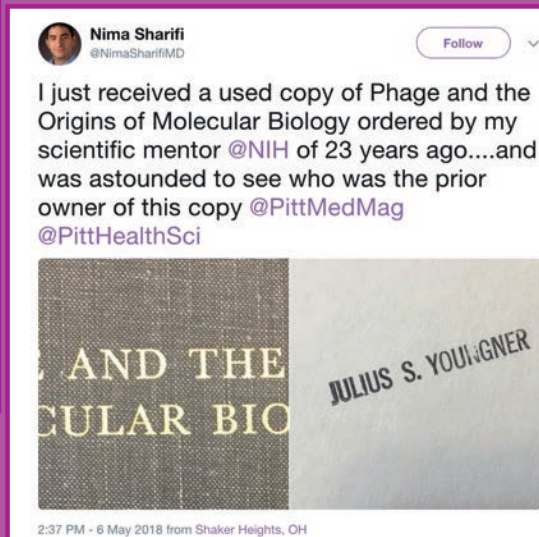
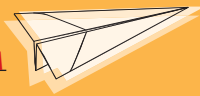


UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SUMMER 2018

PITTMED

DNA'S DARK MATTER

FINDING MEANING IN THE
GENOME'S GREAT UNKNOWN



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ERVIN DYER ["With Love, From Haiti"] is a senior editor for *Pitt Magazine* and former staffer at the *Pittsburgh Post-Gazette*. He first traveled to Haiti in 2008 on a quest to see each of the nations poet Langston Hughes had during his lifetime. Dyer has since returned to the Caribbean nation several times on behalf of the Functional Literacy Ministry of Haiti, a Pittsburgh nonprofit. He earned a PhD in sociology from Pitt, focusing on African immigration, assimilation, and integration.

SARA WHITLOCK ["The Tortoise and the Hare"] was the magazine's intern this spring. Raised in Kansas City, Whitlock graduated from John Brown University in Arkansas with a degree in biochemistry. She is earning a PhD in molecular biophysics at Pitt. If her name sounds familiar, that may be because in 2017, she contributed a regular column called "Under the Microscope" to the national health-science news site *STAT*. Whitlock isn't sure what direction her career will turn, but she plans to keep writing about science.

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, SUMMER 2018
VOL. 20, ISSUE 2



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Anne-Ruxandra Carvunis has upended how scientists think about the genome. Her toolbox includes networks that show molecular interactions.
(Cover: © Shuoshu/Getty Images)



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A planned immunotherapy center will allow Pitt researchers to “swing for the fences” in the search for new understandings and treatments.

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Anne-Ruxandra Carvunis finds meaning in the dark corners of DNA. Her study results keep surprising people—like how some “junk DNA” is actually able to birth brand new genes from scratch. And Carvunis is just getting started.

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BY GAVIN JENKINS

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It's raining viruses! Hallelujah!
(With apologies to the Weather Girls.)

Trillions upon trillions of viruses are falling to Earth all of the time—about 800 million every square meter every day. This estimate was recently reported by researchers who did field-work in the European Sierra Nevada mountains. A *New York Times* story on the discovery describes how viruses seem to rain down from a viral stream cruising above our weather systems. Where does it come from? Most observers believe the stream is created by viruses rising up from soil and water, but some contend the microbes could originate in the atmosphere or in space.

We do know that viruses are elemental to our existence. They are part of our ecosystems and our bodies. Much of our DNA probably arose from viruses; and since life began, pieces of viral genetic material have integrated themselves into virtually all life-forms. As evolutionary biologist Anne-Ruxandra Carvunis notes, “We are very virus-y.” (I encourage you to read this issue’s cover story to learn how Anne is finding meaning amid DNA’s “dark matter.”)

The *Times* story mentions the ARC gene, which a team at the University of Utah has determined includes ancient viral DNA. ARC plays a role in our consciousness and memory. Isn’t it astonishing to consider that the recollections and thoughts we have seem to owe their origins to microbes? These bodies and minds we inhabit are part of the virosphere.

We do not know the extent to which ancient ARC contributes to one of the most interesting examples of a shared memory system, i.e., the common molecular ground between the immune system and the nervous system. In our Spring 2016 issue, I wrote about how both are plastic organs. This April, the School of Medicine’s annual symposium with our partner Tsinghua University was devoted to how both systems learn and create memories.

Indeed, they have a lot in common at the molecular and cellular levels. For example, classic inflammatory cytokines build our substrates for learning and memory. They share RAG gene expression, and both immune and nervous systems are able to take cues from neurotransmitters. Although this is wildly speculative, I can imagine that one viral “hit” in evolution—if not ARC, then something similar—could have been sufficiently small and exquisitely integrated to endow our genome with this transcendent commonality.

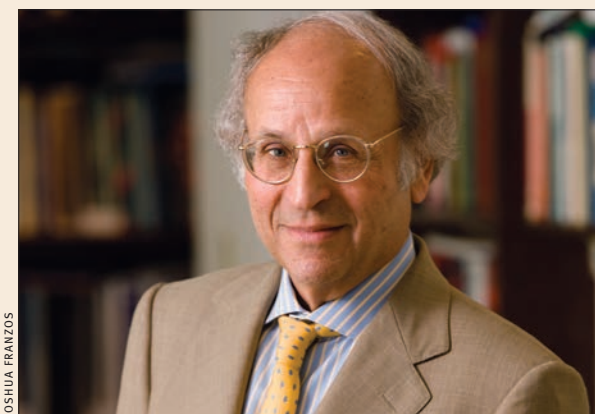
I can’t resist sharing another piece of biology news here. In a startling paper, David Glanzman at UCLA just reported that his lab was able to transfer memories from one snail to another by injecting RNA. (Think ancient viral RNA!)

If he’s correct, it implies that memory resides in cellular nucleic acid, not just synapses, as most neuroscientists hold. Further, it means the capacity of our bodies to learn and remember actually reaches beyond our immune and nervous systems, stretching—perhaps—to the virosphere!

Arthur S. Levine, MD

Senior Vice Chancellor for the Health Sciences

John and Gertrude Petersen Dean, School of Medicine



JOSHUA FRANZOS



*Devoted to noteworthy happenings
at the medical school*

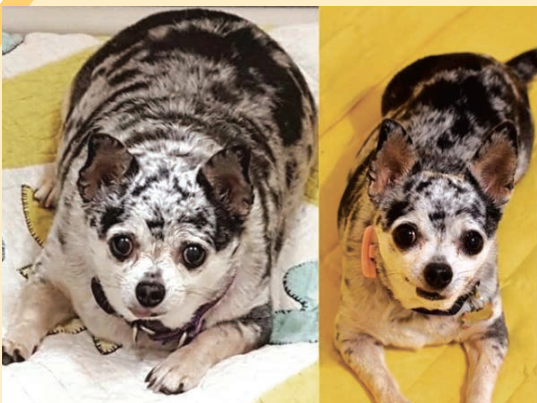
THE MANY ROADS TO THE GOLD

When Kentaro Onishi, assistant professor of physical medicine and rehabilitation at the University of Pittsburgh, was 17, he attended the 1998 Winter Olympics in Nagano, Japan, and thought: *I will be an Olympian one day.* Years later, in California, he realized his track prowess wasn't going to cut it. So, he says, "I changed my plan. [I decided] to be a sports medicine doctor and go to the Olympics as a supporter for the athletes." Sixteen years later, Onishi made it; he was one of three Pitt Med doctors at the 2018 Winter Olympics in PyeongChang.

To become an Olympic doc, Onishi completed a two-year online course "equivalent to a master's degree" and had to "be top 12 in the world" to be selected by the International Olympic Committee. He was

FOOTNOTE

**Lu-Seal, a fetching young thing that
lost half her weight after being morbidly**



**obese, has been featured
in *People* magazine and
has nearly 16k Instagram
followers. The 8-pound
Chihuahua was brought back
to health by her adopted
mama, Pitt Med grad and
emergency medicine resi-
dent Julia Morley (MD '15).**

Lu-Seal is an inspiration

**to many families wanting their chubby pups to become healthy. She
also helps Morley exercise and stay on schedule. (If breakfast is
late, Lu-Seal gets her out of bed by licking her nose.)**

**Those white coats are part of the uniform
of the 2018 U.S. figure skating team.**



one of two Americans working as physicians in an urgent care clinic at the Olympic Village.

Peter Gerbino (MD '86) didn't complete coursework to serve at the games, but he spent 18 years working with figure skaters before going to PyeongChang as team physician for the U.S. team.

Gerbino was selected by U.S. Figure Skating, the sport's governing body, from among 29 other physicians.

Both Gerbino and Gloria Beim (Fel '96), who did her first Olympic stint at the 2004 games in Athens, rotated at the U.S. Olympic Training Center in Colorado Springs before they were eligible. In addition to giving excellent care, Olympic docs need to be team players, says Beim. This year, she led her own crew in PyeongChang as chief medical officer for Team USA at the Paralympic Games, which was her fifth Olympic/Paralympic appointment by the U.S. Olympic Committee.

"I don't know how I got so lucky," says Beim. "It's an amazing thrill ride." —Sara Whitlock



Overheard You Snooze, You Win

Peter Franzen, assistant professor of psychiatry at Pitt, is opening a lot of eyes in Allegheny County school districts. He's campaigning for middle and high schools to commence each day later in the morning. Though the start time recommended by the American Academy of Pediatrics is not until 8:30 a.m., each district in the county currently begins its day before that. Franzen researches the connection between sleep and emotional function. He says that he crusades for later school start times because of the "tight bidirectional association" between sleep and psychiatric disorders. Teenagers who don't get enough sleep, says Franzen, are at a higher risk of developing depression, suicidal thoughts and behaviors, and substance abuse issues. They are also more likely to end up obese or with high blood pressure. Only a third of the adolescent population gets the recommended eight to 10 hours of sleep during the school week.

Why aren't teens getting enough sleep?

Sleep changes a lot as kids progress through puberty. Biologically, slow-wave sleep gets lighter and lighter. This is our homeostatic drive to fall asleep. You build up your homeostatic sleep drive across the day; and if you're awake for a really long time, you build up more drive, fall asleep quickly, and sleep more deeply. That process gets lighter as kids progress through puberty. The other thing that changes is their biological clock. We can look at melatonin as a marker for that. Melatonin is a hormone that gets released about two to three hours before bedtime, and then it's flat during the day. That melatonin onset delays by about one to three hours as kids go through puberty. So not only is there a change to their homeostatic drive, there's also a change to the circadian rhythm that is pushing kids to want to go to sleep later and to have lighter sleep overall. Other contributors to rampant sleep loss are social and environmental—like loss of parental control, digital devices, homework, and, of course, school start times.

Does starting school later help?

More than 400 schools in the U.S. have made this change since the mid-'90s because of what we know about sleep, and they tend to report positive outcomes: School performance goes up, people are late to school and fall asleep in class less often, and there seems to be a reduction in depression symptoms. All but one district has maintained the change.

Why is there pushback against later start times?

It impacts the entire community: teachers, parents, their work schedules, when sports practices or games are going to be, busing schedules. But, if you really think that sleep has this emotional regulatory function, and it's as simple as moving school start times later so kids get more rest and do better, why wouldn't you do that? —Interview by Sara Whitlock

Next Generation

Postdoctoral fellow Akash Verma, a PhD, earned the cover story in November's issue of *Science Immunology* when he identified how the human immune system responds to an oral fungus by the name of *Candida albicans*. Verma works in

the Gaffen Lab, where the team identified the protein responsible for sounding the alarm when *C. albicans* invades the mouth. The research could lead to better treatment options for those suffering from a condition called oral thrush. Verma's advisor, Sarah Gaffen, is a PhD and the Gerald P. Rodnan Professor in the Department of Immunology at Pitt.

Filip Istvanic knows about bubble bursting. The student in Pitt Med's Physician Scientist Training Program developed a method using microbubbles, stimulated by ultrasound, to break apart tiny blood clots in blood vessels. Istvanic gave a talk on the subject at the European Symposium on Ultrasound Contrast Imaging in Rotterdam this past January. The Howard Hughes Medical Institute's Medical Research Fellows Program supported his efforts. Istvanic began this work under his advisor, John Pacella, MD associate professor of cardiology, and Flordeliza Villanueva, MD professor of medicine and vice chair for preclinical research.

Postdoctoral scholar in the Department of Biomedical Informatics **Sarah Aboutalib won a Radiological Society of North America Trainee Research Prize** for her abstract on a computerized method aimed at classifying mammogram images in breast cancer patients. She worked with Shandong Wu, PhD assistant professor of radiology and biomedical informatics at Pitt Med.

Mehret Birru Talabi (MD/PhD '11) was named one of 10 Distinguished Fellows by the American College of Rheumatology in 2017 for her focus on women's health in rheumatic diseases. Birru Talabi, now an assistant professor of rheumatology in clinical immunology at Pitt Med, says she'd like to see a larger focus on women's health in her field. "We need to figure out how to train providers—gynecologists, primary care physicians, rheumatologists—to make sure that issues related to contraception, reproductive health, and pregnancy planning are part of the ongoing conversation with patients."

Pitt Med student Stephen Canton claimed the title Future City 2018 Alumnus of the Year this January, landing him a spot as a judge at the 2018 Future City competition. In both 2004 and 2005, Canton participated in the competition, which exposes middle school students to the principles of engineering. "It's the reason I went into engineering," says Canton, who got his degree in bioengineering from Pitt in 2013. Canton is now developing a virtual reality training program that simulates how to scrub in. —Evan Bowen-Gaddy

CAMI MESA

A MEETING OF THE (FUTURE GREAT) MINDS

It's funny how far bacteria can take you. **Tolani Olonisakin**, a Medical Scientist Training Program student who researches *Klebsiella pneumoniae*, bacteria that cause catastrophic infections in patients with weakened immune systems, was selected to attend the 68th Lindau Nobel Laureate Meeting in June. At the annual gathering, Nobel laureates meet and mingle with hundreds of undergraduate and graduate students, as well as postdoctoral fellows. This year's meeting will focus on gene therapy, a topic that Olonisakin studies.

Olonisakin, who entered college at 16 and will turn 26 during her flight to Germany for the meeting, is looking forward to networking with other researchers. "Lindau fosters collaboration among participants, even beyond the meeting," she says. "Alumni are closely followed, and their continued scientific success is paramount."

This year's meeting not only features geographic diversity (with 43 Nobel laureates and students from 84 countries), but also, for the first time, women will make up half of all student attendees. Eighteen University of Pittsburgh students have attended Lindau since 2004, when the organizers began tracking representation. Olonisakin is the



Olonisakin was picked to attend the June Lindau meeting of Nobelists. Here she's shown at a Howard Hughes Medical Institute session in 2017.

only Pitt student selected this year. Janet Lee, an MD and her mentor, says, "It is indeed a tremendous honor to have Tolani represent our research program and the School of Medicine. I have no doubt she will be a future leader in whatever she sets her mind to accomplish." —*Nichole Faina*

Top Physician-Scientists Honored

Seven Pitt Med physicians joined the ranks of two prestigious societies in Chicago this past April in a joint meeting between the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP). The Chicago meeting serves as a forum for physician-scientists to discuss policy and career issues facing the profession.

ASCI's 2017 honorees include **Susanne Ahmari**, an MD/PhD and assistant professor of psychiatry, **Daniel Kaplan**, an MD/PhD professor of immunology and dermatology, **Matthew Rosengart**, an MD/MPH professor of surgery and critical care medicine and codirector of the surgical trauma intensive care unit at UPMC Presbyterian, and **Alexandre Dombrovski**, MD associate professor of psychiatry.

And this year, the AAP elected to its membership **Daniel Buysse**, UPMC Professor of Sleep Medicine and MD professor of psychiatry and of clinical and translational science; **Aleksandar Rajkovic**, an MD/PhD, who was Pitt's Marcus Allen Hogge Professor and was just named UCSF's chief genomics officer; and **José-Alain Sahel**, chair of ophthalmology and director of the UPMC Eye Center. Sahel also holds the Eye and Ear Foundation Chair. —*EBG*



FICKER COMMONS

FOOTNOTE

Steelers fans are sure to remember Brett Keisel, former defensive end who helped Pittsburgh clinch two Super Bowl wins. Keisel's beard stretched from his face mask to his chest like a mane. These days, he's using his facial hair to help fund cancer research. Since 2011, Keisel has hosted an annual

event called "Shear Da Beard," during which he shaves his winter tangle to raise money for Children's Hospital of Pittsburgh of UPMC. The event has raised hundreds of thousands of dollars in the past eight years. It must be difficult for Keisel to part with his nest of hair every year. He once said it was "the greatest beard of all time."



