan

When we exercise, we put manageable stress on our body, preparing it to handle more stress in the years to come. Pitt's Jay Xiaojun Tan, an Aging Institute researcher and PhD assistant professor of cell biology, thinks the same principle applies to lysosomes, organelles that break down waste material in cells.

Throughout our lives, our lysosomes also face stress and damage, with consequences mounting during aging that impair their function. But what if some stress, earlier on, benefits them? Certain drugs, such as the type II diabetes drug metformin, appear to give lysosomes a mild workout in ways that protect them from future damage.

"The cells have an acute response to repair or remove damage, but they also trigger short-term and long-term changes that help them deal with future similar damages," says Tan, who came to Pitt in 2019 and started his own lab in 2022. "Our goal is to find what types of lysosomal stress and what level of stress can make these lysosomes healthier and make the whole cells healthier."

In recent work with Toren Finkel, director of the Aging Institute, Tan has reviewed pathways that allow lysosomes to repair damaged cells and clear cellular stress. In a 2022 paper in Nature, he identified how lysosomes repair their own leaks in a process dubbed the "PITT pathway." (PITT stands for phosphoinositide-initiated membrane tethering and lipid transport.) With support from a Maximizing Investigators' Research Award from the National Institute of General Medical Sciences, he's now seeing how PITT communicates with other pathways to allow oil-like droplets of proteins in the cytosol to patch holes in membranes.

And in October 2024, he published a paper in Molecular Cell that revealed a protein called STING starts a process that activates genes to produce more lysosomes, which helps clear stress in the cell. STING was already known to be involved in an antiviral response that triggers inflammation to fight infections and diseases. In aging and neurodegenerative diseases, that pathway can become chronically "on," so some scientists are working on interventions to block STING. Tan's findings suggest that might not be the best idea. Because the protein also promotes cell health by clearing stress, it may be better to selectively target its inflammatory effects rather than ditching it altogether.

After learning how these pathways contribute to healthy aging in cells, Tan is now determined to find out whether a little lysosome workout could make these pathways even stronger in the long run. *—AD*

LEFT BY THE TIDES

TRACES OF OCEAN-DWELLING ANCESTORS SEEM TO LIVE ON IN OUR BIOLOGICAL RHYTHMS.

BY ANDREW DOERFLER

Most of us have daily routines—and, thanks to research going back decades, we know our bodies do too. Internal clocks in our cells and genes keep certain important functions running on a 24-hour cycle. While their rhythms are synchronized and regulated by environmental factors, primarily the sun's rise and fall, they operate independently of those influences.

According to Pitt research, though, some of our genes are working on a different timetable, one that could be a holdover from marine ancestors that lived hundreds of millions of years ago.

Bokai Zhu, a PhD assistant professor of medicine in the Division of Endocrinology and Metabolism and member of Pitt's Aging Institute, has been studying biological rhythms in cycles of less than 24 hours since he was a postdoctoral researcher. While some of these "ultradian rhythms" repeat in just minutes, 12-hour oscillations are notably common in marine life like crustaceans and sea anemones.

It makes sense when you consider the animals' environments: Instead of clocks tuned to the cycle of night and day, they are likely synced by the tides, which go through a full cycle of ebbing and flowing roughly every 12 hours.

Zhu's recent work makes it clear that you don't have to inhabit a tide pool to have 12-hour rhythms: Humans have them, too. In a 2024 paper published in the journal NPJ Biological Timing and Sleep, Zhu and Pitt collaborators identified, in a small study of humans, about 3,000 genes with 12-hour rhythms. Many of those genes appear to play important roles in processes fundamental to the flow of genetic information and to the metabolism of proteins.

What's more, the researchers found statistically significant overlap between the 12-hour gene expression of their research volunteers and a species of sea anemone, suggesting the half-day clock has been conserved over the course of evolution.

"I have to admit I was shocked by that," says Matthew Steinhauser, an MD associate professor of medicine, a senior author of the study and a colleague of Zhu's in the Aging Institute. "That a simple, small organism, millions and millions of years old, that isn't even a mammal and lives in the ocean, would have a pattern of gene expression similar to someone who's walking around Pittsburgh—I mean, come on, that's a stretch."

Unlike our Cambrian-era ancestors, of course, most humans aren't spending the bulk of their lives reliant on the ebb and flow of tidal waters.

"It's interesting to think that we would have maintained this ancient rhythm," says Toren Finkel, director of the Aging Institute. "As we crawled out of the sea, I guess we lost our fins, but we didn't lose this."

The team is now trying to find out how and why landlubbers like us held onto their ancestral rhythms. "There's no way a 24-hour light cycle can generate a 12-hour oscillation. It just doesn't make sense," Zhu says.

So what else might be tuning the 12-hour clock? And how much do these rhythms matter to our well-being? Disruptions to 24-hour circadian rhythms—such as daylight-saving clock changes and flights across time zones—can harm health, and many people take pains to maintain their rhythms with consistent eating and sleeping schedules. Perhaps they should be paying attention to their 12-hour rhythms, too.

"As a clinical researcher, I try to move things from the bench to the bedside. This really was an exciting opportunity to be able to do that," says Pouneh Fazeli, an MD, MPH associate professor of medicine and a coauthor on the human study. "There's likely some reason why [the rhythms] have been conserved. Are there diseases, disease states or pathophysiology that we can attribute to potential disruption of these 12-hour rhythms?"

The researchers hope their combined expertise—Zhu as a basic scientist and Steinhauser and Fazeli on the clinical and translational side—can lead to answers.

WATER COOLER TALK

Zhu came to Pitt and the Aging Institute in 2018, not long after he published a paper that found prevalent 12-hour gene expression and metabolic rhythms in the livers of mice. As he continued to investigate these rhythms, their function and what regulates them, casual conversations with Steinhauser at the Aging Institute soon turned into collaboration. Steinhauser directs Pitt's Center for Human Integrative Physiology, and Fazeli is the associate director. (They are also married.)

"The mission that we have for this center is to do human translation around problems or biology relevant to aging," Steinhauser says. Zhu had data suggesting that 12-hour rhythms start to disappear in aging mice. "We thought, boy, it would be a great first project for our center to try to find out their relevance in humans. It's a beautiful example of what can happen from water cooler talk."

Together, they designed a study. Every two hours for two days, the team sampled the blood of three participants during stays in a room at UPMC Montefiore's Clinical and Translational Research Center. They then conducted RNA sequencing on the samples to figure out the peak times for gene expression.

Unlike many other studies of biological rhythms, the researchers tested the volunteers in "free living conditions," letting them maintain their usual sleeping and eating habits. Rather than trying to block out all the environmental "noise" that may obscure 12-hour rhythms, the researchers wanted to find out if the rhythms would still come through in a less-than-ideal setting. For example, the room had a window, so they were still exposed to light and dark cycles.

"I think that's actually the advantage of our study," Zhu says. "We want to know whether people like you and me, living a normal life, would exhibit a robust alternative rhythm."

Overnight, the participants were hooked up to long IV lines that extended outside their room, which let the researchers sample blood without waking up the volunteers to reattach the IV. Allowing the participants to eat normally was also relevant to Zhu's hypothesis for what could be regulating these rhythms for humans who are not spending each day splashing around in tidewaters.

Zhu supposes that the 12-hour rhythms might instead be tuned by periods of metabolic stress, or times when there's a big difference between your energy intake and energy expenditure. The extremes tend to happen twice a day, he says. The first is in the early morning, when you probably haven't eaten for hours but the brain has remained very active overnight. The second is in the evening, after you probably had a large meal but are relaxing and not engaging in strenuous activity.

The discrepancies go in opposite directions, but both put stress on the body's metabolism. In between these times, there's more balance: People are active but eating regularly.

Although their research hasn't proven this hypothesis yet, Zhu thinks the 12-hour rhythms may spring into action to help manage the flow of genetic information during these periods of high stress. He compares it to the opening of a high-occupancy vehicle lane during rush hour: The amped-up gene expression keeps transcription, protein translation and intracellular transport running smoothly amid stress.

It's notable that the same processes break down in aging, neurodegeneration and metabolic diseases—all areas where the team hopes to learn whether 12-hour rhythms play a role.

"It would be really interesting to see whether 12-hour rhythm disruption improves with certain treatments like intermittent fasting, or whether it's also disrupted in disorders like anorexia nervosa and the opposite extremes, like obesity," says Fazeli.

To find out, they want to get funding to enroll more volunteers and pursue studies that introduce a period of time-restricted feeding, which has already been shown to potentially tune the rhythms in mice.

"The steps that lie in front of us are actually much more challenging," says Steinhauser. "It's getting at the underlying mechanisms [of these rhythms]: How do they matter, and can they be manipulated for good or for bad?" ■

Timothy Greenamyre's extraordinarily productive career started with developing a rat model of Parkinson's disease. Twenty-five years later, he's zeroed in on a protein that offers a path to stopping neurodegeneration from the disease.



THE CHEMICAL CONNECTION

TIMOTHY GREENAMYRE HAS MADE MAJOR LEAPS FORWARD IN UNRAVELING PARKINSON'S.

BY CARRIE ARNOLD

PORTRAIT BY FRANK WALSH



In the summer of 1982, a handful of patients appeared in emergency rooms across California. One day, they were completely healthy; the next, they were unable to walk or talk. Many had tremors. The symptoms were classic Parkinson's disease, but the young age of the patients and the abrupt onset of problems said otherwise. A scientific investigation revealed that these individuals had injected themselves with a new type of synthetic heroin that was contaminated with a chemical called MPTP.

The mystery caught the attention of a young Timothy Greenamyre, then a medical student at the University of Michigan, who followed the saga as it unfolded. MPTP, the researchers concluded, selectively and irreversibly damaged the dopamine-making neurons of the substantia nigra. To Greenamyre, this demonstrated that an environmental chemical could cause Parkinson's disease. He began to wonder whether there might be others.

There were, including rotenone, a pesticide considered safe to humans as late as the early 2000s. Greenamyre achieved broad recognition in the Parkinson's field for creating a rat model of Parkinson's using rotenone, which has helped scientists uncover novel risks for the disease. More recently, Greenamyre's work drilled deep into some of the first molecular steps of Parkinson's, opening the way to potential new therapeutics. It's a promising bookend to Greenamyre's notable career.

"If we could slow the progression of disease and expand the therapeutic window in which treatments work, it would be a huge advance," says D. James Surmeier, a PhD neuroscientist at Northwestern University.

When Greenamyre was in medical school, a lecture by neuroscientist Anne Young, who worked on spasticity and muscle disorders, steered him towards pursuing both an MD and a PhD in neuroscience. Around the same time, papers interrogating the MPTP problem also began appearing, which further piqued his interest. Greenamyre followed as molecular studies showed that MPTP killed cells by inhibiting a large complex of proteins called Complex 1. Without Complex 1, mitochondria couldn't produce energy, and the affected cells died. Postmortem studies of people with Parkinson's revealed their Complex 1 enzymes were also malfunctioning.

After graduating from Michigan and completing his residency there, Greenamyre accepted a faculty job at the University of Rochester and later moved to Emory University. Then as now, his focus was on how the brain directed the body's movements, and how that could go wrong. If MPTP could cause Parkinson's symptoms in humans and animals by gumming up Complex 1, Greenamyre reasoned, maybe other Complex 1 inhibitors could, too. He selected rotenone, a pesticide used by home gardeners and wildlife biologists. Greenamyre infused rats daily with a rotenone solution and waited. It didn't take long. After a week, the rats began showing the specific jerky movements that were Parkinson's hallmarks. When Greenamyre peered at brain tissue under the microscope, he saw a dramatic loss of dopamine brain cells in the substantia nigra. In surviving brain cells, he found clumps of a protein known as α-synuclein that is characteristic of Parkinson's. While still at Emory, Greenamyre published his findings in a 2000 paper in Nature Neuroscience.

"There are a lot of ways to kill dopamine neurons, so that wasn't particularly intriguing. But what got people's interest—and ours, too—was the fact that for the first time in an animal model, we saw an accumulation and aggregation of α-synuclein," Greenamyre says. "We had mitochondrial damage linked to pesticide exposure, linked with symptoms, linked with α-synuclein. It was the trifecta of Parkinson's disease."

For Parkinson's scientists, the results were groundbreaking. "It may be the most important discovery he's made. This work raised people's awareness about the importance of environmental agents in promoting Parkinson's. Things that we think are safe may not be safe," says Surmeier.

Importantly for Parkinson's scientists, the rotenone model captured the full molecular and cellular breadth of the disease. Animal models of Parkinson's using MPTP didn't lead to knots of α-synuclein. In other models, disease only appeared in rats that were bred to have specific Parkinson's risk genes, which wasn't relevant for the 90% of Parkinson's patients with no known genetic cause. The work also bolstered support for two emerging hypotheses about Parkinson's: that the disease was intimately connected to dysfunction in the mitochondria, and that pesticide exposure increased Parkinson's risk.

In 2004, not long after publishing his groundbreaking rotenone paper, Greenamyre decamped from Atlanta to head up the Pittsburgh Institute for Neurodegenerative Diseases (PIND). For him, it was love at first sight. At many other universities, labs were siloed, each closed off in its own room with scientists toiling away behind closed doors. At Pitt, however, Greenamyre walked into an open floor plan designed to encourage creativity, where researchers from different labs mingled at benches throughout the space.

"One lab begins where another one has ended. . . . It knocks down the inertia that stops you from going and knocking on somebody's door."

"One lab begins where another one has ended. There's no walls, there's no doors. It knocks down the inertia that stops you from going and knocking on somebody's door to ask if they could help you with a problem or why their Western blots look so much better than yours," says Greenamyre, an MD, PhD who is now the Love Family Professor of Neurology.

Pitt neurologist Edward Burton, the UPMC Professor of Movement Disorders, was drawn to Greenamyre's kindness and understated enthusiasm. "Tim has been an outstanding mentor, scientific collaborator and colleague," says Burton, an MD, DPhil professor of neurology and of microbiology and molecular genetics. "He is full of great ideas, very supportive of junior faculty and overall an incredibly nice bloke."

One of the first trainees to arrive at Greenamyre's new digs at Pitt was Jason Cannon, a neurotoxicologist who shared his mentor's passion for dissecting the rotenone model. Cannon, a PhD, tweaked how the rats were dosed and for how long. Performing these studies would require months of expensive watching and waiting, with no guarantee that the animals would develop Parkinson's. Their gamble paid off when they found that rotenone could cause Parkinson's symptoms even after brief exposures.

Improving the model, however, was also a means to an end. "Tim always pushed us to think about the clinical perspective, so that even if we're doing things at the biochemical or microscopic level, we should think about how it would impact the patient," Cannon says.

In Parkinson's, as with many other neurodegenerative diseases, the genetics revolution led to an explosion of interest into genetic risk factors. While Greenamyre didn't discount the importance of that work, he also knew that genetics alone only explained about 1 in 10 Parkinson's cases. A range of as-yet-unknown environmental and genetic factors set the stage for the rest. The rotenone model let Greenamyre dissect the earliest molecular events on the long path to Parkinson's and determine how different genetic variants interacted with the effects of exposures to pesticides.

"The billion-dollar question in Parkinson's disease is, What is the initial thing that happens? What happens first? If we knew what happened, we could target Parkinson's at the earliest stages," says Sarah Berman, an MD, PhD professor of neurology and of clinical and translational science at PIND.

Painstaking studies over more than a decade fueled a far more complete understanding of Parkinson's. The inhibition of mitochondrial Complex 1 created roadblocks for the flow of electrons that generated energy in the form of ATP (adenosine triphosphate). Dopaminergic neurons were already balanced on the knife edge of stress and starvation, due to their ravenous need to fuel the uptake and release of neurotransmitters and electric impulses. Even a tiny drop in the cells' ability to make ATP was enough to wreak havoc. Nor did the mitochondria flicker out. In the absence of a fully functional electron transport chain, mito-

chondria generated harmful, chemically reactive compounds called free radicals that pinballed around the cell, siphoning spare electrons from any biomolecule they encountered. These reactive oxygen species cause a specific type of cellular damage known as oxidative stress and oxidative damage.

Our oxygen-rich world means that some amount of oxidative stress is inevitable. It's why our cells have evolved a range of antioxidant enzymes and vitamins to protect cells from free radicals. The amount of reactive oxygen species produced when Complex 1 is damaged, however, is amplified by α-synuclein in the substantia nigra, swamping the body's natural protectors. This overwhelming injury from oxidative stress destroys the dopaminergic neurons, Greenamyre concluded in a 2020 paper he coauthored with Burton.