MORE AWESOME, PLEASE

"They were guaranteed nothing, and they gave everything," Arthur Levine, the John and Gertrude Petersen Dean of Medicine and senior vice chancellor for the health sciences, said as he unveiled a digital and interactive tribute to five Pitt physician-scientists who changed the world. Those exiting the fifth floor elevators in Scaife Hall will now be reminded of the accomplishments of Bernard Fisher, who transformed breast cancer treatment and our understanding of cancer, Peter Safar, codeveloper of CPR who established the first modern ambulance service, Thomas Starzl, giant of transplantation medicine, Maud Menten, biochemist whose work made drug development possible, and Jonas Salk, of the killed-virus polio vaccine.

The doctors faced daunting challenges—Safar evaded the Nazi regime; Starzl dealt with medical residents who organized against his early attempts at liver transplantation; Menten, because she was a woman, was not allowed to be a university faculty member in her native Canada through most of her career. "These are the people we want our students to think about as they confront their own obstacles and prepare to write the next chapters in American medicine," noted Levine.



TOP: Now it's even easier to look up to Maud Menten. INSET LEFT: Peter Salk (left) and Joy Starzl (right) with Pitt's Maggie McDonald and Chancellor Patrick Gallagher at the exhibit unveiling. INSET RIGHT: Trying out the interactive display.

Appointments

Boxes tower around **Andrew Feranchak** (MD '92, Res '95) everywhere he goes: his home, his office, his lab—but he doesn't care.



Feranchak

"It's nice to come home," he says of his move from the UT Southwestern Medical Center to Children's Hospital of Pittsburgh of UPMC, where he has been appointed chief of the Division of Pediatric Gastroenterology, Hepatology, and Nutrition. Twenty-two years ago, he was a resident at Children's, and although the hospital has changed locations, he says, "that same special spirit of Children's continues. It's always been a place where children come first." In his new position, Feranchak will continue studying cholestatic liver diseases, where "the liver doesn't make bile or bile formation is abnormal." He also plans to grow the hospital's GI programs, develop new multidisciplinary clinical programs, and expand research. Until then, he says, "if you're ever in the area, we'll give you a box to unpack."

Ronald Poropatich, a retired U.S. Army colonel and MD professor of medicine, is now the director of the Center for Military Medicine Research. In this position, Poropatich says he will "put scientific teams together that can continue to compete for DoD funding," as well as lead the center's unique initiatives: developing Trauma Care in a Rucksack (TRACIR), an autonomous cardiopulmonary resuscitation platform, and establishing, with the Neuromuscular Research Laboratory, a DoD-sponsored Coordinating Center for Human Systems and Readiness.



Poropatich

Paul Duprex has been named director of the Center for Vaccine Research (CVR) and the Regional Biocontainment Laboratory, as well as the Jonas Salk Professor for Vaccine Research and professor of microbiology and molecular genetics. He will begin full-time in December, following his move from Boston University. At Pitt Med, Duprex, a PhD, will continue investigating paramyxoviruses (a family that includes measles and mumps). He says of the center, "New pathogens continually emerge, and keeping one step ahead is critical." —SW



Duprex



WHERE EVERYONE KNOWS YOUR ... BIOCHEMISTRY

It's March 16, and from the convivial confines of Morning Grounds—the coffee shop that opened in January on Scaife Hall's fifth floor—three first-year Pitt Med students watch a stream of people hurry into the Petersen Events Center for the Match Day ceremony. Camila Ortiz, Lauren Auster, and Karen Olson plan to join in the ceremonies (for motivation and free food); they met here before heading across the street because they wanted coffee, obviously, and also because Morning Grounds has become Pitt Med's new meet-up spot.

"It has doubled the time I spend in Scaife," says Olson, a 25-year-old Arizona native.

"I used to go home [after class] and study, but now I study here," adds Auster, a Case Western Reserve University alum.

Ortiz, a 27-year-old Allegheny County native, likes the coffee shop's relaxed vibe. The space is warmly lit, with plenty of seating for those intent on getting acquainted with the Michaelis-Menten equation or fellow classmates. There's a pair of long tables for study groups, and a row

of lounge chairs with adjustable desk arms faces floor-to-ceiling windows overlooking Terrace Street.

"You can have conversations with people and study," says Auster, 23. "And I like white noise when I study, so I like it here."

Morning Grounds was created as part of a Scaife Hall renovation project. The latest phase included replacing the escalators between the fourth and sixth floors with an open staircase, remodeling the lobbies on the fourth and fifth floors (including a glass "storefront" entrance), and adding a fifth-floor tribute to legendary Pitt Med physician-scientists (see p. 6).

William Strober, a second-year Pitt Med student from Portola Valley, Calif., won the coffee shop's naming contest.

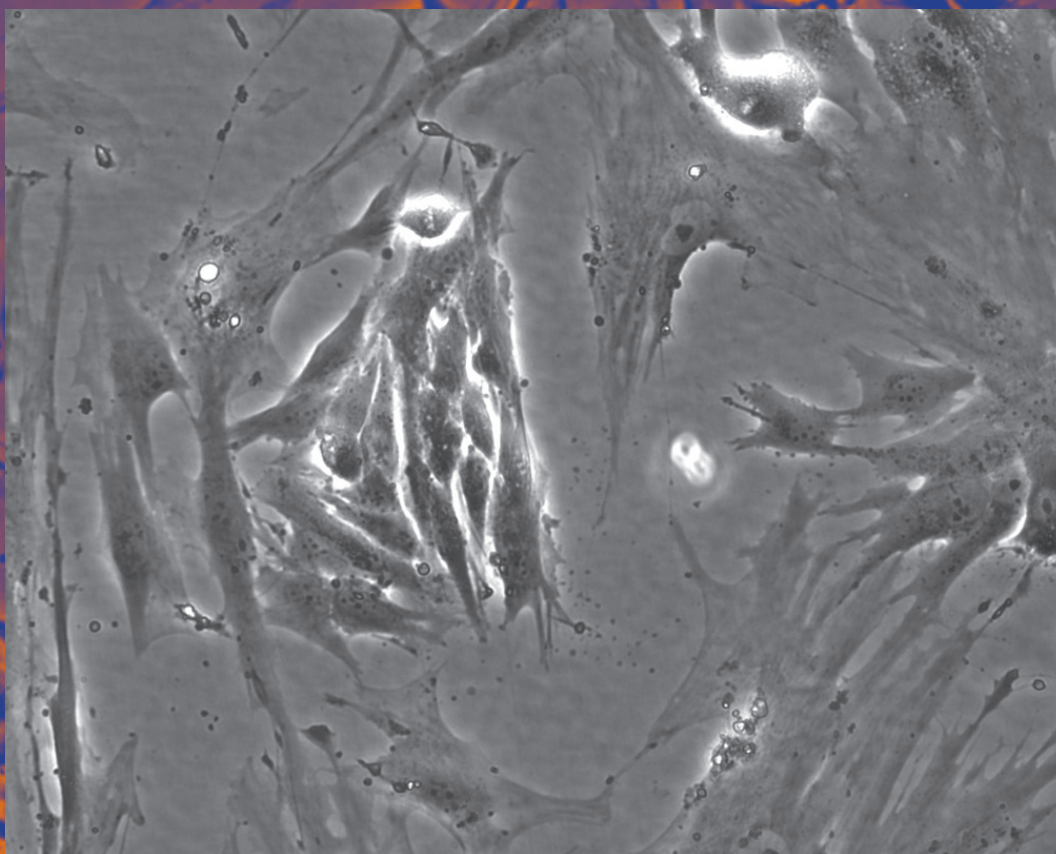
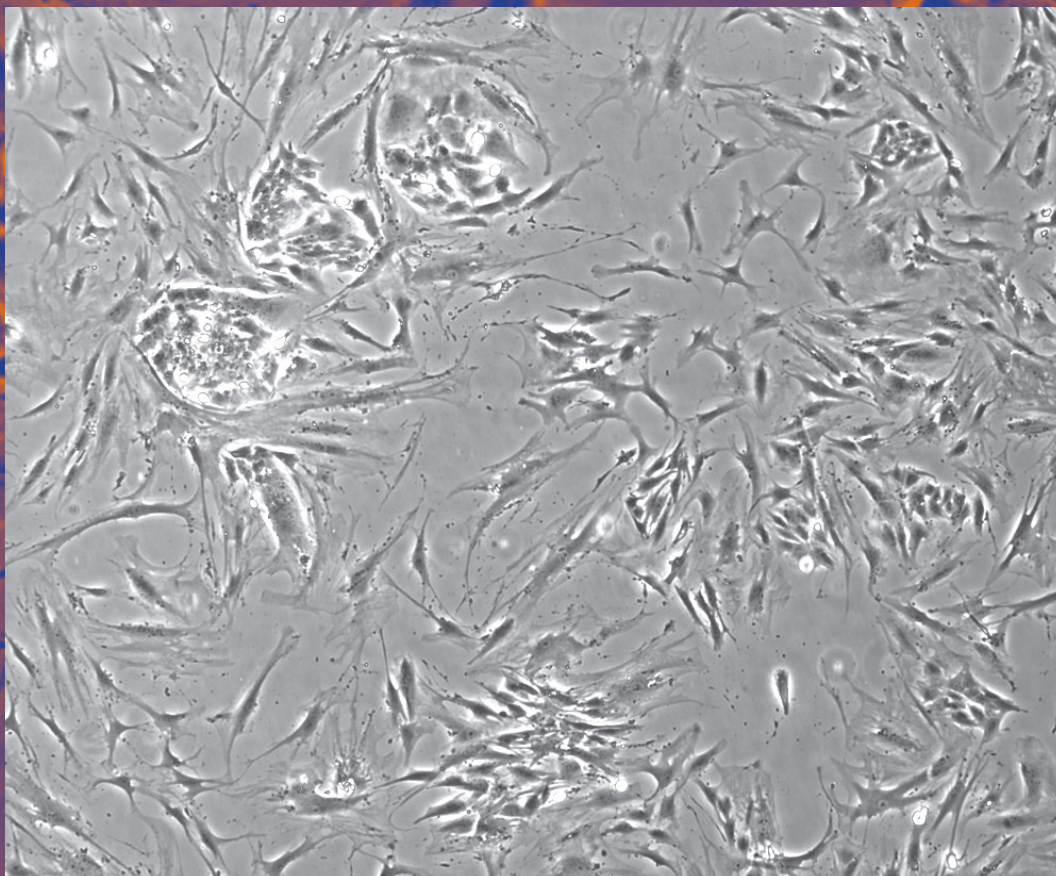
For his cleverness, Strober, 24, received a \$100 gift card to Morning Grounds. He says he passed on puns involving an IV drip and bitter pills before landing on the winner. "I'm really happy that I'll be able to leave my mark on Pitt Med," Strober says.

—Gavin Jenkins

—Photography by Tom Altany/University of Pittsburgh

INVESTIGATIONS

Explorations and revelations taking place in the medical school



MOTOR is a tumor registry and tissue bank at Pitt designed to spur discovery in pediatric osteosarcoma research.
ABOVE: A cell population grows from a registry-derived primary tumor sample.

A MOLECULAR SCALPEL

KURT WEISS PLANS TO FIND
ONE FOR BONE CANCER

BY SHARON TREGASKIS

When orthopaedic oncologist Kurt Weiss tells a family that their child has osteosarcoma (OS), he gives them these words to live by: “treatable and curable.” As evidence, he shares his own story. A defensive end on his high school football team, Weiss was diagnosed with OS at the age of 15 and treated at UPMC. In addition to 25 operations, including amputation of his right leg, Weiss had metastases to his lungs, which pushes a child’s five-year survival prospects from 75 percent to less than 30 percent. “I say, *If we find disease in the kid’s lungs, is it time to freak out?*” says Weiss. “The answer is no. I pull down the top of my shirt and show them the scar on my chest. It’s obviously not good, but it’s not insurmountable. There’s nothing that will change our goal of curing a kid.”

Osteosarcoma survival rates haven’t budged since 1990, when Weiss participated in the clinical trial he credits with his own remission. And so in addition to his work as a clinician treating children and adults with both primary and metastatic bone cancer, the associate professor of orthopaedic surgery founded Pitt’s Musculoskeletal Oncology Laboratory to pursue basic research into the pathogenesis of osteosarcoma, the third-most common cancer diagnosis among people younger than 20. In 2011, soon after he joined the Pitt faculty, Weiss (Res ’08) and colleagues established MOTOR, a tumor registry and tissue bank designed to spur discovery.

“Lots of people have patient databases,” says Weiss. “But it’s being able to capture patient samples that makes us unique. And it makes us strong, because you can take those biological specimens, and [those patients’ out-

comes], and you can use that combination to ask intelligent questions.”

Weiss has focused his own inquiry on the role of aldehyde dehydrogenase (ALDH), a stem cell factor that, combined with a cell signaling pathway that most multicellular organisms have, called Notch1, facilitates metastatic invasion of the lungs by osteosarcoma. After he’d mapped out the basic mechanisms using cells cultured from patient samples, he used a mouse model to test his theories. “But none of my patients are mice,” says Weiss, so he went back to MOTOR to analyze the correlation of ALDH in tissue samples with each patient’s disease trajectory. “The level of ALDH expression in cultured cells perfectly correlated with metastasis,” he says. “It seems like we might be on the right track.”

More recently, he’s begun investigating whether known ALDH inhibitors can slow metastasis. In 2015, *Sarcoma* published his finding that retinol (vitamin A) altered the expression of metastasis-related genes and decreased the proliferation, invasion capacity, and resistance to oxidative stress of metastatic cells.

In a study now under way, Weiss is testing the effect of disulfiram, a compound approved by the FDA as a treatment for alcohol addiction (marketed under the brand name Antabuse). If the compound works, it would mean a level of precision targeting of cancer cells that’s a far cry from the current standard treatment, broad-spectrum chemotherapy that ravages every fast-dividing cell in a kid’s body.

“It’s napalm,” says Weiss. “I want a molecular scalpel.”

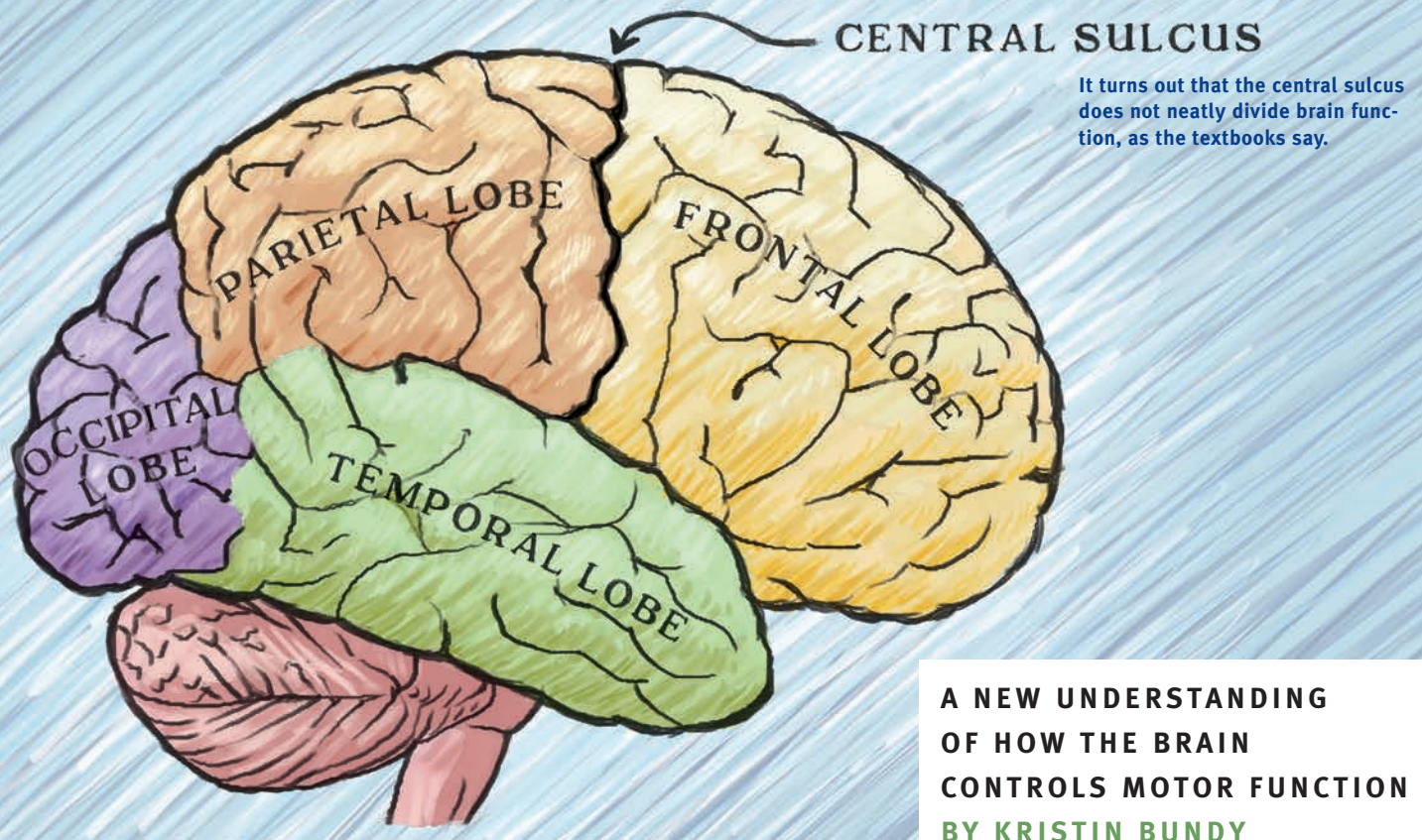
Steffi Oesterreich is professor of pharma-

cology and chemical biology at Pitt and a member of UPMC Hillman Cancer Center. She teamed up with Weiss in 2013 to add samples from people with breast cancer—which can metastasize to the bones—to MOTOR. In 2016, *Clinical Cancer Research* published an analysis showing that mutations in the estrogen receptor gene *ESR1*, which is implicated in resistance to endocrine therapy, were over-represented in metastatic tissue.