"All these things feed forward and feed backward," Greenamyre says. "Over time, the dopaminergic neurons get sick and die."

Work at Pitt added to both the importance and the complexity of the role of oxidative stress in Parkinson's. The connections grew stronger with the discovery of Parkinson's-causing mutations in a protein called LRRK2. Pronounced "lark 2," the protein helps regulate the production of harmful reactive oxygen species. Although LRRK2 mutations cause only a tiny proportion of all Parkinson's cases, Greenamyre and other Pitt scientists, including Roberto Di Maio, a PhD assistant professor of neurology at PIND, found extremely high activity of LRRK2 in the brains of people with the far more common idiopathic Parkinson's, and in two different Parkinson's animal models. The importance of LRRK2 to both inherited and idiopathic Parkinson's made it imperative for Greenamyre to understand exactly how the protein contributed to disease.

A 2018 paper in Science Translational Medicine showed that LRRK2 activity was the lynchpin that connected α-synuclein and oxidative stress. Reactive oxygen species generated by oxidative stress set off a signaling cascade in dopaminergic neurons in the substantia nigra. This cascade activates LRRK2, which leads to a reduction in autophagy, the natural process in which the cell breaks down and recycles old and damaged molecules. Impaired autophagy means cells can't degrade α-synuclein clumps, which subsequently build up in dopamine neurons. Because α-synuclein itself spurs oxidative stress, it creates a positive feedback loop in dopaminergic neurons that ultimately kills them.

"This makes neurons highly susceptible to further oxidative stress. They are the first cells in the body that feel the strong effects of this stress, and it's actually the trigger of a complex downstream pathologic process," Di Maio says.

After three decades of caring for patients with Parkinson's disease, Greenamyre knew that downstream process well. He could identify subtle flutters in the hands or jaw even before the tremors became obvious to friends and family. He watched as a fluid gait slowed to a stutter step, and as once rock-solid balance crumbled. There were other signs, too. Some of his patients acted out wild dreams in their sleep, thrashing about and yelling. Others reported constipation or a loss of their sense of smell.

Not long after he began his work on LRRK2, Greenamyre wasn't just seeing these symptoms in patients. This time, Greenamyre was seeing them in himself. None of his work prepared Greenamyre for the last stage in his career as he watched the disease to which he had devoted his life slowly unfold in his own brain.

"In some sense, it's been valuable for me to get a better, deeper understanding of Parkinson's disease and its symptoms. I feel like I know what patients are talking about much more than I did previously," Greenamyre says.

This development raises the question of whether Greenamyre's work led to his condition. No one knows. Yet the significance of his breakthrough 25 years ago meant that Greenamyre was using rotenone—a lot of it. As Greenamyre noted in his 2000 Nature Neuroscience paper, rotenone was "widely believed to be a safe, natural alternative to synthetic pesticides." Says Greenamyre now, looking back, "I didn't think there was much potential for rotenone [handled as he did] to cause something like Parkinson's disease or cause a problem at all."

As with everything else, Greenamyre remains reserved when discussing his symptoms—just that he knows you can live, and live well, even with Parkinson's. When he disclosed his disease in 2023, his inbox overflowed with messages of both support and shock.

For a 69-year-old soft-spoken scientist seeing retirement looming larger on the horizon, the affection is touching and tolerated so long as it doesn't detract from the science. There, his mind remains as laser-focused as ever, says Briana De Miranda, a PhD who completed her postdoctoral fellowship in the Greenamyre lab and is now an assistant professor of neurology at the University of Alabama, Birmingham. "If I ever have a question, I can expect an email response from him pretty quickly," De Miranda says.

"The billion-dollar question in Parkinson's disease is, What is the initial thing that happens? What happens first? If we knew what happened, we could target Parkinson's at the earliest stages."

Greenamyre's new work is providing a career bookend that is perhaps as important as his early rotenone studies, says De Miranda. As Greenamyre built on his 2018 findings, he found an increasingly central role for LRRK2 in Parkinson's. Notably, blocking LRRK2 activity protects rats from neurodegeneration after exposure to several toxicants. The centrality of LRRK2 to Parkinson's means that ongoing development of drugs to lower LRRK2 could benefit all Parkinson's patients, Di Maio says.

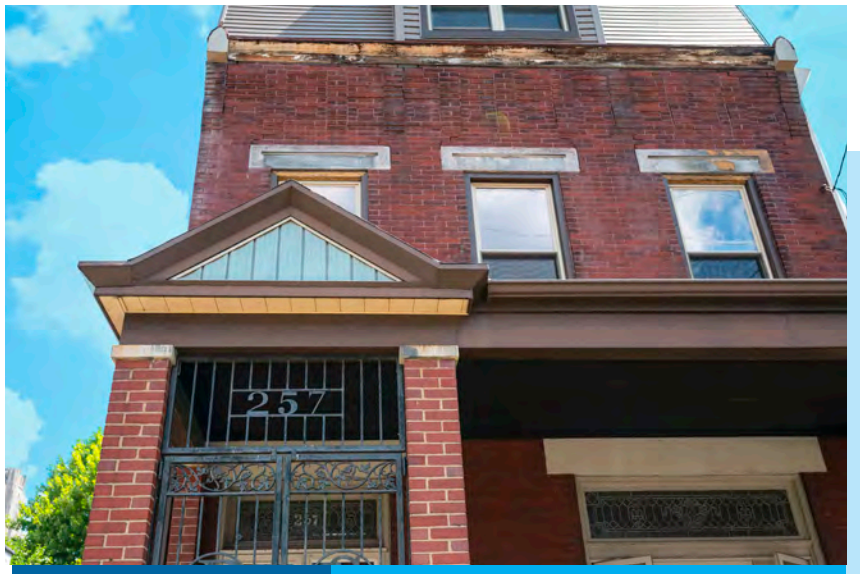
Berman says that Greenamyre's contribution to Parkinson's science can't be overstated, but that his mentorship is just as important.

"Not everyone has a Tim," she says. "He always made sure we had protected time to really focus on our research while we were also seeing patients. He supported us quietly, without a lot of fanfare or asking for anything in return."

Greenamyre remains focused on his patients and Parkinson's itself, not his own disease. He has no immediate plans to close up shop, but he also knows he has far more things he wants to do (in the lab and with grandkids) than he has time remaining in which to do them.

"I know what's in the cards, and I don't expect to remain unscathed," he says. Greenamyre's findings probably have not arrived in time to halt his own condition, but thanks to his work, the next generation should be much better off. ■

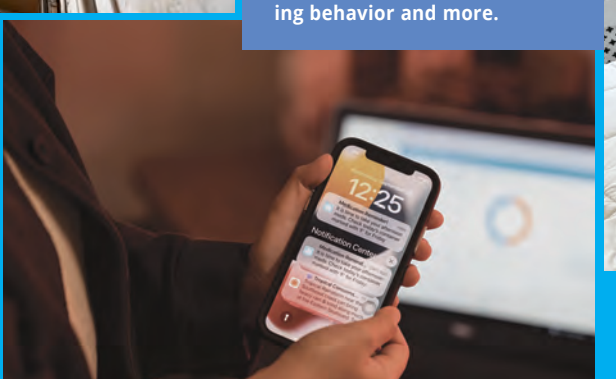
Designs on aging-ready





Research engineer Zachary Roy, of the School of Health and Rehabilitation Sciences, demonstrates a prototype of RailBot, a movable handle system that aids with stair ascent and descent.





HHL's Smart Home Tech Division develops technology for monitoring medication intake and reminders, wandering behavior and more.

PITT'S HEALTHY HOME LAB, THERE'S NO PLACE LIKE IT.

BY LINDY KRAVEC WITH ERICA LLOYD

This article was adapted from FACETS magazine.

More than three-quarters of adults over the age of 50 want to age in place, yet according to the U.S. Census Bureau, only 10% of U.S. homes are "aging-ready."

You can imagine how difficult it is for people determined to age in place in Pittsburgh—a land of hills, gorges, cobblestones and stairs—to remain independent and in their homes. And that makes the city a perfect test bed for interventions designed to make aging in place possible, some University of Pittsburgh researchers say.

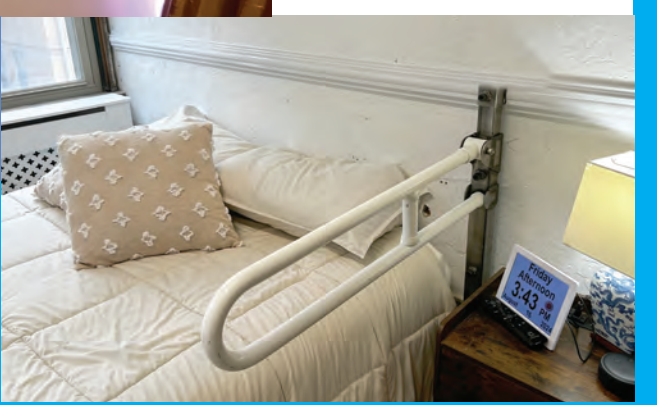
At Pitt's Healthy Home Lab (HHL) on Oakland Avenue, just steps from the Cathedral of Learning, a more than 100-year-old former family home has taken on a new life. In this three-story brick house, faculty and students from the Schools of Health and Rehabilitation Sciences (SHRS), Medicine, Nursing, Public Health and Engineering work together with community partners to make the average home much more accessible. They assess common conditions, evaluate and implement technology, and suggest interventions to optimize health and independence for older adults, as well as people of all ages with mobility issues.

"The Healthy Home Lab is both a concept and a place. It provides common ground and unites different communities of interest through a shared lens," says Pamela Toto, PhD director of the Healthy Home Lab and a professor of occupational therapy.

"We hope that everything we do will eventually filter out to the whole community."



Mobius is an adaptable rail system used in place of decorative architectural molding. It can serve as an anchor for a range of accessibility components, including handrails, grab bars and stair lifts.





As the Healthy Home Lab team comes across obstacles they believe an older person might struggle with, they bring in other experts as needed to help develop solutions, says Jonathan Pearlman, chair of rehabilitation science and technology in SHRS.

BELOW: Graduate students Joey Engelmeier and Jemima Ohwobete monitor indoor air quality.





Search high and low

Researchers at the HHL are developing high- and low-tech solutions that add stability where needed. The team explores alternatives that range from an ergonomic movable handle system that is positioned in front of a person to provide support while going up and down the stairs to an adaptable rail system that can be changed based on a person's needs to help them move within and between rooms.

They are also creating assessments to monitor air quality in the home and exploring ways in which older adults can embrace smart technology to improve their safety and well-being.

"After testing our products and services in the Healthy Home Lab, we partner with organizations like the UPMC Health Plan, Allegheny County AAA and businesses in the AARP AgeTech Collaborative to deliver them to people in need," says Everette James, a JD and MBA who is director of the University of Pittsburgh Health Policy Institute.

PHOTOGRAPHY BY TOM ALTANY, AIMEE OBIDZINSKI AND JOHNATHAN WRIGHT/UNIVERSITY OF PITTSBURGH



Partners for fall reduction

In 2024, HHL received a $1 million grant from the U.S. Department of Housing and Urban Development for its "Moving Beyond Home Modifications: Using Smart Home Technology to Support Safe Living for Older Adults" project. The grant is co-led by Steven Handler, an MD, PhD associate professor of medicine who is also HHL medical director, and Yong Choi, a PhD, MPH assistant professor of health information management, School of Health and Rehabilitation Sciences. The grant supports HHL experts as they work with partners from the Allegheny County Housing Authority and its three older adult public housing units in Homestead to create solutions.

Falls are the most common cause of injury for older adults, Handler says, but most public housing units won't allow structural changes to install effective home modifications. Smart technology offers an alternative.

In their shoes

HHL is also an education hot spot. In July 2024, wearing safety goggles covered in Vaseline, Svea Cheng navigated a walker through a cramped kitchen, simulating the experience of an older patient with glaucoma recovering from surgery. Her tasks included making a peanut butter and jelly sandwich, walking downstairs to feed the cat and going outside to water plants.

Cheng, a medical student in her Adult Outpatient Medicine Clerkship, was participating in a learning experience developed for health sciences students at HHL to help them better understand challenges facing patients as they return home. The case study was codeveloped with the Pitt Vaccination and Health Connection Hub; organizers began offering the experience in spring 2024.

"We just don't get anything like this in the classroom. It was the first time that we had a role-playing experience where we were in the shoes of the patient," Cheng said.

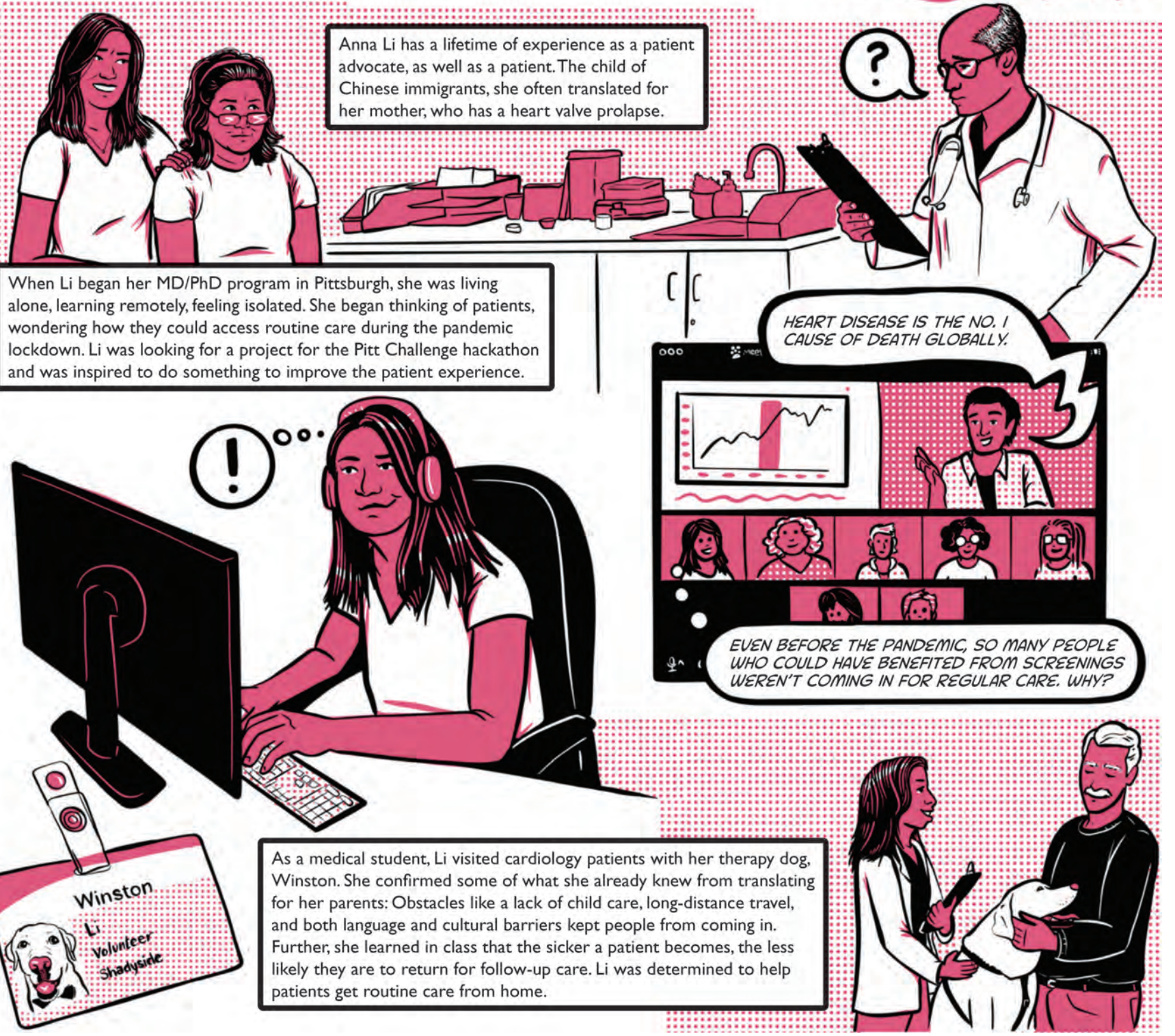
—Megumi Barclay and Isabel Doshi

Pitt Med student making sound waves in telehealth

IDEAS to REALITY



Written by Katy Rank Lev • Drawn by Maggie Lynn Negrete



Li, whose PhD will be in computational biology, partnered with Akshaya Anand, a machine learning scientist, to create a device that pairs with a web interface offering verbal and visual instructions. Li used on-campus makerspaces to build a prototype while Anand began developing the web interface. There was a steep learning curve around FDA regulatory processes, yet the two were confident they could push through and get their device approved.