“Kurt’s studies are very comprehensive—from the nitty-gritty mechanistic details to cells, to mice, to treating patients,” says Oesterreich. “He’s obviously super busy clinically, but he’s absolutely excited about research.” ■



Weiss on the West Rim of the Grand Canyon in 1998.



SPLIT REVISION

Four decades ago, a neuroscientist at Johns Hopkins University put forth a revolutionary new idea—and took a lot of heat for it. Some said he lacked evidence. “When he proposed his command hypothesis, Vernon Mountcastle got a lot of grief,” says the University of Pittsburgh’s Peter Strick, a PhD, Thomas Detre Professor of Neuroscience, Distinguished Professor and chair of neurobiology, and scientific director of the Brain Institute.

It might have taken 40 years, but Strick and colleagues finally vindicated Mountcastle and validated his work. The original hypothesis? That the central sulcus—a prominent fold in the middle of the brain (right about where a tiara might sit, between the anterior and the posterior portions)—does not, in fact, neatly divide the brain between motor control in the front and somatosensory in the back. (The somatosensory encompasses our senses of touch, position and movement, and immediate physical surroundings.) That clean division of labor was in all good anatomy and physiology textbooks at the time.

Instead, Mountcastle proposed that a region called the posterior parietal cortex, an area behind the central sulcus, had its own

direct link to the spinal cord, giving it a major role in motor control and hand movement.

This was a striking new theory, Strick explains. Mountcastle said that the posterior parietal cortex wasn’t just involved in perception—it also had a command role. “This was just a dramatic change in people’s notion of the function of the cortical area,” says Strick.

He met Mountcastle as a young postdoctoral fellow, and years later, Strick independently conceived of a way to define the cortical areas that connect directly to the spinal cord to command motor function.

Since then, Strick has found eight different pathways that control motor neurons—from the premotor and motor cortex in front of the central sulcus to some areas behind the central sulcus, including the posterior parietal cortex, as Mountcastle postulated years ago.

“This is an important aspect of motor control—that there isn’t just one route to Rome,” says Strick. These different pathways may be important for some people with brain or spinal cord injuries.

For example, Strick explains, “If you have a stroke, and it’s limited to one of these cortical areas, there are other cortical areas that have access to the spinal cord. This can play a role

in compensating for the stroke and promoting recovery of motor function.”

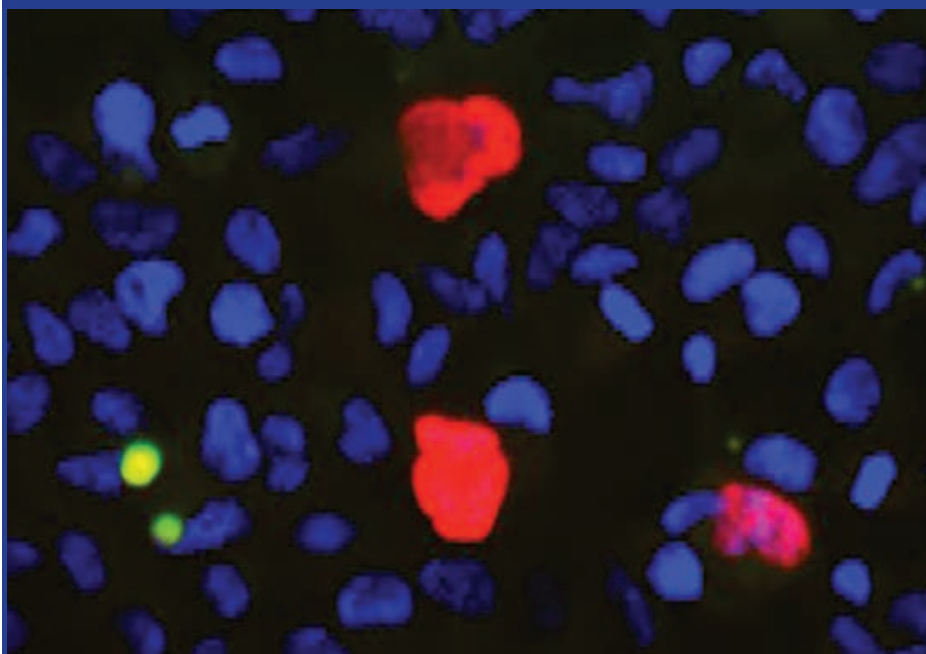
In addition, implanted electrodes in the posterior parietal cortex of the brain have shown promise in sending signals to prosthetic devices, giving people who are paralyzed the ability to move again.

While advances in the clinic continue, Strick is actively researching these pathways, digging deeper to understand: *Why do we have so many pathways to control motor neurons? What does each of them do? And how do they do it differently? Why are multiple systems dealing with the task of motor control?*

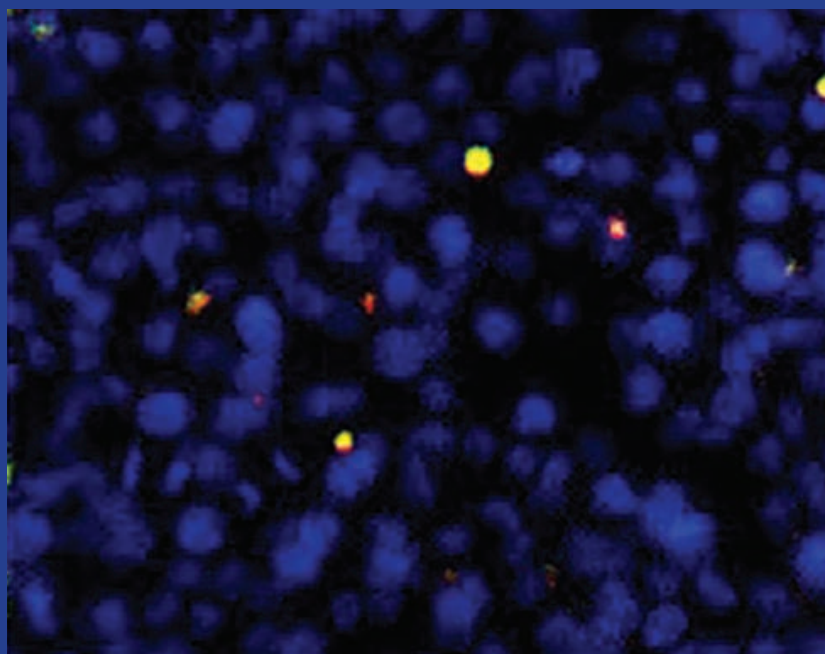
Mountcastle lived to be 96. Fortunately, he was able to learn about Strick’s experimental techniques—they kept in contact throughout the years.

However, Strick regrets that Mountcastle was not able to see his hypothesis borne out in the pages of *Proceedings of the National Academy of Sciences*, in a paper penned by Strick last year.

“I wanted to send him the paper before I submitted it,” he says. “It could have been titled ‘Mountcastle Was Right!’ He would have enjoyed the results.” ■



The Chang-Moore team was the first to observe Merkel cell virus replicating in a lab. Here, their mutant virus (left, in red and yellow) infects a new crop of cells (blue, on the right).



**HOW CANCER WINS THE
RACE IN MCV INFECTION**
BY SARA WHITLOCK

THE TORTOISE AND THE HARE

Yuan Chang and Patrick Moore are virus-hunting superstars. Ten years ago, they discovered—not their first, but their second—cancer-causing virus. (Only seven are known.) The virus is called Merkel cell polyomavirus (MCV), and it is responsible for 80 percent of Merkel cell carcinoma cases. Although this cancer is rare—only about 1,500 cases per year at the time of the virus’s discovery in 2008—Merkel cell carcinoma is on the rise, and it’s one of the deadliest forms of skin cancer.

To learn how this virus works, researchers in the Chang-Moore lab tried to infect cells in a petri dish with the virus’s DNA, thinking they could observe MCV’s life cycle. But it didn’t work. Despite the crew’s best efforts, “no one [had] ever seen MCV replicate” by infecting cells with the viral genome, says Moore. “It’s just always been dead, and we didn’t know why.”

Then, a researcher in the Chang-Moore lab named Hyun Jin Kwun, who now has her own virus lab at Penn State, noticed that the protein responsible for MCV replication—called LTag (large T antigen)—has several tags that signal for its own breakdown. She

mutated the protein to remove those tags and tried to infect cells with the virus again. And then, it worked. “If we make these mutations,” says Moore, “we see—*boom!*—[the virus] is actually replicating, and now it can be transmitted.” By eliminating these degradation signals on LTag, he says, “I can do a better job of making a replicating virus than Father Darwin. Why?”

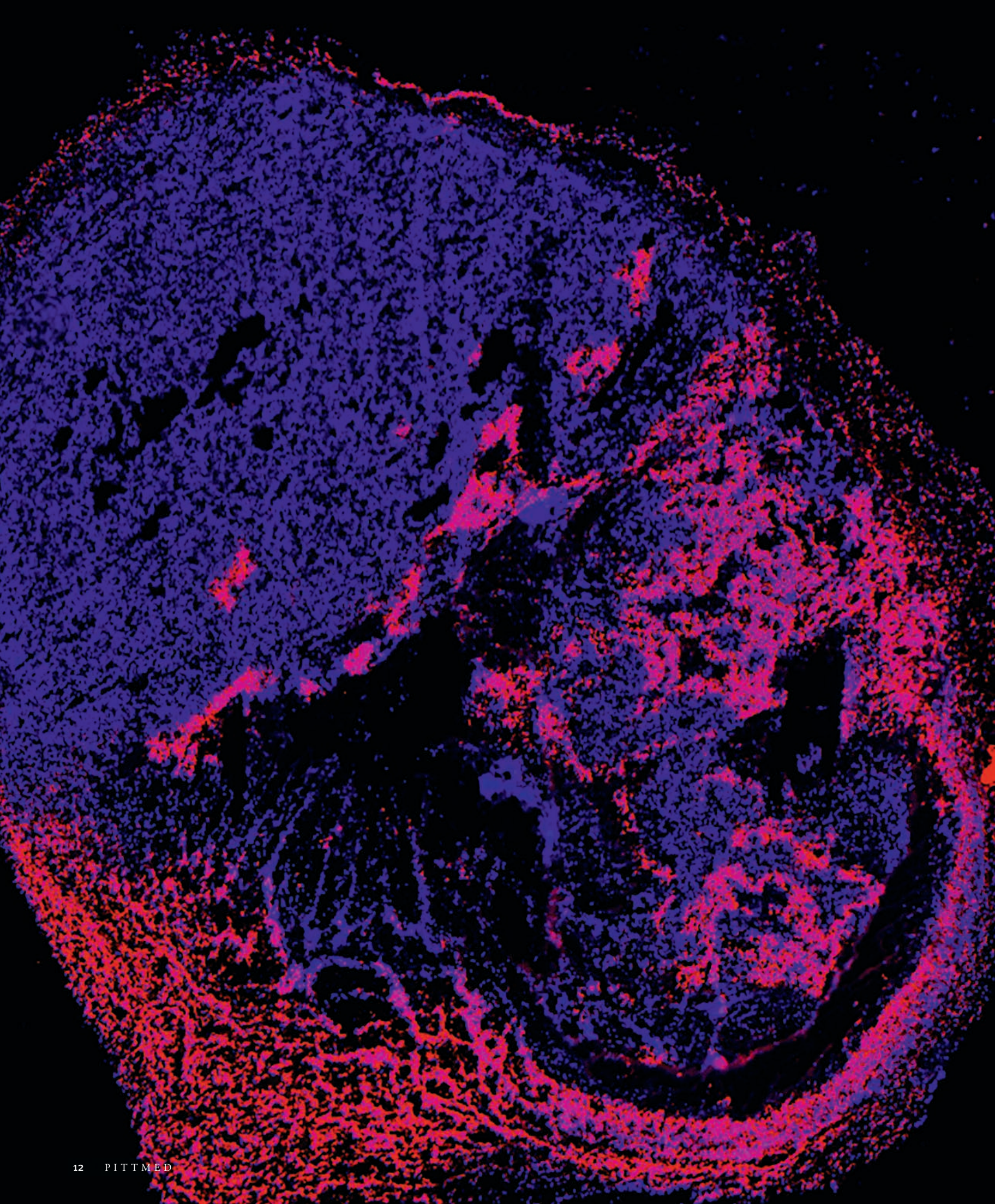
It turns out that no one in the lab had ever caught the virus replicating because, without LTag, the virus lies dormant, or latent, in cells. Unlike, say, a highly contagious virus like influenza, which replicates and moves on to the next cell at a rapid pace, MCV “stays there like a little rock,” says Moore. It only replicates when the host cell copies its genome—which takes time. Kwun’s mutation of the virus gave LTag the freedom to do its thing, which is prying open DNA and allowing it to be copied. That’s when the slow-mo switched to fast-forward.

Understanding how latency hides MCV in cells is key, says Moore, because “most people are infected with this virus, and it’s harbored in their skin. Once you’re infected it’s a life-long infection.” But most of us don’t have

Merkel cell carcinoma, he assures, “because it’s a silent infection.”

The team found that cancer arises through a series of unfortunate events: Stress in the host signals can stop the LTag breakdown signals (this is like what Kwun did in the mutants), and the virus begins replicating fast. As the virus copies itself, it can make mistakes. “You get incomplete replication that occurs, ... genetic fragments that occur,” says Moore. The host human cells “stick those fragments into chromosomes to try and deal” with the extra DNA. If the right fragment is knit into the human genome, the cell becomes cancerous. These findings were reported in *PNAS* in May 2017.

For most of us, this series of unfortunate events doesn’t happen. The cancerous DNA fragment isn’t knit into the genome, or a savvy immune system recognizes funny business in a cell. But the bodies of immunosuppressed patients, like those getting an organ transplant or people with AIDS, aren’t surveilling for cells that behave oddly. So if a cancerous integration of the viral DNA occurs, their defenses are down. That’s how many Merkel cell carcinoma cases start. ■



DENYING TUMORS WHAT THEY NEED

CARA MASSET

FEAST TO FAMINE

When cancer immunotherapy works, it's swift and brawny like a lumberjack. Stage IV melanoma? *Whomp*. Felled. That was the case for President Jimmy Carter, who remarkably recovered in 2016 from melanoma that had spread to his brain and liver. He was treated with a PD-1 blocker, an immunotherapy drug that recruited his own immune system to chop down all the cancerous cells.

President Carter was lucky. A minority of cancer patients respond to this therapy despite it's becoming a first-line treatment for melanoma and lung cancer since the FDA approved it in 2014. Most don't get any benefit. Why is it a windfall for only a few?

When cancer patients respond to immunotherapy, they do so beautifully. But only a minority of patients do. Greg Delgoffe's team shows us how the microenvironment of the tumor can make or break a therapy. LEFT: Red and pink stains show where a melanoma tumor is beginning to lose oxygen.

COURTESY DELGOFFE LAB

Pitt immunologist Greg Delgoffe has figured out a big part of the reason why. Even if a patient's immune cells have been nudged by PD-1 blockers or other immunotherapy drugs to prune away cancer cells, they may struggle to use their axes once inside the peculiar world of a tumor, a space that scientists refer to as the tumor microenvironment. Delgoffe's team has shown that when immune T cells enter the tumor microenvironment, their mitochondria begin to shrink and disappear, indicating that the T cells are starving and don't have enough energy to fell tumor cells. (See the write-up in August 2016 *Immunity*.)