Li met with potential investors during the pandemic virtually. She explained to them and others that teaching people where to place the stethoscope proved challenging. So her developers used augmented reality filters to analyze placement and positioning through the web platform. The device begins to record when the patient aligns it with the red dot on a screen.



Using the device, patients can record their heart and lung sounds from home and send the recordings to their doctors. This saves patients cumbersome trips to doctors and specialists, Li says.

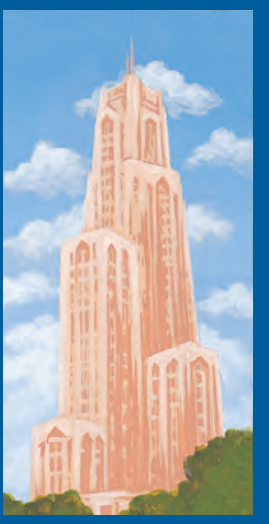
The device started winning every pitch competition it entered; and under the guidance of faculty advisor Eric Dueweke, an MD and MBA clinical assistant professor of medicine, Li and Anand formed a startup to get serious about bringing the stethoscope to the public. They chose the name Korion for the company -- a play on the Latin word "cor" for heart and Orion, the archer constellation. Korion was a finalist for the Hult Prize, and as part of that program, Li and Anand spent a month in a castle in the United Kingdom, learning about social entrepreneurship with like-minded innovators.

In 2024, Korion Health won the $1 million Hult Prize. With a patent and the Hult funding now in hand, the Korion team is on track to get FDA clearance, which they aim to achieve by late 2025.

After that?



Li says she "imagines a future where everyone has access to an affordable, easy-to-use home medical kit that recreates the physical exam and helps them understand their own bodies better -- in the comfort of home."



CLASS NOTES

'70s

Alice Feller (MD '77) has written the clinical memoir "American Madness: Fighting for Patients in a Broken Mental Health System." Feller, a retired psychiatrist based in California's Bay Area, says, "I wanted to explain how and why our mental health system, such as it is, is failing so badly." For instance, since most of our psychiatric hospitals have been closed, many who need those beds are living behind bars or on the streets. Feller says the book, which is focused on those with severe mental illness, provides a road map for repair. Through patient vignettes it shows, from the inside, the obstacles we face today and how to provide good care.

Oscar Reicher (MD '79), an orthopaedic surgeon, practiced for more than 40 years before his recent retirement. Early in his career, he served as the youngest president of medical staff at Chilton Medical Center in northern New Jersey. As a physician, he says, the most enriching part of his career has been his patient relationships: "You get to know people from all walks of life, hear their stories and become part of their lives. It broadened my view of the world."

Reicher celebrated his 45th reunion with classmates during Pitt's Reunion and Homecoming Weekend in September. More than celebrating, he had a hand in organizing the event, working with the Medical Alumni Association on an organizing committee for his class year.

'80s

Recognized by Newsweek in 2024 as one of the nation's top 200 vascular surgeons, **Scott Tapper** (MD '86), has been serving as president of the Florida Vascular Society for 2024–2025.

When thinking about the influence of his Pitt Med education, Tapper shared a memory of renowned surgeon and educator Henry Bahnson, the former chair of surgery who died in 2003. As a fourth-year medical student sitting in on an operation during a rotation, Tapper correctly answered a question asked by visiting surgeon David Sabiston—a question relating to the genetic blood vessel disorder Osler-Weber-Rendu syndrome. Tapper recalls seeing Bahnson, who was in the operating room, look curiously at him, wondering how a fourth-year came up with the answer. Bahnson took a liking to Tapper, ended up mentoring him and was influential in shaping his career.

'90s

A telehealth pioneer, **Robin Gehris** (MD '97, Pediatrics Resident '01, Dermatology Resident '05, Pediatric Dermatology Fellow '06) is chief medical officer of clinical operations for DermatologistOnCall, a telemedicine service that connects patients with dermatologists in an exclusively telehealth setting. She's triple board certified in pediatric dermatology, dermatology and pediatrics and is licensed to see patients in more than 30 states. "There are many regions in America where there's limited or no access to a dermatologist, and the wait times to see somebody might be several months—or if you can't travel, you might not be able to see somebody at all," she says. Gehris has helped thousands of pediatric and adult patients get vital treatment for diseases ranging from eczema to skin cancers.



Feller



Tapper



Gehris



Geskin

For her groundbreaking contributions to skin cancer research, **Larisa Geskin** (MD '98, Dermatology Resident '01, Cutaneous Oncology Fellow '03) received a Lifetime Achievement Award from the United States Cutaneous Lymphoma Consortium in 2023. Her ongoing research focuses on the diagnosis and treatment of cutaneous T-cell lymphomas (CTCL). For the past 25 years, the attending dermatologist and professor of dermatology at Columbia University Irving Medical Center has participated in every major clinical trial leading to FDA approval of CTCL therapies. "I take great pride in combining compassionate care with cutting-edge research to provide hope and solutions where there may have been none," she says.

'10s

After winning a prestigious recognition for his body of research last year, **Georgios Kitsios** (Pulmonary and Critical Care Medicine Fellow '17) continues his work on the human microbiome, mechanical ventilation and infection diagnostics—and in treating patients with acute respiratory distress syndrome and severe pneumonia. Kitsios, an MD, PhD assistant professor of medicine at Pitt, won the 2024 Jo Rae Wright Award for Outstanding Science as part of the 2024 American Thoracic Society's Respiratory Health Awards. The award recognizes demonstrated potential for significant achievement and contributions in science. "This recognized the persistent grit and consistency of output of work as opposed to one thing," Kitsios says. "It resonated with me deeply."

'20s

Emily Cai (Dermatology Resident '23) has joined the Dermatology Partners office in Drexel Hill, Pa.—one of the practice's nearly 40 offices in three states. "I specialize in medical dermatology and treat a wide variety of conditions, including lupus, dermatomyositis and other cutaneous connective tissue diseases," she says. She also treats blistering diseases and melanoma and other skin cancers, including in patients with complex medical



Kitsios



Cai

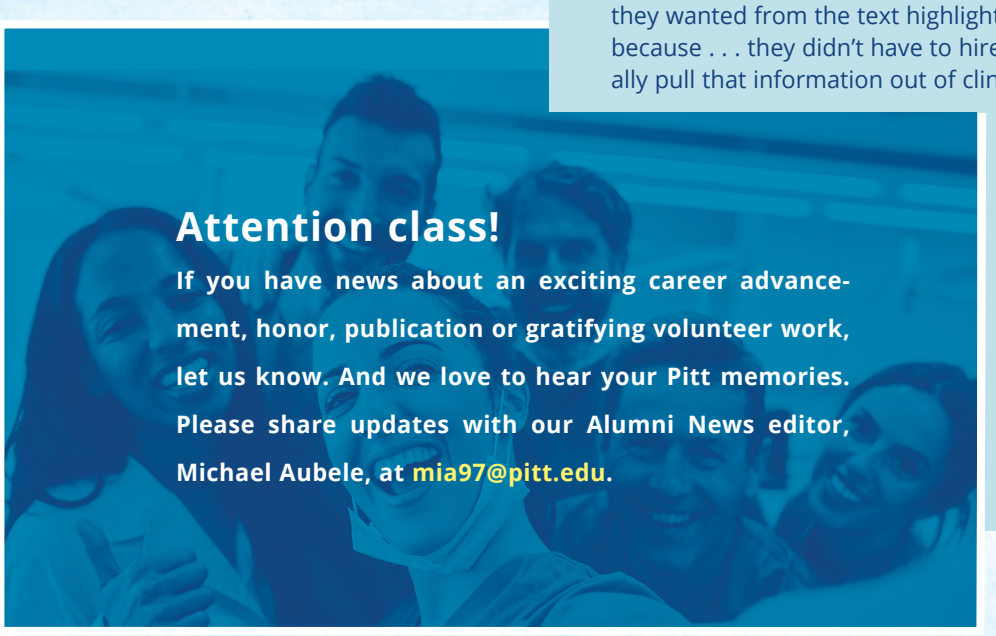


Harvey

histories, such as transplant patients. "I find dermatology to be a unique specialty because of its strong emphasis on visual diagnosis," she says. "Because skin conditions are so visible, it provides a great opportunity to work together with patients to address specific concerns on appearance and symptoms. Dermatology has strong overlap with many other medical fields, in immunology, rheumatology and oncology, and presents strong opportunities for interdisciplinary care."