"We found that T cells are not only in a nutrient-dearth environment, but they also start to suppress the ability to even process those nutrients," says Delgoffe, a PhD assistant professor of immunology who specializes in the subfield of immunometabolism. ("It's a five-dollar word, but we go with it," he says of the subfield's name.)

Immunologists "always ask T cells how they do their job," says Delgoffe, but he also asks

sidekick rather than a blue ox. The Seahorse XFe96 Analyzer is what his team uses to evaluate cell metabolism. Put any cell into the machine, and it'll offer a report on the cell's respiration and glycolysis.

The Seahorse is also helping Delgoffe meet others around campus. It's an "instrument of collaboration" that various researchers use to gain insight into metabolism, he says. "People are like: 'Hi, I want to study my cell type.'"

Delgoffe bought the Seahorse soon after he came to Pitt in 2014. He was drawn to Pitt, in part, because of the University's strong foundation in immunology, dating back to the "dark ages" of the 20th century when the medical community largely doubted the viability of immunotherapy. Luminaries like Olivera Finn—founding chair of Pitt's immunology department who, by the way, won the 2017 Cancer Immunology Prize from the American Association for Cancer Research—kept the candles burning despite skepticism. Finn welcomed scientists exploring the newest areas of immunology. (Hello, immunometab-

their environment and how that affects their behavior. He coauthored studies that not only explained the importance of nutrient sensing in T cell function but also forged the subfield of immunometabolism.

Along the way, Delgoffe got curious about another type of T cell: regulatory T cells that serve an immunosuppressive role to keep the common T cells (the cytotoxic, ax-wielding ones) from overrunning healthy tissue. For his postdoc, he headed to St. Jude Children's Research Hospital in Memphis, where he trained with Dario Vignali, who is now the Frank Dixon Professor of Cancer Immunology at Pitt. They reported in *Nature* in 2013 on a signaling pathway for regulatory T cells that, when blocked, can lead to complete tumor regression in mice. Preliminary clinical trials are expected to begin later this year.

In his Pitt lab, Delgoffe is investigating the metabolism of both types of T cells in the tumor microenvironment. His team has found that tumors not only starve T cells (remember those shrinking mitochondria), but they also

He was drawn to Pitt, in part, because of the University's strong foundation in immunology, dating back to the "dark ages" of the 20th century when the medical community largely doubted the viability of immunotherapy.

them metabolic questions, like whether they've eaten lunch so they can stay energized. He and his team are uncovering a surprising number of metabolic problems in the tumor microenvironment—and they are learning what can be done to fix them so that immunotherapies can help more people with cancer.

If you enter Delgoffe's microenvironment of suite 2.19 in the research wing of the UPMC Hillman Cancer Center, four out of five scientists are likely to be wearing plaid.

"Plaid is in," insists Delgoffe, who says lab-mates dressing alike was at first a coincidence, then a look they embraced. They even posted a photo of themselves in plaid shirts on the lab Twitter account to announce their trip to the latest Society for Immunotherapy of Cancer meeting. Their hashtag? #lumberjackscientists.

Delgoffe denies that his lab's penchant for plaid has anything to do with his upbringing in Michigan's Upper Peninsula, though if one were to tell a tall tale about this lumberjack scientist, he'd probably have a seahorse as his

ism!) "We need to bring people here who do immunology just for the hell of it," Finn told *Pitt Med* in 2002.

Delgoffe, who started college as a mathematics major (though he wasn't sure how he'd use the major), is that kind of person. His helluva interest in T cells began when his molecular biology professor at Western Michigan University hired him to help unearth what the plague bacterium *Yersinia pestis* does to the immune system. When Delgoffe got to Johns Hopkins University for graduate school, he was surprised to learn that when T cells first encounter disease cells, their immediate reaction isn't to chop them down. "The first signal is not to turn on. It's to turn off," he says reiterating his disbelief. He quickly learned that's a good thing—for gathering intel to mount bigger attacks or to prevent autoimmune diseases. But that also presented a challenge. How could he make T cells turn on? And what better way to lure them than with food?

At Johns Hopkins, Delgoffe ultimately explored how T cells sniff out nutrients in

feed immunosuppressive regulatory T cells. Delgoffe received the 2017 NIH Director's New Innovator Award to further scrutinize the metabolism of regulatory T cells and explore ways to rebalance the feast-or-famine dynamic in the tumor microenvironment.

"Greg's groundbreaking work in reprogramming energy use by tumor cells will lead to the development of new drugs that can substantially enhance cancer immunotherapy," said UPMC Hillman Cancer Center Director Robert Ferris when the award was announced last fall. Ferris holds Pitt's Hillman Chair of Oncology and is a professor of otolaryngology, immunology, and radiation oncology. His own research focuses on head and neck cancer; Ferris is a big supporter of immunotherapy and speaks of it as the "fourth modality" alongside the prevailing cancer treatment modalities of surgery, radiation, and chemo. He and Vignali colead the Tumor Microenvironment Center. Delgoffe is the center's first recruit.

Delgoffe's lab members are testing a num-



COURTESY PAOLO VIGNALI

Delgoffe (right) and his team prefer plaid.

ber of ways to metabolically reprogram the tumor microenvironment. They're genetically modifying T cells to make them super lumberjacks who can work long hours with little food. They're trying out oncolytic viruses (viruses that infect and kill cancer cells) to see whether they're good tools for reprogramming tumor cell metabolism. They're taking T cells modified by CAR T-cell therapy (a means of adding receptors directly to a patient's T cells) and looking at what happens to the metabolism in the tumor microenvironment of individual patients, investigating whether reprogramming would be beneficial. Their March 2018 report in the *Journal of Experimental Medicine* demonstrates that activating 4-1BB proteins on the surface of T cells (which tend to lie dormant in the tumor microenvironment) enables the T cells to increase their mitochondria and regain their energy. And combining that 4-1BB therapy with a PD-1 blocker in mice is particularly effective for equipping T cells to do their cancer-felling job. On the regulatory T cell front, the team has assisted Vignali's lab with

showing that an interferon protein that causes immunosuppressive cells to become more fragile could also make a PD-1 blocker therapy more effective. Those findings, first-authored by Abigail Overacre-Delgoffe, Delgoffe's wife and a trainee working in Vignali's lab, were published in *Cell* in June 2017.

There's more good news. Delgoffe's lab (with help from the trusty Seahorse) has shown that the tumor microenvironment not only starves T cells of nutrients, but oxygen, too. They've found that metformin—a drug typically used for type 2 diabetes that's also promising for cancer treatment—has the ability to reoxygenate the tumor microenvironment and can reduce tumors in mice if given in combination with PD-1 blockers. When Delgoffe talked about these findings at a campus grand rounds soon after they were reported in *Cancer Immunology* in 2016, he was approached afterwards about teaming up for a clinical trial to see whether this tack might benefit the majority of patients who don't respond to the PD-1 blockade.

The clinical trial for skin cancer is now

open, just a year and a half later, which Delgoffe thinks is pretty phenomenal. "This is exactly why I came here: to get involved," he says of the translational research infrastructure in place at Pitt. He's partnering on the trial with Yana Najjar, an MD assistant professor of medicine, and John Kirkwood, MD director of the Skin Cancer SPORC, a National Cancer Institute Specialized Program of Research Excellence at the UPMC Hillman Cancer Center. Delgoffe is looking to rev up more bench-to-bedside projects as a member of the new UPMC Immune Transplant and Therapy Center announced in February. (See story on page 16.)

Delgoffe is proud that his team's work may generate more solutions for cancer.

"We can do all sorts of things to give T cells back their mitos to allow them to compete better," he says. "I don't think we're going to fix the antitumor responses by just changing metabolism, but we have to be thinking about it. We have to think about it in order for us to realize the potential of these awesome immunotherapies." ■

In March, at the grand unveiling of the UPMC Immune Transplant and Therapy Center (ITTC)—a new partnership between Pitt and UPMC—the century-old former Ford assembly line and showroom at 5000 Baum Blvd. was transformed, with displays celebrating Pittsburgh's past as well as Pitt/UPMC's role in shaping its future.



OUT OF THE PARK

WHERE HOME-RUN IDEAS GET SOME PLAY TIME

BY ELAINE VITONE

PHOTOGRAPHY BY AIMEE OBIDZINSKI



INSET, TOP: Some 150 gathered for the announcement of the new center, envisioned as an epicenter for the city's new innovation district. "This represents the first-of-its-kind partnership . . . that will bring not only the research, but the entrepreneurial capacity and industry, together to be able to translate more of our research into the clinic and into society," said University of Pittsburgh Vice Chancellor for Economic Partnerships Rebecca Bagley. BOTTOM: Pittsburgh Mayor Bill Peduto (left) with Bagley (right).



An exhibition of vintage Fords, some of which were contemporaries of the ones built on the site from 1915 to 1932, rolled in for the event. When ITTC opens in 2020, the eight-story, 200,000-square-foot structure will "spur development that will mean jobs for everyone, not just the PhD, but the GED as well," said Peduto.

For most biomedical researchers, the main source of funding is the National Institutes of Health. "To use a baseball analogy, they're looking for contact hitters," Toren Finkel, who worked for the NIH for 25 years, told CBS Pittsburgh recently. "If you come to them with a home-run proposal, they're worried more about you striking out than hitting home runs."

So when the University of Pittsburgh and its clinical partner, UPMC, came courting with the promise of a very different approach, Finkel was game. Finkel joined Pitt last year as professor of medicine as well as the G. Nicholas Beckwith III and Dorothy B. Beckwith Professor of Translational Medicine. "We're making a bet on the talented faculty to say, 'Let's hit it out of the park and find some unique, novel solutions.'"

Pitt and UPMC are looking for new pitches for radically effective new therapies. They want to bring new understanding

to the field of immunotherapy, a principle behind some of the most exciting advances in recent memory. Modulating the immune system is key not only in cancer and organ transplantation, but also in aging and its consequences, including chronic diseases, says Finkel, who directs the Aging Institute.

As part of a \$200 million commitment to funding research that builds on our knowledge of the immune system, a new eight-story facility called the UPMC Immune Transplant and Therapy Center (ITTC) will house labs, offices, startups, and industry partners. The facility, located at 5000 Baum Blvd., near UPMC Hillman Cancer Center and UPMC Shadyside, will be an anchor in the city's innovation district. The hope is that by putting researchers and industry together under one roof, and providing funding for innovative new pitches, Pitt and UPMC can bring new treatments to the clinic much faster. The ITTC is slated to open in 2020. ■

Anne-Ruxandra Carvunis's studies show that translation is widespread, even in the dark corners of our DNA.



CARVUNIS FINDS MEANING IN
THE GENOME'S GREAT UNKNOWN
BY ELAINE VITONE

DNA'S DARK MATTER

For decades, we thought that genes were a lot like us: forged from the same stuff as our parents, and their parents before them, and so on, dating all the way back to Common Ancestor Immemorial. Every gene on Earth was thought to have used as its template one of the small number of genes that were around when life began.

But then, when it became possible to compare the genomes of various species against each other, researchers started finding misfits—so-called “orphan” genes that looked nothing like their neighbors. They didn’t have any counterparts in other species either—not even in close cousins. If we Earthlings all got here solely by gene duplication, this made no sense. So for years, many scientists didn’t believe orphan genes were real genes.

And if you sequenced the genome of an organism and found something that looked like a gene but didn't have a "family"? Sorry, it couldn't be a gene.

In 2006, a group at Harvard University was scratching their heads over how the literature could've been so wrong about their model organism, yeast. Anne-Ruxandra Carvunis, then an aspiring PhD student, joined the lab just as they were taking a closer look at these orphans and finding their behavior remarkably . . . unremarkable.

They were just ordinary genes, albeit oddballs.

Carvunis, who's now an assistant professor of computational and systems biology at the University of Pittsburgh, was perplexed. *Wait. These genes are perfectly normal, but they don't have families? So where do they come from?* To answer this lingering question, Carvunis looked to evolution, which has become a focal point of her career.

"I didn't have a passion for it growing up," she says. "I mean, like a lot of children, I was a fan of dinosaurs and all that, but I didn't think [evolution] was my scientific calling. It just came because of data that pulled me in. And, once you're in, you're in."

Carvunis ended up studying network biology at Harvard for her PhD. In parallel with her dissertation, which was on protein inter-

for the field. Search Google Scholar today, and "*de novo* gene birth" yields 325 hits. More than 250 of them cite Carvunis.

As it turns out, within the genome, there's an awful lot going on beneath the surface.

In humans, the 20,000 protein-coding genes that researchers typically study only account for about 25 percent of our DNA. Then there's "the rest," Carvunis explains—a mysterious expanse that some call "dark matter" or, far less flattering, "junk DNA," basically, because nobody could figure out what it was there for. It's turbulent, constantly changing. It's also very messy: tons of repetition and traces of our bodies' many tangles with viruses along the way. ("We're very virus-y," she says.)

In her studies of brewer's yeast, Carvunis examined 108,000 short sequences from that genome's great unknown and found that more than 1,000 of these elements were engaged with the cell's protein-production machine—evidence that the so-called junk had the potential to become proteinaceous.

For reasons like this, many prefer the term "intergenic" to "junk."

And, amid darkness and chaos, Carvunis saw order. If a new element was bad for the cell, it was game over for that material. If it was neutral, what happened next was left to chance. And if the element turned into something useful, then natural selection could take hold. Beneficial mutations would snowball, and eventually, this little nugget of nothingness would gain all the characteristics of a gene, invented wholly from scratch.

"So, those elements—I call them proto-genes," says Carvunis, "I found thousands

The New York Times and *New Scientist*. This spring, she was named a Searle Scholar, one of the most prestigious honors awarded to early career biologists. Her proto-gene paper remains a popular favorite in scientific journal clubs from a variety of fields. At conferences, and in e-mails from young scientists around the world, she often hears that her work has been a source of inspiration—and a reason to rethink dissertations.

Carvunis's colleagues will tell you she loves big ideas. She relishes a good confab over morning coffee in the lab. (The native Parisian spent much of her teen years haunting cafes and talking, talking, talking with friends). She loves to talk science. And broader context/perspective. And evolution! And Where All This Is Going! (Sometimes, when she gets *really* excited, she lapses into French.)

In her latest paper, a coauthored commentary in *Nature Immunology*, Carvunis applied her evolutionary systems biology approach to one of the most perplexing challenges in biomedicine: Why is it that 90 percent of phase I clinical trials fail to advance? That is: Why *isn't* what's good for the mouse more frequently good for the man or woman, as well?

Today, we know that somewhere between 2 percent and 30 percent of genes are *de novo*. Not much is known about all these newly identified genes as of yet, but we do know *de novo* genes in general vary a lot between species. And between individuals (among yeast, anyway), they vary significantly, as well, in terms of their presence, sequence, and expression.

And so Carvunis says it's tempting to



Carvunis

"So, those elements—I call them proto-genes," says Carvunis,

"I found thousands of them in the yeast, which only has 6,000 genes. It was crazy."

actions, she began to design her own studies of *de novo* genes, as the literature had begun to call them (from the Latin word for "new"). At the time, just over a dozen papers on the topic existed.

After Carvunis finished her doctorate, she wrote up an exhaustive *de novo* gene treatise, using yeast as her model. The paper, which was published in *Nature* in 2012, proposed a plausible mechanism for *de novo*-gene genesis for the first time. And it marked a tipping point

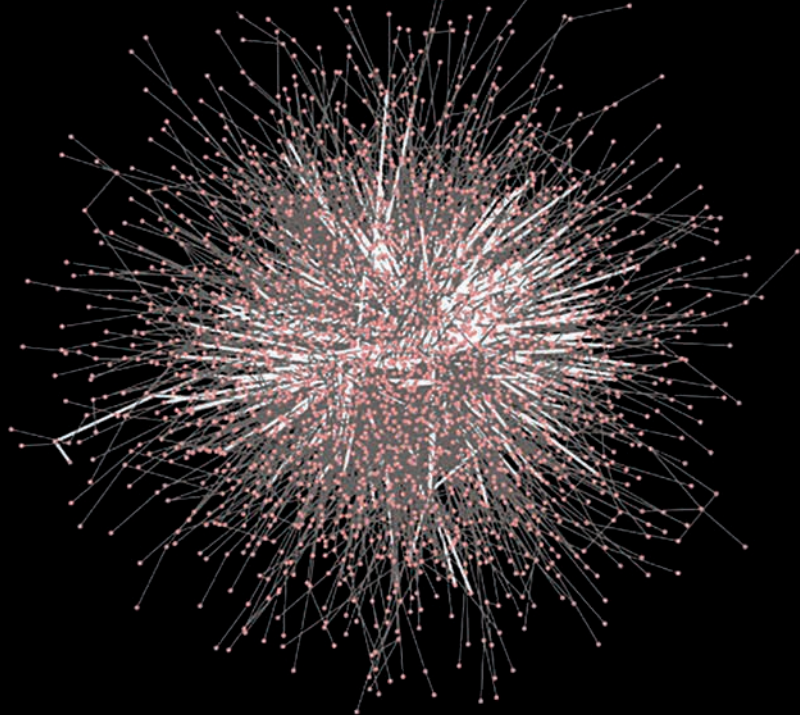
of them in the yeast, which only has 6,000 genes. It was crazy."

In January 2017, Carvunis came to Pitt as a cofounder and executive committee member of the Pittsburgh Center for Evolutionary Biology and Medicine (slated to open this summer). At 37, she's an international leader in evolutionary systems biology—a new field at the nexus of evolutionary theory, genomics, and computational and systems biology. She's been quoted in stories about gene birth in

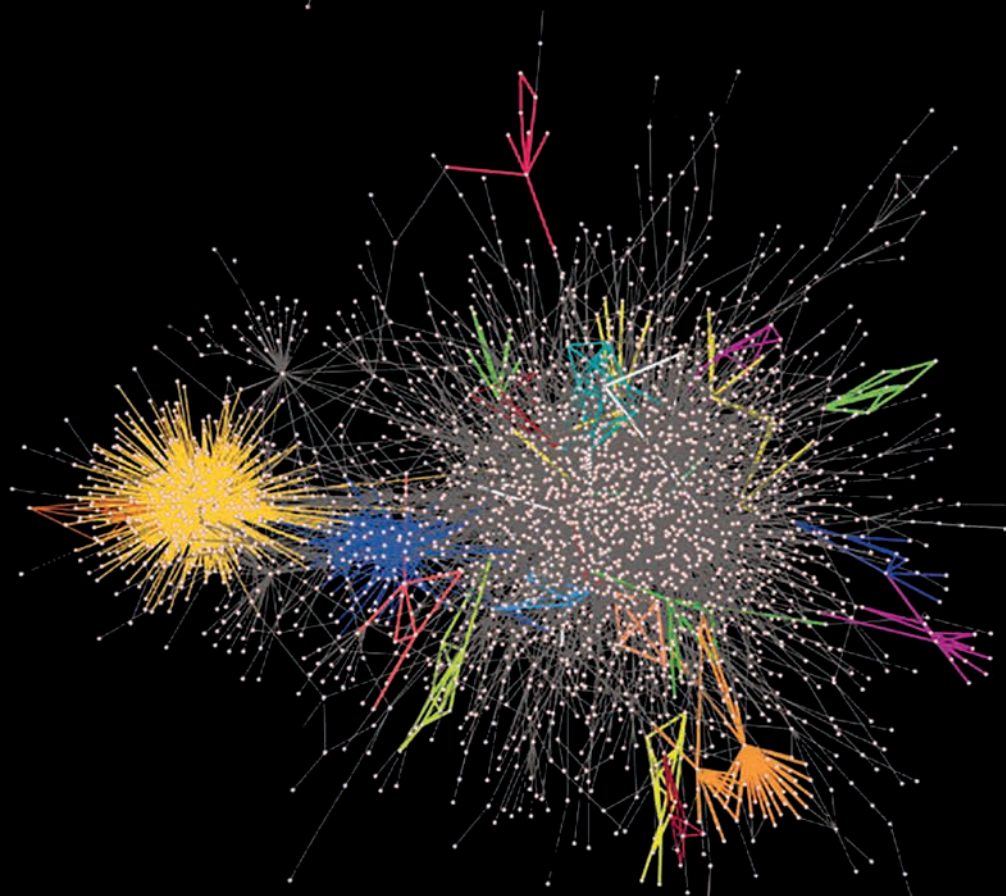
explore: Could *de novo* genes have implications for what makes humans, humans, and mice, mice? Or, what separates sickness from health?

"We *don't* know," she says, sounding delighted by this open end.

Carvunis's work isn't focused on one gene, or one specific question of how something works. "We are trying to understand, generally, the whole genome, the whole cell—actually, the whole organism," she



As a PhD student, Carvunis built the first-ever interaction map for a plant's proteins. The figures here, from a 2011 *Science* paper, show these interactions are not organized randomly. If they were, the network would look like a big meaningless hairball (see simulation, top image). The bottom image shows what Carvunis found: communities of proteins that work closely with one another on specific biological processes. And in another *Science* paper published that very same day, Carvunis described how the job of one of these communities is to fight off different types of pathogens. The proteins in this community evolve rapidly to keep up an arms race with their microbial enemies.



says. “How does it work from a systems point of view, or really, from an evolutionary point of view?”

De novo gene birth is still a long way off from scientific consensus. Some people tell her they find her work very novel. Others sort of nod and agree, *Well, yeah, it's obvious!* And then there are holdouts who still cry “orphan” and reject this field altogether.

She laughs. “That’s how I know it’s really interesting and worth pursuing.”

In the 17th century, English scientist Robert Hooke magnified a thin sliver of cork and spied thousands of hollow box shapes. To him, they looked like the spare little quarters where monks lived. So he dubbed them “cells.”

Later, industrial era scientists reimagined these fundamental elements of life in the likenesses of engines, boats, and lenticular bridges, the mechanical achievements of their time.

And at the start of the 21st century, scientists of the Internet age looked to the natural

world and saw networks abound—in food webs, for example, and certainly in the inner workings of cells.

“Like any model of the world, our view of the cell is inescapably bound by the time and place in which we live,” Carvunis wrote in a paper published during her postdoc. Scientists, she believes, don’t just automatically shed their perspectives when they clock in at work. (Put a pin in that paper—we’ll come back to it.)

Carvunis came of age in the network years; she was just starting college in Y2K. At first,

she was drawn to neuroscience, intrigued by the complex networks within the brain and curious as to how they might shape consciousness and humanness. “Then I realized that networks are everywhere,” she says.

In the new field of network biology she saw fascinating possibilities: It’s a way to probe both the intricate dynamics of complex systems, and how they amount to so much more than the sum of their parts. It’s quantitative and big picture. It’s collaborative and interdisciplinary. It holds promise in applications to immunology, cancer, developmental biology, and more. And as a computational approach, it could potentially help correct for some of that pesky human subjectiveness in the scientists who apply it. Carvunis was in.

Think of the network biologist’s realm like this:

Our genes write the blueprints for the molecular interactions that keep our cells going. These networks are shaped by their environment (that is, our bodies and *their* environments). And what goes down at that network/environment face-off is exactly why cells are the way they are: sick or healthy, surviving or not.

In other words, networks are the intermediaries between genomes and cells—really, between our genes and us. It’s all the same continuum.

When Carvunis fell hard for evolutionary theory in grad school, things really came together. She began to recognize it pressuring every organism this way and that on a constant basis, shaping our genomes, molecular networks, and phenotypes all at once. (What are phenotypes? Oh, just the differences you can observe within any given species: Tall versus short. Resistant to virus A versus not. Responds to cancer drug X versus doesn’t.)

For her PhD, in the lab of Harvard’s Marc Vidal, Carvunis built the first-ever interaction map for a plant’s proteins. She found that the interactions of proteins made by genes that were products of gene duplications were subject to natural selection. Until then, everyone modeled this as a random process in a constant state of change. She also studied protein interactions between the immune system of plants and the pathogens that plague them and found telltale signs of coevolution—which was also new news.

Both findings made the pages of *Science*.

And she ran both projects concurrently with her groundbreaking *de novo* study.

The proto-gene paper was a big deal, and not just for gene-birth researchers. It threw cellular biology in general for a loop because it challenged a fundamental assumption. We used to think only nonjunk DNA could make a full-fledged protein. Carvunis’s yeast studies showed that, really, translation is widespread, even in the “dark” corners of our DNA.

Also: The proteins that the proto-genes made? Those were species-specific—and no one had ever even seen them before. Carvunis suspects that these previously unrecognized “proto-peptides,” as she dubbed them, may be in all complex organisms—which would mean a possible treasure trove of new leads for drug discovery, if she’s right.

And so far, her hypothesis is holding up. Just this March, a team in Barcelona showed widespread transcription in the intergenic regions of a mouse (that was in *Nature Ecology and Evolution*).

Mar Albà, the lead author on that paper who heads the Evolutionary Genomics group at the Research Unit on Biomedical Informatics in Barcelona, is one of the few scholars who studied *de novo* genes before they were cool. She says Carvunis’s 2012 paper unified many disparate threads into a cohesive whole and “had a huge impact on the field.”

Albà and Carvunis are collaborators. They got together via e-mail a couple of years ago, along with teams in Germany and Croatia, for a multi-institutional response to a paper out of the University of Michigan that had broadly criticized *de novo* gene research and the validity of these teams’ methods. (Their search algorithm, the Ann Arbor coauthors posited, wasn’t sensitive enough, and introduced bias into evolutionary pattern inferences.) Soon after she arrived at Pitt, Carvunis and her far-flung colleagues published their reply in the very same journal, *Molecular Biology and Evolution*. (After reanalyzing the Michigan team’s data, removing questionable sequences, and even factoring in a false negative rate of up to 15 percent, Carvunis et al. found the tools of the trade were indeed working reliably.)

Albà and Carvunis didn’t get to meet in person until months later, at a conference in Austin. They’d been following each other’s work for years, and fell effortlessly into that deep, specialized, no-explanations-needed kind

of discussion. The insta-friends felt like they went way back.

“It’s very exciting when you can talk at that level with someone,” says Albà. “You’ve been thinking about the same thing for so long. . . . For a scientist, this is not only a job, it’s a life. It’s really hard to stop when you go home!”

THE TRANSCRIPTION CLOCK

Carvunis’s postdoc mentor, Trey Ideker—who directs the Cancer Cell Map Initiative, the National Resource for Network Biology, and the San Diego Center for Systems Biology at UC San Diego—clearly misses those Carvunis convo sessions terribly. “She’s totally brilliant,” he says, and gushes about what she accomplished while they were labmates.

During that time, Carvunis’s main project was on how transcriptional networks evolve across species. But she saw a big problem: Each breed of researcher (pardon the phrase) was using a different approach—separate toolboxes for fly studies, bird studies, rodent studies, and so on. The longstanding joke among bioinformatics folk, says one *eLife* editor’s commentary on Carvunis and co.’s work, is that these scientists would sooner share a toothbrush than use someone else’s code—so Carvunis “cleaned everyone’s teeth with the same toothbrush.” That is, the team applied one common analysis methodology in studying raw data gathered from a number of species of complex organisms (insects, birds, and mammals—including humans).

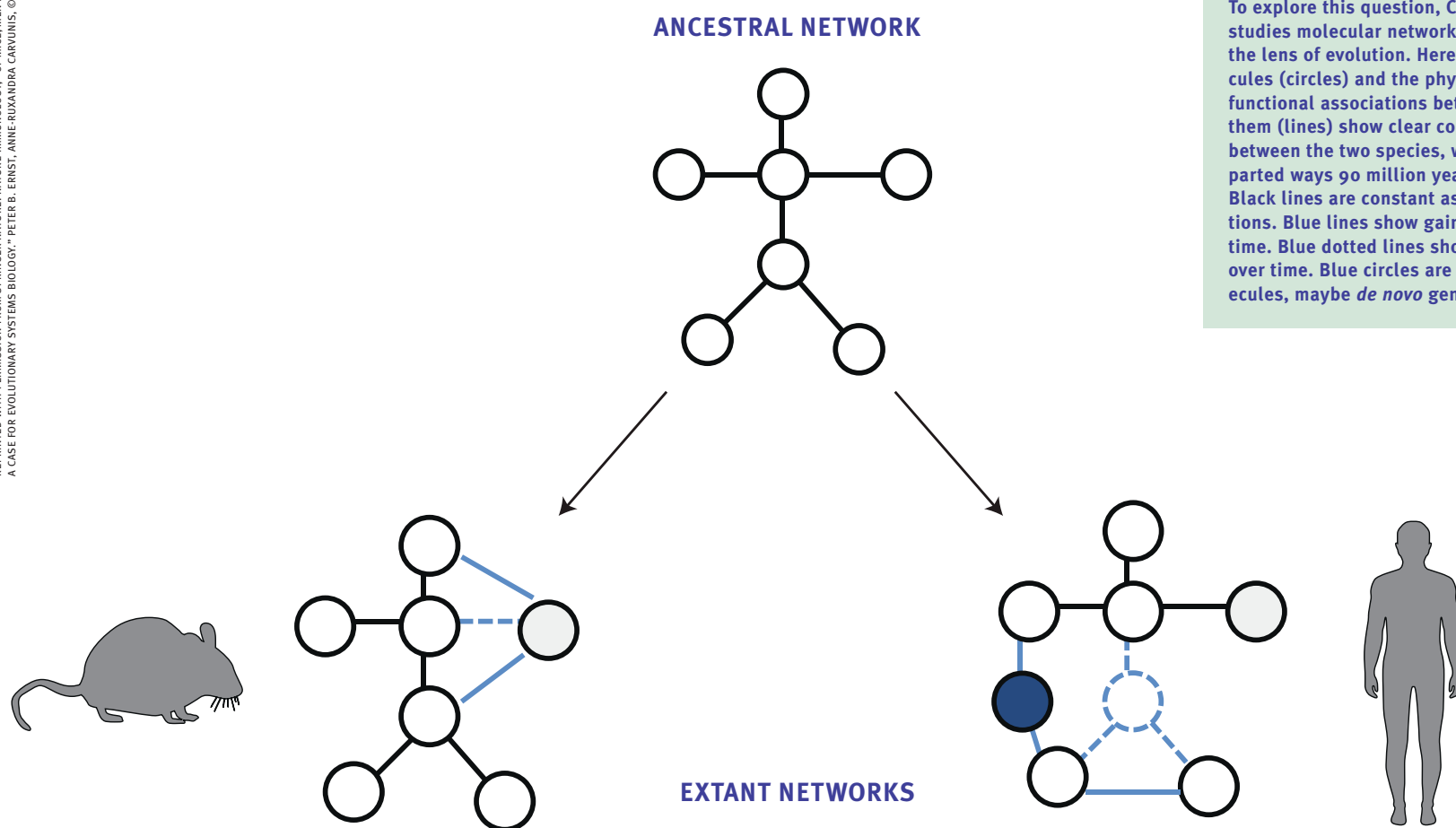
Then they found something no one was expecting.

For some reason, even though all these different species reproduce at very different rates, somehow the networks that regulate transcription evolve at the same rate.

In other words, the fly on my wall, for example—whose little fly family will have umpteen generations in the course of my one lifetime—will not evolve any faster than I will. Which raises the question: Do the fly, and I, and the two dozen other species in the team’s sample all have some kind of molecular timekeeper in common?

Carvunis stresses she does not understand what is going on here. Verifying this phenomenon, figuring out its mechanisms (“If your readers have an idea, contact me!”), and probing its consequences are long-term goals

Why *isn't* what's good for the mouse more often good for the human, too? To explore this question, Carvunis studies molecular networks through the lens of evolution. Here, molecules (circles) and the physical or functional associations between them (lines) show clear contrasts between the two species, which parted ways 90 million years ago. Black lines are constant associations. Blue lines show gains over time. Blue dotted lines show losses over time. Blue circles are new molecules, maybe *de novo* genes.



of her lab. But she says it does make sense, if you think about it: "If how species change were really proportional to their reproduction rate, then, from the time I'm a child to the time, I don't know, I have grandchildren, I cannot tell a story about flies. Because they don't exist. They're a completely different animal now."

In addition to the clock paper, Carvunis and Ideker also collaborated on the beginnings of a project that has since become a major focus in Ideker's lab. It came out of one of those big-picture coffee talks back in California:

Where, the scientists wondered, was the future of "omics" and high-throughput biology really going? What was the road ahead for big data?

Recall how cells looked like monks' quarters to the Renaissance scientist, like machinery to the industrialists, and like a network to Generation Web 1.0? Well, naturally, as the San Diego duo pondered this four or five years ago, they first consulted their smartphones.

In 2014, Ideker and Carvunis published

in *Cell* a vision for the way forward in their paper, "Siri of the Cell: What Biology Could Learn from the iPhone." The new model of the cell, they explained, was turning into much more than data points and straight lines between them. Add your given genome, gene products, metabolites, and other biomolecules, and then link them together with physical interactions and other functional associations, and the schematic gets ... complicated. A bunch of wires running to and fro can't capture the complexity of multiscaled hierarchies.