For his outstanding contributions to cardiovascular disease research, **Lloyd Harvey** (MD '22, PhD '21) was honored with the Young Investigator Award in Basic and Translational Science from the American College of Cardiology in spring 2024. His research investigates pulmonary arterial hypertension— "a devastating and historically neglected vascular disease," he says—and establishes a genetic and metabolic paradigm for the disease. Harvey, who will begin his cardiology fellowship at UCLA this summer, plans to build a career as a physician scientist. "I would love to stay within the field of pulmonary vascular disease," he says, "as I find the science exciting."

—Michael Aubele, Rachel Mennies, Anvi Jain



Attention class!

If you have news about an exciting career advancement, honor, publication or gratifying volunteer work, let us know. And we love to hear your Pitt memories. Please share updates with our Alumni News editor, Michael Aubele, at mia97@pitt.edu.

SPOTLIGHT

MOWERY TRANSLATES DATA FOR PATIENT AND DOCTOR BENEFIT



Mowery

As a Pitt graduate student, **Danielle Mowery** (MS '10, PhD '14) wrote a report exploring the field of translational medicine that became an oracle for her career.

Mowery, the inaugural chief research information officer (CRIO) at the University of Pennsylvania Perelman School of Medicine, recently rediscovered the report upon returning home; her mom had saved it in a bin of college papers. "When I wrote that essay," she says, "I had no idea where I was going to end up. I didn't realize that I was drawing the map for the next 10 years of my training."

Mowery also is an assistant professor in Penn's Department of Biostatistics, Epidemiology and Informatics and scientific director of the Institute for Biomedical Informatics' clinical research informatics core. In all these roles, but especially as the CRIO, she develops "people, processes, and platforms" for facilitating clinical and translational research. This means "translating insights from data to solutions both at the bench side to the point of care and well beyond." Mowery also teaches courses on AI in medicine, an ever-growing area of interest and one of her specializations.

More than a decade after writing that graduate essay, what drives Mowery to work in translational science today? Being in service to others, both patients and providers, through understanding large-scale population health outcomes—and helping advance medical care through data-driven approaches as a result. Of an experience directing a natural language processing service line during her postdoctoral studies at the University of Utah, she recalls: "I can remember showing [clinicians] the variable that they wanted from the text highlighted—and their faces would light up, because . . . they didn't have to hire a large army of abstractors to manually pull that information out of clinical data.

"It made me realize my potential, helping to empower science at a level where we could really work at a larger scale than we ever could have prior." In her personal life, Mowery sees herself as something of a steward as well, for her community and with her inner circle of friends and family. "I want to make sure I'm a good resource for them, too," she says. *—Rachel Mennies*

SPOTLIGHT

ON HIS MIND— BRAIN RESEARCH



Samarasinghe

"Broadly speaking, intellectually, I find the brain intriguing and interesting," says **Ranmal Samarasinghe** (MD '13, PhD '13), an assistant professor of neurology at the UCLA David Geffen School of Medicine who grows 3D brain-like structures called organoids in a laboratory dish.

Samarasinghe, who graduated from the Medical Scientist Training Program (MSTP) jointly run by Pitt and Carnegie Mellon University, has his own lab at UCLA, which is one of a relatively small number across the country dedicated to human brain organoid research. His lab uses the organoids—which are about 400-600 microns in size and are derived from stem cells—to study epilepsy, autism and other disorders affecting the brain.

There are several potential benefits to this science. "One," Samarasinghe says, "is this idea of personalized medicine, and that's the promise of stem cells, especially for rare diseases—ones where it'll be very difficult to have one generic drug that treats everything. And epilepsy and autism can [also] fall under this regime, where there are differences between patients. So, when stem cells are taken from a patient and used to generate an organoid model of their disease in their brain, you could test drugs on those organoids. And in that way, you could select one that's efficacious versus not."

Moreover, Samarasinghe says, organoids could be helpful in developing drugs. "You could generate 100 organoids and try 100 different compounds and do medium- to high-throughput drug screening."

Another, he says, "is the idea of using organoids to understand something really fundamental about biological computation.

"When you're having a conversation, your brain is doing a lot of things, it's computing, it's trying to understand, and it's managing a lot of tasks. And fundamentally, I think our understanding of how the biological brain does computation versus, say, an in silico chip isn't that great."

An organoid, Samarasinghe says, could help researchers better understand how synapses and neurons can compute and eventually provide answers to questions such as why learning is impaired in disease states and why some people learn more quickly than others.

That Samarasinghe is among a select group of scientists pursuing this research—keep in mind he's also a practicing neurologist—doesn't surprise Don DeFranco, a PhD and Pitt professor of pharmacology and chemical biology who mentored Samarasinghe and who describes him as one of the most impressive students he has ever encountered.

DeFranco shared a letter of recommendation he wrote for Samarasinghe in which he stated: "I can't think of another student from our MSTP . . . that I have known who has as much potential to be a highly productive physician scientist as Ranmal. Training Ranmal was one of the highlights of my academic career."

—Michael Aubele





Twenty years before "Saturday Night Live" launched, Pitt Med Class of '55 graduates kicked off their own irreverent comedy production, which this year celebrates its 70th anniversary—it was named Scope and Scalpel by the next graduating class. LEFT AND TOP: The 1955 playbill and cast. BELOW: Gwen Miller, her son Andy (MD '91) [right], faculty advisor Allison DeKosky (MD '08) [left] and students hold S&S memorabilia. Gwen Miller's husband, Bebe (MD '55), was a major force in bringing the production to life.



RON STEWART

OCT. 11, 1942–OCT. 22, 2024

Should disaster strike, be it a mass casualty event, severe flu outbreak or some other form of catastrophe, the emergency department's response rests heavily on the medical director. One of the most respected physicians to ever hold that position, Ron Stewart, an MD and pioneering leader who greatly advanced emergency medicine and paramedicine in North America, died at 82 in October.

Stewart, the son of a coal miner from Cape Breton, devoted more than 50 years to the health of others, working in both Canada and the United States. Elected to Nova Scotia's Legislative Assembly in 1992, he served as health minister under Premier John Savage. Leveraging his background in emergency medicine, Stewart aimed to reform health care by promoting community-oriented and accessible health services. His political career emphasized improving emergency response systems and reevaluating how health care served nonemergency patients.

Stewart served as the first medical director in the Los Angeles paramedic program and went on to start the University of Pittsburgh's emergency medicine residency. He also was key to developing Pittsburgh's emergency medical response system.

Initially serving as section and then division chief at Pitt, Stewart developed cross-site partnerships that led to the creation of the Center for Emergency Medicine of Western Pennsylvania. His work paved the way for the acute care services we rely on today.



Stewart

Donald Yealy, an MD Distinguished Professor of Emergency Medicine and chair of the department, was recruited early in his career by Stewart to join Pitt Med's emergency medicine residency program. Yealy didn't anticipate being drawn to the program, but Stewart's influence quickly changed his perspective: "I was immediately impressed with not only his enthusiasm for emergency medicine, but his enthusiasm for people. No matter who you were, he multiplied whatever interest you had in taking care of people who were acutely ill and injured."

People knew Stewart for his passion and zeal, not only in his professional life but in life in general. Yealy recalls him as "an incredibly articulate and charming man, always full of energy and eclectic."

Stewart's contributions to EMS have been described as immeasurable. The Pittsburgh Bureau of EMS honored him in a Facebook post that reads, "While it is probable that no one will be able to accurately measure the contribution that Dr. Stewart has truly made to emergency medicine and the Emergency Medical Services, it is certain that visionaries and pioneers such as Dr. Stewart have served as the architects to what EMS has been built into today." —*Anvi Jain*

STEP UP: PITT MED TRIVIA



GETTY IMAGES/CAMPWILLOWLAKE

Can you answer these without going online?