But perhaps, eventually, intelligent simulations of cells, tissues, organs, and whole patients could. Imagine a doc asking for a consult: "Hey, Siri? Patient P's cancer came back—and this time, with new mutations A and B. What should I prescribe now?" It's early days yet, but Ideker is working to make this dream a reality.

Now, as an independent investigator, Carvunis is building on the blockbuster findings from her graduate work and training. She's hoping to better understand how proto-genes evolve and create new traits in organisms. Through systematic experiments in yeast,

and complementary computational surveys, she's working to develop broad taxonomies of proto-gene product functions.

Eventually, she hopes to use these new insights on evolution in an ambitious application, to recreate *de novo* gene birth in the lab—a potential boon for biomedicine that's hard to even fathom. To do it, her lab is attempting to design a strategy to speed up the evolution of proto-peptides. So far, it's looking promising, but "this is not even a hint of a submission" to a scientific journal, she's quick to add.

"It's very, very exploratory research. But it's fun," she says, beaming, and calls this her most exciting project of all.

Nikolaos Vakirlis, a collaborator/mentee from afar, says Carvunis is one of the most enthusiastic people he's ever worked with. Vakirlis is a postdoc in the Dublin lab of Aoife McLysaght, a founding member of the field of gene birth who identified the first known *de novo* gene in humans. Carvunis and the Irish team are working to identify *de novo* genes in yeast and determine the why, and how, and when of their evolution.

OF MICE, NOT MEN

Say you're a mouse. You live in a hole in the ground and forage for food among filth. For countless generations, your ilk has been shaped by natural selection for optimal mouse-ness. Your immune system, for example, is the product of millions of years of bottom-feeding and excrement-eating—especially nasty primordial microbes have coevolved with your ancestors' bellies. By now, you are really good at being a mouse.

Now (I know, it's a stretch) let's say you're a human. You are (hopefully) none of the above. Because you and the rodent parted ways, evolutionarily speaking, lo, 90 million years ago.

Animal models of human diseases are just that—models, writes Carvunis in her *Nature*

candidate can even be detrimental to humans, he points out.

In the paper, Carvunis calls it “the illusion of similarity.”

“Mice are not little humans who like cheese,” she tells me in her office in Biomedical Science Tower 3. “We know that. Yet, our genomes are quite similar with mice—80 percent. That's an interesting number. What does it mean? Yes, it's quite similar, but we also know it's the 20 percent that are why we are not mice. So how to identify what matters in those 20 percent?” Some, but not all, will be reasons why you can use a given therapy to cure cancer in a mouse, but not in us. “So can we understand what part of the genome, and the networks, really translate across species,

who would call into question our understanding of what genes are and how they evolve. She would learn that once essence insinuates itself into the scientific literature, it can be hard to extricate. Consider labels like “junk DNA” and “orphan gene.” In yet another collaboration, Carvunis got together with a rhetoric scholar at University of San Diego, a protein chemist in Texas, and a philosopher in Italy. The interdisciplinary team represents a range of personal belief systems, as well, from religious to agnostic. And together they are probing the question of how scholars interpret terminology differently within the sciences—specifically, the term *function*.

In reviewing a sample of the literature, the team found that sometimes scientists wrote

The fly on my wall, for example—whose little fly family will have umpteen generations in the course of my one lifetime—will not evolve any faster than I will. Which raises the question: Do the fly, and I, and the two dozen other species in the team's sample all have some kind of molecular timekeeper in common?

Immunology commentary. They are approximations. But seen through the lens of evolution, and aided by the tools of network biology, the fundamental differences between these two species aren't just stark; they're concrete.

For this paper, Carvunis teamed up with Peter Ernst, a veterinarian, professor of pathology, and director of comparative pathology and medicine at UC San Diego, who studies animal models of inflammatory bowel disease (IBD). Using several examples of animal-model successes that failed the human test, the team walked through the architecture of how gene products interact with one another, and how that differs between the species.

Let's say, for example, that molecule 1 interacts with molecule 2, which in turn interacts with molecule 3. And that might be the case in both mice and men. But it's not just the molecules that are important—it's how they talk to one another. A bond between molecules in the mouse might be a completely different conversation in you.

“You get enthralled” with the commonalities, says Ernst, “and it can be that the same tissues in both are affected. Or maybe even some of the same cells or molecules. But it ends there.” And sometimes, a given drug

and which cannot? That's my dream.”

This is not, she notes, a way to predict for certain what will and will not work. But it will be a useful tool in ruling out candidates that have very little chance of success.

Ernst notes that, recently, a colleague who was studying inflammatory bowel disease in rodents mapped a genetic region relevant to the disease and found that this region predicted microbiota in people—and their susceptibility to IBD. “And ironically, it's an intergenic region,” Ernst says.

If that pans out in the clinic, he says, “then clearly, that's a new data point that most people would be missing completely.”

WATCH YOUR LANGUAGE

Jean-Paul Sartre was required reading in Carvunis's high school in Paris. *L'existentialisme est un humanisme* changed her perspective on life, and on science. “Existence precedes essence,” Sartre famously wrote. Individuals create identity and value and meaning—and there is no moral absolute.

Carvunis realized: *What I do is up to me. It's not because somebody said something that it's true. I must go and see and decide for myself.*

It was a fitting launch pad for the scientist

“function” when they really meant “expression.” Other times, they meant “interaction.” And other times they meant what the gene is “there for”—what nature has selected it to do.

The scholars are having so much fun that they're thinking of what to tackle next—perhaps the word *gene*. That one is a huge problem, Carvunis says, because it has so much history; it existed before we even knew about DNA.

“It's very interesting how language and knowledge are intersectionalized,” she says. Scientific knowledge is growing at a fast clip, and language can't keep up. If the words we have don't fit, they can even impede knowledge. “But then we cannot also invent words every five minutes, either.”

Carvunis hopes the team will provide useful frameworks to help scientists become more aware of the words they choose.

And to keep their perspectives in check—they bring them to the bench whether they realize it or not.

“As scientists, sometimes we think that we are just pure minds, but it's not true,” she says. “We are people, and we are inspired by what happens around us.

“We must not forget that. It can be bad, or it can be good. We must make it good.” ■



Vivian and Michael Scholze stand in their living room in Harrison City, Pa. In 2017, after taking ineffective medication for years, Vivian went to UPMC for a deep brain stimulation implant to relieve her essential tremor.

“TODAY IS A SUNNY DAY IN PITTSBURGH.”

WHEN MEDICATIONS NO LONGER HELP

BY GAVIN JENKINS

PHOTO BY MARTHA RIAL

Harry McGreevy is a 76-year-old retired machinist with Parkinson's disease. It's 6:44 on a March morning, and he is lying in the postanesthesia care unit at UPMC Presbyterian. The room buzzes with doctors, nurses, and other patients as McGreevy waits to begin a procedure to implant a stimulator in his head. The device will send electrical impulses deep into his brain, to the basal ganglia, which are gray matter nuclei associated with motor control, procedural learning, emotion, and routine behaviors (like eye movement).

McGreevy's medication stopped working well several months ago, and he hopes this intervention, known as deep brain stimulation (DBS), will alleviate his Parkinson's symptoms. He stumbles when he walks, has fallen four times in the past year, and this morning, his tremor blurs the U.S. Navy tattoo on his right

"Let's get it done."

Less than two hours later, McGreevy is in the operating room; his head is fitted into a stereotactic frame. He's had a CT scan, which Richardson merges with a recent MRI, so he can pinpoint where in the basal ganglia to implant the electrodes. (It's more complicated than this, but one goes on the right side and one on the left.)

This is the first of two surgeries. Today, Richardson's team will implant the electrodes. In the next couple of weeks, during a second surgery, they will place a pulse generator in McGreevy's chest and connect the electrodes by a wire running up the neck.

Along with the stereotactic frame, McGreevy has a smaller, box-shaped frame secured to his skull. Some of his white hair has been shaved off, and a wall

of plastic over the stereotactic frame separates McGreevy's body from his scalp and from the team. The surgeon cuts a semicircular incision on the right side of McGreevy's head. Using a retractor, he spreads open the incision, and then he is handed a drill designed to make small cranial openings.

Richardson, who is director of both Pitt's Brain Modulation Laboratory and the Movement Disorders and Epilepsy Surgery Program at UPMC, calls DBS the "gold standard" for treating cases of Parkinson's disease like McGreevy's, where there are treatment-re-

sistant motor complications. DBS is not a cure, but it has a 70 percent success rate for easing symptoms in Parkinson's disease patients. It's even more effective for patients with essential tremor, working in 90 percent of cases.

For invasive brain surgery, the procedure is pretty safe for motor control patients. There's a 1 percent chance of a stroke due to bleeding in the brain during the procedure and a 5 percent chance of infection.

Of course, an abundance of caution surrounds the procedure—not just among the surgeons who might recommend it.

Just reading about the surgery can be a deterrent. Vivian Scholze, a 67-year-old with essential tremor, received the procedure in September; but she first learned about DBS more than a decade ago. "I said, *There's no way I'd ever—*" she recalls. "It's extreme. I thought, *Yeah right, and shave my head.*"

Richardson has performed more than 300 DBS surgeries in seven years at Pitt. DBS is designed to be reversible. It's more targeted than current interventions that bathe the brain and the rest of the body in chemicals.

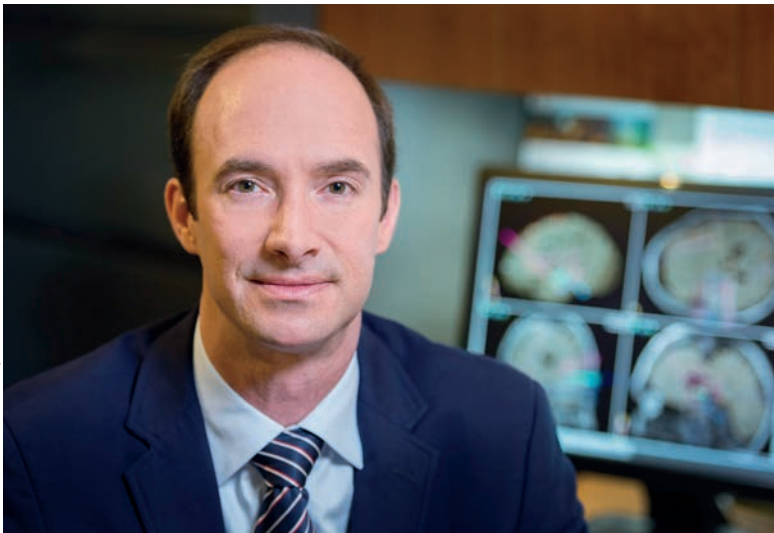
Yet, he understands why there are hesitations about the procedure. He's implanting foreign objects into a brain, placing a pacemaker-like battery into the chest, and connecting it all with a wire under the skin. Do we know enough about the brain to fiddle with it in this way? Can DBS somehow change who these patients are?

"The counterargument is," Richardson says, "that we're trying to restore these people's identity."

Scholze says she's still amazed that she has a brain implant. Her life has become so normal—back to the way it was two decades ago—that she forgets she's had the procedure. But then she bumps her chest, where the pulse generator slightly protrudes, and then she remembers how frail she once was.

"You're not the same after," she says. "You can see the difference in what you can do again."

Patients undergo a neuropsychological evaluation before and after the procedure. The pre-DBS analysis is critical, because patients can be desperate or have unrealistic expectations. The evaluation also can identify whether cognitive symptoms of disease have progressed too far, in which case the team wouldn't recommend



Richardson

forearm.

When R. Mark Richardson, an MD/PhD associate professor of neurological surgery, arrives at the foot of his bed, McGreevy expresses his eagerness to return to boxing class. Boxing can help Parkinson's disease patients improve their balance and strength, but since McGreevy's medication lost its effectiveness, he says he doesn't have the coordination to work around his house, let alone punch a speed bag.

Richardson asks if McGreevy has any questions, and he shakes his head. "Nope," he says.

surgery. The difficulties of mental decline, according to Richardson, can overwhelm a patient's ability—and sometimes a patient's family's—to appreciate motor improvements. Psychiatrists suggest also screening Parkinson's disease patients for problems with impulsiveness, since some have developed impulsive disorders after the procedure. (This can happen after taking Parkinson's medications, too.)

The most profound DBS issue for Richardson: so few patients who qualify for the help actually get the procedure. Medical-device makers estimate that only 10 to 13 percent of eligible Parkinson's patients receive the surgery.

On another winter day, Scholze demonstrates how effective DBS has been for her.

She is sitting at her dining room table at her home in Harrison City, Pa. A photograph of Scholze with her husband, Michael Scholze, together since they were 15, hangs on the wall.

Scholze clicks off her "brain pacemaker" with a remote control. Michael sets a glass of water in front of her on the table.

"Before the surgery, I had to hold my glass with two hands," she says.

The pulse generator has been off just seconds, and there's already a quiver in her voice. Before his wife had the DBS implant, Michael had to carry her plate through buffet lines. He cut her food and painted her toenails. She quit her office job because she couldn't write, and one time, when she tried to make pancakes for her granddaughter, she flung batter all over the kitchen. She was diagnosed with essential tremor in the late 1990s, and by 2017, the amount of medication she took made her feel foggy and didn't prevent the tremors. She felt embarrassed to leave the house.

"I literally didn't have a life," she says.

Scholze lifts up the glass, but she can't even make it halfway to her mouth. Her arm trembles, splashing water on the table. She sets the glass down and turns the pulse generator back on.

After a few seconds, her arm tingles as the stimulator kicks in, and she picks up the glass.

"It's gone," she says of the tremor.

The quiver has left her voice, as well, and she sips the water without spilling a drop.

This switch-like effect is typical for DBS in essential tremor patients, according to Richardson. In the operating room, the im-

COURTESY ABBOTT



Deep brain stimulation is a treatment in which an electrode is implanted into the brain and a pulse generator into the chest; a thin wire beneath the skin connects the two. Patients can turn DBS off with a remote control; and during checkups, a doctor can adjust the pulse frequency and width, as well as the amplitude. The electrode lead has four sections, or contacts. In the latest models, the middle contacts are divided into thirds to help steer the current.

COURTESY RICHARDSON



diate impact makes it easy to determine whether the electrode has been inserted into the correct place.

Scholze gets emotional recounting how Richardson's team helped get her through the surgery. Scholze suffers from claustrophobia, and she felt unnerved waking up wearing the frame. Danielle Corson, Richardson's physician assistant, held Scholze's hand throughout the operation and testing.

"Thank God she was there," Scholze says.

Once awake, essential tremor patients perform a drawing test, spiraling a pen in circles, and then signing their name. Scholze hadn't signed her name in a decade before the procedure.

At her dining room table, Scholze's eyes fill

are connected to the cerebral cortex by a series of loops that send signals through the thalamus to promote different kinds of behavior. There is a motor loop for modulating movements, a limbic loop for regulating emotions, and an associative loop for decision making. DBS disrupts pathological communication within a loop, while also allowing normal communication to occur.

Before DBS, some surgeons treated Parkinson's and essential tremor with a lesioning surgery. Surgeons would place an electrode in the brain and apply a current to the area, giving the patient symptomatic relief. The pulse was increased until a permanent lesion formed. The lesion knocked out part of the circuit, allowing information to pass through

will provide a foundation for expanding the benefits of DBS," he says.

Karp and Richardson have received FDA approval for a clinical trial of DBS for late-life, treatment-resistant depression, but they haven't secured funding, yet.

And along with colleagues in the Department of Psychiatry—including Susanne Ahmari, Robert Hudak, and Lalith Solai—Richardson and Karp are expanding programs to treat patients with obsessive compulsive disorder (OCD).

In 2009, the FDA approved DBS to treat severe cases of OCD under the humanitarian device exemption. Richardson says the DBS success rate for OCD is unknown because no large-scale trials have been reported.

Richardson hopes that these recordings will push his team closer to understanding speech production and how to design a DBS that can modulate speech separately from other motor activity.

with tears at the memory of signing her name in the operating room.

Richardson is hopeful that DBS can give relief to others whose lives have been put on hold. He's attempting to find ways to make DBS effective beyond offering patients renewed motor control.

Jordan Karp, associate professor of psychiatry, says "It's an exciting time in clinical neuroscience here at Pitt." That's "in large part because of the clinical and research expertise that Mark Richardson and his functional surgery team have brought to our system. His work to advance the care and understanding of patients living with severe neurological diseases . . . really puts Pitt and UPMC in the vanguard."

At the Medical College of Virginia, Richardson chose to study neurosurgery for DBS. He was drawn to the idea of improving a patient's quality of life when medications stop working and there are no other options.

DBS also offers an extraordinary opportunity to learn more about the brain.

It used to be that doctors didn't know why DBS was effective, but Richardson says that isn't entirely true anymore. The basal ganglia

the loop in a less pathological way.

In 1987, French neurosurgeon Alim Louis Benabid discovered that an electrode could be set to a lower charge and left on without causing permanent damage. A decade later, the Food and Drug Administration approved DBS in the United States as a treatment for essential tremor and tremors associated with Parkinson's disease. The FDA approved DBS for advanced Parkinson's disease symptoms in 2002.

DBS has also been attempted and studied for the alleviation of chronic pain and certain psychiatric conditions.

Two large, industry-sponsored trials of DBS for major depression were aborted by the sponsor when analyses showed that the primary endpoints would not be met. Richardson coauthored a paper with 35 other experts for the *Journal of Neurology, Neurosurgery and Psychiatry* that discussed concerns about the trials.

Richardson says the trials were begun prematurely by the device manufacturers, and in doing so, they muddled the waters for advancing DBS.

"Programs like [the National Institutes of Health's] BRAIN Initiative are funding human neuroscience studies that we hope

Despite the uncertainties, Randall Hirt, a 38-year-old West Mifflin, Pa., resident who was diagnosed with OCD in 2001, did not hesitate to get the procedure. Medication couldn't help him control his morning routine obsessions. Habitually late, Hirt got fired from 17 jobs in four years, and his sense of self-purpose eroded to the point where he had a passive death wish.

But things changed following his 2016 surgery. "I was able to start getting places on time and early," Hirt says. "I wasn't impeded with different issues getting in my way. I could skip taking a shower or something like that."

Hirt has become one of the most vocal patients in promoting DBS. He spoke at a neural ethics symposium held at Pitt last year and was featured on a KDKA News segment.

"One of the rewarding aspects of this comes from how much the patients want to participate in research and contribute to finding answers," says Witold Lipski, a PhD and research instructor in the Department of Neurological Surgery.

Though his symptoms have improved, Hirt faces daily challenges because of OCD.

He still takes medication and hasn't been able to return to the workforce. His stimulation parameters probably need to be adjusted at his next doctor's appointment. Tweaking a patient's DBS during a regular checkup is common, even for a disease where the therapy is more effective, like Parkinson's disease.

For example, in March, Dennis Troy, a 66-year-old Cranberry Township, Pa., resident, attends an appointment with Houman Homayoun, an MD and assistant professor of neurology, in the Kaufmann Medical Building in Oakland. Troy received a DBS implant last August for Parkinson's and related conditions.

Homayoun begins the appointment by checking Troy's rigidity. A retired computer programmer, Troy has read the neurostimulator's clinical manual, and he has the checkup routine memorized.

As Homayoun asks him to perform a set of movements: *Close your eyes. Now open. Give me your hands. With your right hand, open and close; now tap your fingers. And the left, open and close; now tap. Good. . . .* Troy is a few seconds ahead of each command.

After observing Troy's gait, Homayoun turns off the DBS, and they start the movements over. This time, Troy's tremor is more noticeable, and he isn't as fast. On his right side, Troy struggles with dystonia, a disorder in which muscle contractions result in unusual fixed postures; and in his feet, Troy has dyskinesia, an involuntary movement disorder similar to a tic or spasm. Troy guesses that, overall, his symptoms have improved 60 percent since having the surgery.

DBS for motor control benefits patients until they die, according to Richardson, but disease progression eventually outpaces the device's ability to keep up with symptoms.

Using an iPad, Homayoun turns the DBS back on and increases Troy's stimulation from 2.1 milliamps to 2.3 on his right side (to target his dystonia) and 2.1 to 2.2 on his left. He also adjusts the frequency and pulse width (the duration of the jolt) and gives Troy the ability to control the stimulation level on his remote. (Troy can't turn it up higher than 2.5 milliamps.)

Homayoun rolls his chair around and shows Troy what he's doing on the tablet. The screen displays a diagram of the tip of

the electrode in his brain. The lead is 7.5 millimeters long, 1.27 millimeters in diameter, and it contains four contacts, which are each .5 millimeters apart. In the latest models, the two middle contacts are divided into thirds to help steer the current. Patients aren't in control of which contacts are being used.

At the end of the appointment, Homayoun asks Troy if he would volunteer to speak to a group of Pitt Med students during a presentation. Troy and his wife, Linda, agree to be there. They didn't hesitate to help. "I had a ton of the stupidest questions, and Dr. Richardson answered all of them," Linda Troy says. "I love that man. He's our hero."

Richardson is leading a multidisciplinary team of experts from Pitt, Carnegie Mellon University, and Johns Hopkins University in a study exploring how Parkinson's disease impacts speech. The research is supported by a \$3.3 million grant, awarded over a three-year period, and is part of the BRAIN Initiative. DBS doesn't usually help Parkinson's disease patients with speech difficulties, and can sometimes make those difficulties worse. Richardson would like to change that.

Richardson's study attempts to understand what activities in the subthalamic nucleus (STN)—which is part of the basal ganglia—are responsible for different aspects of speech (like articulation, pitch, efficiency, and volume). To do this, researchers record brain activity during DBS surgery as patients are asked to perform a variety of speech tasks.

Patients are placed under conscious sedation (also called twilight anesthesia). And yes, they are then woken up in the middle of brain surgery. As you may recall, patients have to be awake anyway for Richardson's team to make sure the electrodes have been inserted in the right places. (Although some patients may be eligible for a new "Asleep DBS" option at UPMC.) Like most of Richardson's patients, McGreevy is happy to volunteer.

"If it works for me, it's going to work for someone else," he says.

Corson, the physician assistant, stands next to McGreevy in the operating room. Holding his hand, she pats his arm and asks him to wake up for the speech

production task. A hair-thin microelectrode has been implanted on the right side of his brain. Richardson's team is recording brain waves from the cortical surface and from the lens shaped STN, as well as single neuron activity. Richardson hopes that these recordings will push his team closer to understanding speech production and how to design a DBS that can modulate speech separately from other motor activity.

While the speech task is going on, McGreevy's brain also is being mapped by the same microelectrode to verify that the team has reached the target site to treat his Parkinson's symptoms. The team listens in on his neuronal activity. They'll know they are in the right spot when the neurons make a specific firing pattern. This typically takes about 30 minutes.

Meanwhile, Lipski adjusts a microphone in front of McGreevy. A video camera also is aimed at him. McGreevy says he's ready to begin, and Corson asks him to repeat after her: "Today is a sunny day in Pittsburgh."

"Today is a sunny day in Pittsburgh," he says.

Richardson says he asks each of his patients to say this to assess baseline speech.

"I like this line because it often gets an interesting response," Richardson says. "And my typical response for those who challenge its veracity, is that it's a philosophy, not necessarily a weather report."

Next, McGreevy repeats syllable strings that are told to him through headphones. "Vah, tee, shoo." He's asked to say some sets softly, others loudly, and then at a normal tone: "Ta, see, vee."

At one point, the team had to move the electrode to a different location in McGreevy's basal ganglia, and they are about to do the speech task again. Corson drapes a blanket across McGreevy to keep him warm and wets his mouth with a water-soaked sponge.

When Richardson asks if he's okay to do more testing, McGreevy says yes without hesitating. He's had a metal frame affixed to his head for several hours. There is a coin-sized opening in his skull, and he wants to help.

"Repeat after me," Corson says, "today is a sunny day in Pittsburgh."

"Is it?" McGreevy says, sarcastically. And the operating room erupts in laughter. ■

ATTENDING

Ruminations on the medical life



At birth, Marian and Michelle Bernard were attached through their livers and a fused xiphoid process, in the lower portion of the sternum.

Photos this page and opposite page courtesy Children's Hospital Los Angeles.

WITH LOVE, FROM HAITI

A NATIVE SON, TWO BROTHERS, AND THREE LITTLE GIRLS

BY ERVIN DYER

In November of 2014, David Bernard sat with his wife, Manoucheca Ketan, in the modern Mirebalais University Hospital (Hôpital Universitaire de Mirebalais), which is situated on a patch of flatland in rural, central Haiti.

After carrying triplets for 36 weeks, Ketan was recovering from the C-section needed to deliver her three daughters. Tamar was born healthy and separate. Michelle and Marian were conjoined and “omphalopagus,” connected at the abdomen, facing each other.

When the ultrasound showed three babies, the mother was stressed. When diagnosed with conjoined fetuses, she kept asking herself, “How will I deal with it?”

Some Haitian folklore casts conjoined siblings as cursed. A prevailing myth is that the births are punishment from the gods; the stigma can cause parents to struggle to accept the children. Often, they are left to die.

For two weeks, Ketan refused to see or hold her conjoined daughters. She was hesitant to bond with them and not sure she ever could.

“Disabled people are not valorized in Haiti,” she said recently from her hilltop home in Pétionville, a suburb of Haiti’s capital, Port-au-Prince.

If her babies could not be separated, she wondered, “How could they go to school, and how would they make it day by day?”

“If I’m their mother, and I am having these doubts,” she kept asking herself, “what about society? How will society not [see] them as being monsters?”

Not long after their birth, Henri Ford (Fel

’89, ’93), the vice president and surgeon in chief at Children’s Hospital Los Angeles, was called to come see the family. To connect on a more personal level, he spoke with them in Haitian Creole, the lyrical dialect that mixes French, African, and indigenous speech. He told the parents the babies were precious and that he was confident the girls could be separated.

He assured the family that even though the rare and complex operation to separate the girls would take place in a nation severely strained by inadequate medical infrastructure, their little bodies could still become two. They could lead independent lives.

Ford is a son of Haiti. Though he is now the newly appointed dean of the University of Miami Leonard M. Miller School of Medicine, he grew up in Port-au-Prince, near Carrefour Feuilles, a district of French colonial homes and a hub for the intellectual class. From his childhood home, he could walk to the national seminary, the national stadium, and the medical school of Haiti.

Every morning, the young Ford listened to the radio. It’s where he learned the fundamentals of diseases such as malaria and smallpox. He liked science, and the radio programming was his introduction to public health and medicine.

Ford’s father, an activist minister, spoke out against the policies of Haitian dictator François “Papa Doc” Duvalier. In 1972, the family fled to the United States for safety.



Henri Ford (Fel '89, '93) successfully led the first separation of conjoined siblings in Haiti. He keeps in touch with the Bernard girls.

They settled in Brooklyn, N.Y. Ford was 13.

At first, Ford felt like an outsider in America; he struggled with English, and his schoolmates ostracized him for being different. He eventually excelled. He was accepted into Princeton and then Harvard Medical School. He came to the University of Pittsburgh, where he completed a research fellowship in immunology (1987–89) in the Department

of Surgery and a clinical fellowship (1991–93) in pediatric surgery at Children's Hospital of Pittsburgh of UPMC. For several years, he stayed on at Pitt, eventually becoming chief of pediatric surgery. He left Pittsburgh when he felt called to tend to a population with a greater need in East L.A.

He was working in California when the 2010 earthquake struck Haiti, killing an estimated 300,000 people. Wracked by images he saw on television of children homeless and desperate amid the rubble, Ford raced to Haiti the second day after the airport opened. He cared for people in hospitals set up in fields. In the years since he left Haiti, he'd only returned three times. He now travels there four to five times a year.

"I do this out of a sense of duty and to

is as intertwined as their DNA. They perform surgeries together. They share an e-mail account. They often don't distinguish themselves by using their first names. "Please," they say, "we are simply the Docteurs Bitar."

They call Ford their brother and get emotional describing the imprint that he has made on Bernard Mevs and the larger Haitian medical universe. During a week at Bernard Mevs or another hospital, Ford will perform surgery and teach. He often brings a team with him; those physicians, nurses, and anesthesiologists are focused on advancing care for infants and children.

Before Ford's regular consultations at Bernard Mevs, the staff was overwhelmed by some pneumonia cases in infants. Ford taught the doctors procedures to clear the lungs; then

ma, hydrocele, gastrostomy. And when they tried more complicated procedures to correct newborn surgical emergencies such as intestinal atresia, abdominal wall defects, or Hirschsprung's disease, the children often died because the hospital didn't have the equipment to resuscitate or the wherewithal for proper aftercare.

Routinely now, seven years after Ford began bringing in equipment and specialists to provide training and protocols to Bernard Mevs, the Docteurs Bitar and other surgeons there have been able to manage difficult pediatric operations such as reconnecting intestinal perforations, removing obstructions in the gastrointestinal tract, and repairing congenital anomalies in the lower intestines.

In 2014, Haitian physicians performed

More than half of all conjoined siblings are stillborn. And generally, mothers in Haiti are 12 times more likely to die giving birth than mothers in the United States. So, just by surviving their birth, Marian and Michelle beat the odds.

try to make a difference in strengthening the health care infrastructure."

He is now convinced that if 10 percent of the Haitian diaspora—especially the engineers, computer scientists, biologists, and other professionals who are scattered around the world—would commit to doing something for Haiti, conditions in the country would be vastly different.

"Haitians are tenacious," he says. "We can't just come over once and be done. We have to come back and build sustainability."

Ford works closely with the teaching hospital in Mirebalais and with the 50-bed Bernard Mevs Hospital. They are two of the top hospitals in Haiti and regularly provide pediatric surgical care. Bernard Mevs, in Port-au-Prince, even has pediatric and neonatal care units and a residency program; it offers trauma care, critical care, and rehabilitation.

A few months after the 2010 earthquake, Ford met the Bitar brothers. The Bitars are identical twins and surgeons at Bernard Mevs, and their drive to advance medicine in Haiti

the babies started going home after a few days.

To whom much is given, much is required, Ford tells the staff. Keep learning, he says, because it's a way to rise above mediocrity, frustrations regarding the lack of equipment, and other obstacles.

"God brings him back so that we can go far, far, far," say the Docteurs Bitar. "He is like oxygen for us."

Sure, Ford brings compassion. He once came on 24-hour notice for a case. He once postponed an important meeting in California to stay in Haiti and assist with a procedure on a sick baby.

But he also brings the international training to build competency, infrastructure, and critical skills. He invites residents from other Haitian hospitals to observe and practice.

"Partnership is important," says Ford. "We're not itinerant," he says of his team. "We don't do surgical tourism. We come to Haiti to improve health care outcomes and build surgical capacity."

Before Ford, the Docteurs Bitar and the staff at Bernard Mevs tended to take on less complex pediatric surgeries: hernia, lipo-

1,475 complicated procedures at Bernard Mevs; 595 of them were on patients younger than 18 years old. The majority of these procedures have been successful. Before and in the aftermath of the earthquake, such feats would have been impossible.

Marian and Michelle were 6 months old when Ford began leading preparations for surgical separation.

Little is ordinary about their case. Conjoined newborns occur once in every 200,000 live births worldwide. (More than half of all conjoined siblings are stillborn.) Omphalopagus twins represent 30 percent of those births. Rarer still, conjoined siblings within a triplet pregnancy occur in fewer than one in a million deliveries. More generally, mothers in Haiti are 12 times more likely to die giving birth than mothers in the United States. So, just by surviving their birth, Marian and Michelle beat the odds.

Still, they were attached by their livers and a fused xiphoid process, the breastbone in the lower portion of the sternum. The girls did



FROM LEFT: Michelle, Tamar, and Marian Bernard. Photo courtesy David Bernard.

not share a pelvic attachment, which meant the surgery required for separation was not as complicated as it would have been for some conjoined siblings. Nevertheless, the procedure, considered a massive undertaking at any hospital, had never been attempted in Haiti.

Ford assembled a crew that included the Docteurs Bitar and 16 other U.S. and Haitian surgeons, nurses, respiratory therapists, intensivists, anesthesiologists, and ob/gyn specialists. Each week, teams in Haiti monitored the girls' progress and teleconferenced with their U.S. colleagues to discuss equipment, procedures, and logistics. The yellow team looked after Michelle, and the red team attended to Marian. On May 22, 2015, shortly after 1 p.m., Maclee Jean-Louis, Mirebalais University Hospital's chief of surgery, made the first incision toward separation.

Early on, the teams encountered episodes of cross circulation: When the surgeons gave Marian blood, medication, or other fluids, she quickly passed it through her liver, sending the benefits to her sister.

The teams remedied that issue by quickly

separating the liver and hydrating the girls individually. As the procedure went along, the girls needed to be resuscitated, an ovarian cyst was removed in Michelle, and both girls' abdominal walls were reconstructed. The teams built them belly buttons.

After seven hours, Ford had successfully led the first separation of conjoined siblings in Haiti.

That night Michelle and Marian slept in separate cribs. Twenty-four hours later, their parents held them. In three days, the girls were eating. Nine days after that, they were discharged.