(We encourage you to call doctors-in-the-know for consults.)

1. Pitt Med faculty members Elvira Pirondini and Marco Capogrosso started working together on spinal cord stimulation research in Switzerland about a decade ago and, since moving to Pittsburgh in 2020, have collaborated on several projects through Pitt's Rehab Neural Engineering Labs. What other common bond do they share?

2. True or False: Known as the Class of 1943-B, 80 Pitt Med students studied year-round in nine-month segments with only a week off between terms to earn their MDs on an accelerated schedule to support the war effort. With few exceptions, they wound up heading into World War II as active-duty officers.

3. Opportunity didn't always knock. Pitt Med was coeducational until 1909, when it barred women from admission. But the medical school eventually capitulated. When did women students return?

A) 1911
B) 1913
C) 1921
D) 1919

Done? Now, check our inside back cover to find out if you aced this one. And if you have an idea for a Pitt Med–related trivia question, send it our way; we're all ears: medmag@pitt.edu.

ELIZABETH SAGAN

FEB. 1, 1953–JAN. 31, 2025

To Kate Brown and her siblings, Mom was Mom, regardless of how successful she was in her professional life.

"We knew she was this badass in her arena, but she was just our mother at home—never bragged," Brown says of Elizabeth Sagan (MD '79, Res '84), who died Jan. 31, the day before her 72nd birthday.



Sagan

Pamela Moalli, an MD, PhD professor of obstetrics, gynecology and reproductive sciences at Pitt and interim executive director of the Magee-Womens Research Institute, was a student of Sagan's before working closely with her at UPMC Magee-Womens Hospital.

Under Sagan's tutelage and as her colleague in the operating room for years, Moalli learned much about Sagan's journey. She was the only woman among the 30 residents in the urology program during her time and "distinguished herself for her exceptional clinical acumen, technical skills and an unwavering commitment to her patients," Moalli says.

Upon completing her residency, Sagan dedicated herself to women's urologic care—among the first in the country to do that, and the first in Pittsburgh, Moalli says. She established a private practice at Magee in 1990 before joining UPMC in 2012.

Sagan taught Pitt Med urology and obstetrics and gynecology residents, and did it so well that she twice won the ob/gyn teaching award, even though she was a urologist.

Moalli says that those who trained under Sagan were well versed in the "Sagan way" of doing things. She notes the residents performed dozens of cystoscopies and stent replacements as part of her training regimen, which was atypical. "We also learned urology procedures like bladder biopsies, diverticulum resections and suburethral slings, and that was not typical of an ob/gyn residency.

"She was very strict. But I still hear her voice and make sure I'm abiding by the Sagan rules: 'Take the time to define the anatomy before starting a case.' Or, 'Proper retraction and visualization are key to a good surgical outcome.'"

Sagan's daughter Molly O'Brien shares a story that illustrates just how deep her mother's influence ran:

Sagan interrupted what should've been a peaceful time for O'Brien, her husband and their newborn twins during the pandemic. O'Brien had just delivered at Magee, and Sagan was able to sneak in because, while retired, she still had her badge.

"Here I am luxuriating in the birthing room at a time when no one else can visit," O'Brien says. "We have four other kids at home, it was quiet, and throughout the day, no one else came to visit me."

But after her mother arrived, people caught wind—and went out of their way to say hello. "People who worked in the office, ob/gyns—they all came in saying, 'Oh, Dr. Sagan, we heard you were in here.'

"The breadth of the people who worked in the hospital showed up to see her. They got her really nice flowers—her, not me!" O'Brien says it with a smile. —*MA*

The family encourages donations to the Magee-Womens Research Institute and Foundation in Elizabeth Sagan's memory.

IN MEMORIAM

'40s

ROBERT GALEN, MD '47
NOV. 14, 2024
MELVIN LEVENDORF, MD '49
SEPT. 4, 2024

'50s

WILLIAM BARNES, MD '53
DEC. 13, 2024
RUTH BIELO, MD '54
JAN. 7, 2025
LESTER BOLANOVICH, MD '51, RES '57
JAN. 22, 2025
DONALD KETTERING, MD '59
JAN. 5, 2025
WILLIAM POMMERSHEIM, MD '58
FEB. 2, 2025

'60s

TIMOTHY EISAMAN, MD '65
DEC. 6, 2024
LEON J. KUTNER, MD '63
SEPT. 26, 2024
M. RUSSELL LESLIE JR., MD '62
NOV. 23, 2024
MARVIN LEVICK, MD '60
JAN. 24, 2025
WALTER NETTROUR III, MD '64, RES '71
NOV. 15, 2024
THOMAS WELTY, MD '69
NOV. 14, 2024

'70s

IRA BAUMGARTEL, MD '77
NOV. 16, 2024
HEINZ KUNZ, PHD '78
FEB. 10, 2025
ELIZABETH SAGAN, MD '79, RES '84
JAN. 31, 2025
CHARLES SRODES, MD, RES '70, FEL '72
JAN. 6, 2025

'80s

MOUFID MOHEDDINE ALSAWAF, MD, RES '89
JAN. 12, 2025
SHEILA WARD, MD, FEL '87
JAN. 4, 2025

FACULTY

MARK WHOLEY, MD
FEB. 25, 2025

STUDENT

LUIS ESPINOZA (CLASS OF 2028)
JAN. 24, 2025

Please send In Memoriam notices to mia97@pitt.edu.

REFINED FOCUS

WASHINGTON SAYS FUNCTIONAL EYE TRANSPLANTS ARE COMING.

BY MICHAEL AUBELE



UPMC/PITT HEALTH SCIENCES

Kia Washington

"People are saying it's a pipe dream, a moon shot, which it is. But I think it will happen in my lifetime."

In 2016, Kia Washington (Plastic Surgery Resident '11, Hand and Upper Extremity Surgery Fellow '12) said that about functional whole eye transplants in humans; and boy, could that turn out to be a self-fulfilled prophecy. She said that after playing a central role in successfully completing the first viable rodent eye transplant model ever developed.

The U.S. Department of Health and Human Services committed as much as $125 million through its Advanced Research Projects Agency for Health (ARPA-H) to develop the first complete eye transplantation procedure, and Washington, an MD professor of plastic-reconstructive surgery at the University of Colorado, is the principal investigator and lead scientist on a $46 million arm of the project at Colorado's Anschutz Medical Campus. She and her colleagues will focus on developing novel stem cell and bioelectronic technologies to promote nerve regeneration and performing transplant surgeries. (Researchers from Pitt's Department of Ophthalmology are contributing to another arm of the ARPA-H project, with José-Alain Sahel, an MD who is the Eye and Ear Foundation Professor and Chair, leading Pitt's involvement.)

"My portion of the surgery would likely involve helping to dissect out the donor graft, specifically the blood vessels and the optic nerve, and sewing together the blood vessels and optic nerve between donor and recipients," Washington says.

That moon shot she talked about nearly a decade ago is starting to look a lot more like a "not-if-but-when" thing now, and: "Yes," she says, "I believe that I will play an instrumental part in making it a reality."

While surgeons haven't yet been able to take a donor's eye and transplant the organ into a patient to restore their vision, in 2023 they transplanted an eye during a partial face transplant at NYU Langone Health. The patient, who was injured in an electrical accident, couldn't see through the transplanted eye, yet the fact the eye could be used at all has excited researchers.

The major hurdle has been regenerating the optic nerve, which is responsible for vision. "It is essentially part of the brain, and we have not yet found a good way to regenerate brain tissue," Washington says.

Although she specializes in hand and upper extremity surgery, Washington says the surgical skills involved and the nuances and similarities in some physiological aspects of the hand and eye, notably in terms of nerve regeneration, parlay well into expertise in eye transplantation.

Washington spent two years doing basic science research at the Thomas E. Starzl Transplantation Institute at Pitt and, through her research there and work on rodent brains, cultivated an interest in how the brain modifies and nerves regenerate after transplantation. There's a parallel there in hand transplantation, she says.

"Eye transplantation for vision restoration is regenerating the optic nerve, and so that is an extension of my interest in peripheral nerve regeneration, which is a part of hand transplantation and a part of hand surgery," she says. "A lot of times we're doing surgery on peripheral nerves—trying to see what the best way is to get them to regenerate to restore the best function."

Washington's mentors at Pitt Med included Dan Simons, a PhD professor emeritus of neurobiology, and renowned plastic surgeon W.P. Andrew Lee, an MD who is now dean of the University of Texas Southwestern Medical School. She says the training and the specialized research she participated in here paved the way for her to reach this point in her career where she is leading an arm of this massive project.

"Kia was a talented research fellow who was focused on her research goals," Lee says. "She sought out collaborations from different disciplines and made meaningful contributions to our understanding of face transplant and the brain. Her energy and focus have followed her throughout her career." ■



GETTY IMAGES/KATARZYNA BIALASIEWICZ

Channel your inner superhero: You can save a life with CPR.

FOR REAL! TWEEN SCIENCE



Imagine it's a Sunday afternoon and you're hanging out at the park with your friends, enjoying the fresh air. Then someone nearby collapses to the ground. They don't seem to be breathing, and everyone starts to panic. But you don't have to freeze—you can channel your inner superhero.

How? First, get backup. Call 911 and ask an adult to help. Next, use your senses: Look, listen and feel for any signs of breathing. If they aren't breathing normally or at all, they might need CPR.

You've probably heard of CPR, but you might not understand why it can save a person's life. CPR stands for cardiopulmonary resuscitation, and it can help a person who's suffering from cardiac arrest. When the heart stops beating, it no longer pumps blood around the body. Blood carries oxygen, which cells throughout the body need. If oxygen doesn't reach these cells, they die.

Yet by doing chest compressions—pushing down hard and fast on the person's chest during CPR—you can actually take over for their heart and keep blood moving. This keeps their brain and other important organs alive a little longer, giving the person a better chance of surviving until paramedics arrive.

Peter Safar, who was a professor right here at the University of Pittsburgh, helped to develop CPR in the 1950s. He also helped create the original mannequin used to train people in the technique. Maybe you've heard of Resusci Anne.

Even if you don't think you know CPR, you can still perform chest compressions. If you're on the phone with 911, they can walk you through the steps. Place your hands in the center of the person's chest, interlock your fingers and start pressing hard and fast—about 100 to 120 times per minute. You want to push at least 2 inches down. To keep the rhythm, you can hum a song to yourself. "Crazy in Love" by Beyoncé or the Bruno Mars song "Uptown Funk" both have the right tempo. And if you get tired, remember: When someone steps in quickly to provide CPR, a person is three times more likely to survive.

—Anvi Jain

Special thanks to Ankur Doshi (MD '00), an associate professor of emergency medicine, for helping us understand the lifesaving science of CPR.

CALENDAR

SAFAR SYMPOSIUM
MAY 15-16
University Club and Winter Institute for Simulation, Education and Research
www.safar.pitt.edu/safar-symposium/2025-safar-symposium/

SCOPE AND SCALPEL
MAY 15-16
Eddy Theatre, Chatham University

DIPLOMA DAY
MAY 18
Soldiers and Sailors Memorial Hall and Museum

HEALTH SCIENCES REUNION WEEKEND
SEPT. 19-20
For information: Alex Rigby at +1-412-789-5866 or hsalumni@pitt.edu

To find out what else is happening at the med school, visit health.pitt.edu and maa.pitt.edu.





Pitt Med Trivia

(from page 37)

Answers:
1. Marriage
2. True
3. B—1913

NEW SUBSCRIPTIONS

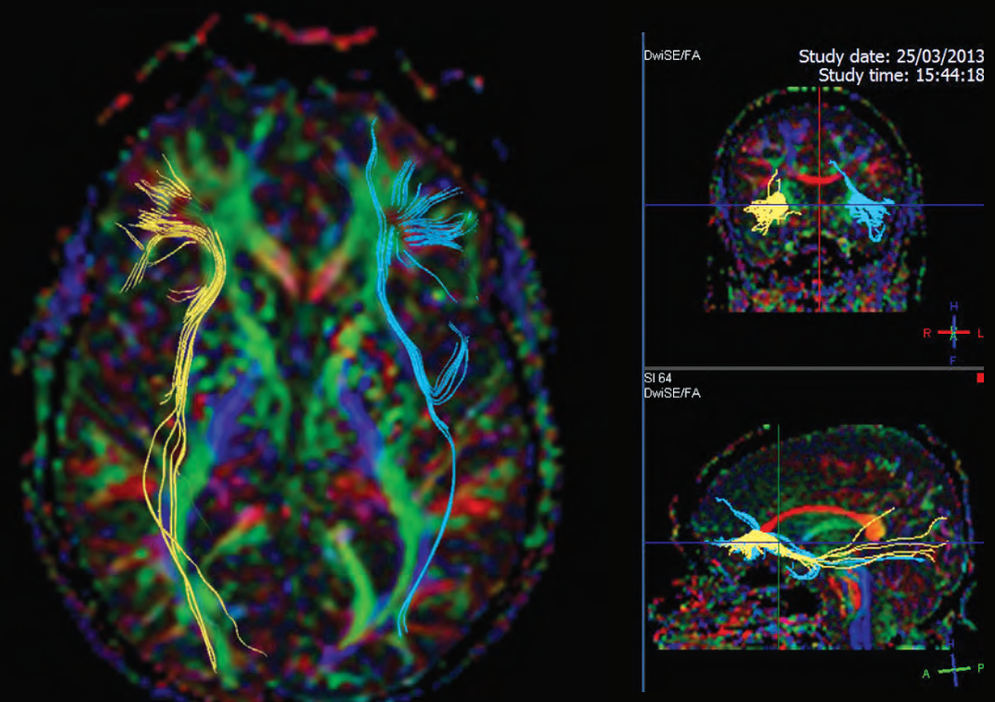
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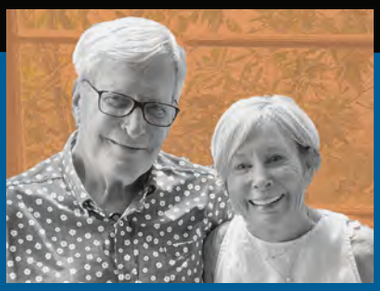
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The Thompsons' gift will advance neurology at Pitt.



GETTY IMAGES

A gift for generations



Robert and Susan Thompson

Robert Thompson's connection to the University of Pittsburgh runs deep. "In three generations of the Thompson family, we count seven Pitt undergrad alumni, five medical school graduates, two nursing grads and one MBA," he says. "We don't have a family crest, but if we did, it would be blue and gold." The bond with Pitt is a key reason Thompson and his wife, Susan, gifted $1 million to the Department of Neurology in 2024.

Thompson, a Pitt Med MD and resident alumnus, built a distinguished career in general clinical neurology. Throughout his career, he remained guided by the mantra of his mentor, Henry Higman: "Focus on the patient!"

"In medical school I wasn't sure what specialty to pursue," Thompson says. "I considered ophthalmology, internal medicine and even spent six months in psychiatry during my internship. I was at a loss with only a few months left before my residency was due to start. I remembered Higman, then the neurology chair, giving several illuminating and entertaining lectures to our class. I approached him about a spot as a first-year resident."

Thompson says it took a stroke of luck, but he got in and couldn't have been more pleased with Higman as a mentor.

He also learned from other giants in the field, including John Moossy and Lowell Lubic. "I'm sure I speak for all my fellow trainees when I say they molded us into competent, compassionate and confident clinicians.

"Both the neurology and neurosurgery residents rotated through [Moossy's] four-month neuropathology course. I don't think any of us missed a neuropathology question on the written boards after completing his vigorous curriculum."

Thompson also recalls the excitement in the room when the wonders of modern science took hold: "The miracle of the CAT scan was introduced during my last year, 1976. I still remember Lowell exclaiming when he saw his first CAT scan image, 'Oh my God, you can see the third ventricle!'"

The Thompsons' gift will advance the department's efforts to treat stroke, traumatic brain injury, multiple sclerosis, epilepsy, movement disorders and other neurological conditions. Their gift will also help the department recruit top-tier faculty who will shape and enhance its programs, perhaps leading to tomorrow's miracles of neurology.

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