The news was widely reported. The first lady of Haiti and the nation's minister of health visited the family. Once, a mother feared her society would reject her babies; now her daughters are symbols of national pride.

The girls are seen as miracles. Michelle and Marian needed rehab to strengthen their spines and stand straight. But they walked before their sister, Tamar.

Ford has kept in touch with the family. He gave the sisters vaccinations. He speaks with

them on the phone. This past Christmas, the Bernards videotaped the triplets singing a message to the doctor in front of a decorated tree. (Catch them caroling at pittmed.health.pitt.edu. See "Bonus.")

Their development and growth are emblematic of the progress that Ford believes teamwork and increased medical infrastructure can bring to Haiti.

This January, the Bernard family celebrates the father's birthday in their sunny dining room in Pétionville. His three little girls enter in red shirts and blue pants, their pint-sized Afros sitting like crowns upon their heads.

A little later, their mother will join them from the kitchen and hug each girl warmly. She'll sit down and place Tamar and Michelle on her knees while Marian, the most introverted of the three, slides behind her back.

But first, Tamar, Michelle, and Marian, now 3 years old—healthy, happy—one by one walk up to their father and kiss him in celebration. Gifts from Dr. Henri Ford and friends. ■

MATCH RESULTS

CLASS OF 2018

ANESTHESIOLOGY

Chop, Nadeige
Johns Hopkins Hospital & Bayview Medical Center, Md.
Hsu, Jessica
University of Maryland Medical Center
Kutten, Johannes
University of Massachusetts Memorial Medical Center
Nguyen, Anh Vinh
UPMC/University of Pittsburgh, Pa.
Rakholia, Milap
Stanford University Programs, Calif.
Tian, Ling
Ronald Reagan UCLA Medical Center/
University of California, Los Angeles
Van Ham, Raymond
University of Michigan Hospitals
Zhao, Yujing
McGaw Medical Center of Northwestern University, Ill.

DERMATOLOGY

Dando, Emily
UPMC/University of Pittsburgh, Pa.
Friedman, Blake
Rhode Island Hospital/Brown University
McClanahan, Danielle
Oregon Health & Science University Programs
Meenan, Chelsea
University of Tennessee Programs
Patel, Parth
University of Texas Southwestern Medical Center

EMERGENCY MEDICINE

Agi, Chika
UPMC/University of Pittsburgh, Pa.
Chen, Neil
Montefiore Medical Center & Jacobi Medical Center/
Albert Einstein College of Medicine, N.Y.
Chen, Zean
University Hospitals Cleveland Medical Center/
Case Western Reserve University, Ohio
Guzman, Billy
Duke University Medical Center, N.C.
Keller, John
Ronald Reagan UCLA Medical Center/
University of California, Los Angeles
Larsen, Jennifer
UPMC/University of Pittsburgh, Pa.
Marcott, Matthew
Brooklyn Hospital Center/
Icahn School of Medicine at Mount Sinai, N.Y.
Mu, Yijia
Jackson Memorial Hospital/University of Miami, Fla.
Truong, Sandra
University of Washington Affiliated Hospitals

FAMILY MEDICINE

Amin, Paula
OhioHealth Grant Medical Center
Bechis, Margarite
North Colorado Medical Center
Chan, Ramey
UPMC St. Margaret/University of Pittsburgh, Pa.
Gianforcaro, Alexandro
University of Toronto, Ontario
Lu, Jessica
University of Washington Affiliated Hospitals
MacDonald, Serena
Vidant Medical Center/East Carolina University, N.C.
Salesi, Lauren
UPMC St. Margaret/University of Pittsburgh, Pa.
Villalobos, Shantal
UPMC McKeesport/University of Pittsburgh, Pa.

INTERNAL MEDICINE

Abay, Rebecca
University of Washington Affiliated Hospitals
Allbright, Kassandra
Johns Hopkins Hospital, Md.
Attaar, Adam
Emory University Hospital & Grady Health System, Ga.
Bursic, Alexandra
UPMC/University of Pittsburgh, Pa.
Ding, Xuan
Vanderbilt University Medical Center, Tenn.
Dolezal, James
University of Chicago Medical Center, Ill.
Drohan, Callie
UPMC/University of Pittsburgh, Pa.
Falvello, Virginia
University of Michigan Hospitals
Feroze, Rafey
University of Michigan Hospitals
Koldhekar, Amol
Emory University Hospital & Grady Health System, Ga.
Moore, Nathan
University of Washington Affiliated Hospitals
Neill, Colin
Vanderbilt University Medical Center, Tenn.
Patel, Devan
Barnes-Jewish Hospital/Washington University, Mo.
Radder, Josiah
UPMC/University of Pittsburgh, Pa.
Rearick, Corey
University of Chicago Medical Center, Ill.
Rosenberger, Emily
UPMC/University of Pittsburgh, Pa.
Schub, Micah
Duke University Medical Center, N.C.
Segal, Michael
University of Wisconsin Hospital and Clinics
Shah, Maulin
Cedars-Sinai Medical Center/University of California,
Los Angeles
Tahata, Shawn
Mayo Clinic, Minn.
Thalappillil, Alvin
UPMC/University of Pittsburgh, Pa.
Xu, Jeffrey
Barnes-Jewish Hospital/Washington University, Mo.
Zalewski, Shannon
Barnes-Jewish Hospital/Washington University, Mo.

INTERNAL MEDICINE— PHYSICIAN-SCIENTIST

Morenes, Jared
Yale New Haven Hospital, Conn.

INTERNAL MEDICINE— PRELIMINARY

Lukach, Alexis
Abington Hospital—Jefferson Health/
Thomas Jefferson University, Pa.

MEDICINE—PEDIATRIC

Cooper, Paul
University of Illinois at Chicago Programs
Park, Ashley
MedStar Georgetown University Hospital, D.C.

NEUROLOGY

Markantone, Desiree
Mount Sinai Hospital/
Icahn School of Medicine at Mount Sinai

NEUROLOGY—PEDIATRIC

Ibarra, Jordan
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.

OBSTETRICS/GYNECOLOGY

Algarroba, Gabriela
NYU Winthrop Hospital/New York University
Baradaran-Shoraka, Massoud
UF Health Shands Hospital/University of Florida
Cheung, Jessica
Abington Hospital—Jefferson Health/
Thomas Jefferson University, Pa.
Du, Angela
Ohio State University Medical Center
Dwomor, Leticia
Women & Infants Hospital of Rhode Island/
Brown University
Silverstein, Rachel
University of North Carolina Hospitals
Wright, Megan
Western Pennsylvania Hospital

OPHTHALMOLOGY

Davenport, Connor
Wake Forest University Baptist Medical Center
Durrani, Asad
U-M Kellogg Eye Center/University of Michigan
Huang, Marshall
University of Utah Affiliated Hospitals
Jensen, Adrianna
Johns Hopkins Wilmer Eye Institute, Md.
Park, Daniel
USC Roski Eye Institute/University of Southern California
Wang, Bo
Johns Hopkins Wilmer Eye Institute, Md.

OTOLARYNGOLOGY

Patel, Vishaal
Temple University Hospital, Pa.

PEDIATRICS

Bowen, James
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Chen, Connie
St. Christopher's Hospital, Pa.
Chen, Sarah
Nationwide Children's Hospital/Ohio State University
Devine, Danielle
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Eddens, Taylor
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Elliott, Thomas
Johns Hopkins Children's Center, Md.
Fernandez, Xenia
University of Connecticut Health & Connecticut Children's
Gunawardena, Naomi
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Hogan, Caroline
Seattle Children's Hospital/University of Washington
Israel, Joseph
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.
Kassiff, Sivan
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.



On March 16, Pitt Med held its annual Match Day ceremony at the Petersen Events Center. ABOVE RIGHT: Class of '18 grads Sandra Truong (far left), Shriya Kaneriya, and Paul Cooper pose while wearing "Match Madness" shirts as they wait to see where they'll land. Truong matched with University of Washington Affiliated Hospitals, Kaneriya matched with UPMC, and Cooper will go to the University of Illinois, Chicago. Shih-Dun Liu (far right) will take one more year to graduate because he's in the Clinical Scientist Training Program. Liu was there to support his friends.

Lee, Wei-Wei

Children's Hospital of the King's Daughters,
Eastern Virginia Medical School
Mortenson, Jeffrey
University of Tennessee Health Science Center &
Le Bonheur Children's Hospital

Nathan, Suresh
Cohen Children's Medical Center/
Hofstra University, N.Y.

Patel, Neema
Benioff Children's Hospital—Oakland/
University of California, San Francisco

Perera, A.G. Nuwan
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.

Pollock, Netanya
Boston Children's Hospital/
Harvard Medical School, Mass.

Pritz, Benjamin
University of Michigan Hospitals

Sinder, Adam
Children's Hospital of Pittsburgh of UPMC/
University of Pittsburgh, Pa.

Whaite, Erin
Nemours/Alfred I. duPont Hospital for Children/
Jefferson Medical College, Pa.

PHYSICAL MEDICINE & REHABILITATION

Brane, Lucas
UPMC/University of Pittsburgh, Pa.

PSYCHIATRY

Alhassan, Jamil
UC San Diego Medical Center/
University of California, San Diego

Brent, Jacob
UPMC/University of Pittsburgh, Pa.

Chung, Daniel
UPMC/University of Pittsburgh, Pa.

David, Christopher
UC San Diego Medical Center/
University of California, San Diego

Diehl, Jessica
Vanderbilt University Medical Center, Tenn.

Geramita, Matthew
UPMC/University of Pittsburgh, Pa.

Greenspan, Kiefer
University of Illinois at Chicago Medical Center

Holliday, William
Harbor-UCLA Medical Center/University of California,
Los Angeles

Kaneriya, Shriya
UPMC/University of Pittsburgh, Pa.

Lim, Sarah
UPMC/University of Pittsburgh, Pa.

RADIATION ONCOLOGY

Chen, Katherine
Mt. Zion Medical Center & Moffitt—Long Hospital/
University of California, San Francisco

Dohopolski, Michael
UT Southwestern Medical Center/
University of Texas Southwestern

Prabhu, Arpan
Winthrop P. Rockefeller Cancer Institute/
University of Arkansas for Medical Sciences

RADIOLOGY—DIAGNOSTIC

Chen, Angela
UC San Diego Health/University of California,
San Diego

Kundu, Shinjini
Johns Hopkins Hospital, Md.

SURGERY—GENERAL

Beache, Sydney
Barnes-Jewish Hospital/Washington University, Mo.

Beck, Andrea
University of Utah Affiliated Hospitals

Craig, Ethan
University at Buffalo Affiliated Hospitals, N.Y.

Edwards, Joseph
University of Maryland Medical Center

Khodakov, Anton
ULH, Norton Children's Hospital, and Jewish Hospital/
University of Louisville, Ky.

Labiner, Hanna
Robert Wood Johnson University Hospital, N.J.

Nwaiwu, Chibueze
Rhode Island Hospital/Brown University

Song, Yi
SUNY Downstate Medical Center/
State University of New York

Wang, Simeng
New York University School of Medicine

SURGERY—MAXILLOFACIAL

Cho, Jason
UPMC/University of Pittsburgh, Pa.

Ziegler, Erik
UPMC/University of Pittsburgh, Pa.

SURGERY—NEUROLOGICAL

Cavaleri, Jonathon
LAC+USC Medical Center & Keck Hospital of USC/
University of Southern California

Kim, Win Jin
UCLA Medical Center/University of California,
Los Angeles

Wozny, Thomas
UPMC/University of Pittsburgh, Pa.

SURGERY—ORTHOPAEDIC

Akpinar, Berkcan
NYU Langone Medical Center/New York University

Kanakamedala, Ajay
NYU Langone Medical Center/New York University

Kromka, Joseph
UPMC/University of Pittsburgh, Pa.

Lee, Andrew
University at Buffalo Affiliated Programs, N.Y.

Murawski, Christopher
UPMC/University of Pittsburgh, Pa.

Sayeed, Aatif
Beaumont Health System/Oakland University, Mich.

Thorne, Cara
University of Virginia Medical Center

Wang, Juntian
Cedars-Sinai Medical Center/
University of California, Los Angeles

Wilson, Alan
UPMC/University of Pittsburgh, Pa.

Wollstein, Adi
Johns Hopkins Hospital, Md.

SURGERY—PLASTIC

Guest, Rachel
University of Kansas Medical Center

Zhu, Xiao
UPMC/University of Pittsburgh, Pa.

SURGERY—PRELIMINARY

Wu, Rebecca
University of Massachusetts Medical School Baystate

SURGERY—THORACIC

Yousef, Sarah
UPMC/University of Pittsburgh, Pa.

SURGERY—VASCULAR

Xie, Bowen
UPMC/University of Pittsburgh, Pa.

UROLOGY

Argade, Shilpa
Barnes-Jewish Hospital/Washington University, Mo.

Jones, Cameron
UPMC/University of Pittsburgh, Pa.

Nikas, Christine
University of North Carolina Hospitals

*Note: Many of these programs also have the
VA Health System as a training site.*



CLASS NOTES

'80s

If you stop by Pitt's orthopaedic surgery department this fall, be sure to admire a bust of the late Albert Ferguson, former chair. The sculpture was created by **Vincent Russo** (Orthopaedic Surgery Resident '81), a surgeon based in Scottsdale, Ariz.,



Russo

specializing in joint replacement. Russo says he crafted the bust to commemorate a legend who inspired him. (Ferguson, who died in 2014, trained generations of surgeons, including 30-some department chairs and leaders of programs worldwide.) Creating

sculptures that represent personalities, relationships, and the human experience is integral to Russo's life. His patients appreciate his artistic side. He says they seem comforted by the idea that "if I can do a sculpture, I can probably do their surgery."

'90s

The family of **Marjorie Brennan** (Anesthesiology Resident '92) left Haiti when she was a toddler. After the 2010 earthquake, Brennan flew to Haiti for 10 days to provide medical assistance to survivors. She founded the JDT Foundation later that year. (JDT are the initials of Joseph Denis Thomas,

Brennan's grandfather.) The foundation offers scholarships to Haitian students studying the health sciences and funds projects aiming to restore Haiti's natural environment and agricultural practices. In addition to leading the foundation, Brennan is an assistant professor of anesthesiology and critical care medicine and of pediatrics at George Washington University and medical director of the Children's National Health System Montgomery County Ambulatory Surgery Center in Rockville, Md.

Bhargavi Gali

(Anesthesiology Resident '96, Critical Care Medicine Fellow '97) has been thinking a lot about the safety of robot-assisted hysterectomies versus traditional open hysterectomies. **Gali** An assistant professor of anesthesiology and perioperative medicine at the Mayo Clinic, Gali and colleagues posited that patients undergoing the robotic procedure could "have higher incidences of pulmonary complications" because surgeons must inflate the abdominal cavity with carbon dioxide to see what they're doing, in turn increasing pressure on the lungs. (It's not necessary to inflate the abdominal cavity during open hysterectomies.) Higher transpulmonary pressures—the force lungs feel from surgical ventilation—are typically associated with negative patient outcomes, Gali explains. Contrary to expectations, she found no significant difference in patient outcomes between hysterectomy



type, as published in *Anesthesia & Analgesia* in January. Now, she's planning studies asking why patients of robot-assisted hysterectomies don't have more complications.

Magnetic resonance imaging has only been in the clinic for a few decades, says **Gulay Alper** (Pediatric Neurology Resident '96), yet today doctors rely on it for diagnosing and monitoring patients with acquired demyelinating disorders—such as multiple sclerosis (MS)—because there are no blood tests to characterize the diseases. Alper, Pitt associate professor of pediatrics and director of the Clinical Neuroimmunology Program at Children's Hospital of Pittsburgh of UPMC, uses MRIs when working with children with multiple sclerosis, noting that, not too long ago, "people didn't realize [MS] existed in kids." Children often struggle with cognitive problems—even the children with MS who appear to have no motor impairment, who are able to walk and talk. Alper is participating in clinical trials of adult MS therapies in children to learn how to combat these issues.



Alper

In response to brain injuries **Elad Levy** (Surgical Intern '98, Neurosurgery Resident '04) saw in patients who had played youth football, he founded the Program for Understanding Childhood Concussion & Stroke. Levy, chair of the University at Buffalo's Department of Neurosurgery, says the organization provides video resources and research to parents and kids to spread concussion awareness and prevent injuries. Since 2011, "we raised half a million dollars, and all that has gone back to the community," he notes. Levy is a neurotrauma consultant for the Buffalo Bills. And last year, Levy and the team he oversees as medical director of Neuroendovascular Services at Gates Vascular Institute made news by successfully using a stent that hadn't been used previously in children to reconstruct blood vessels in the brain of a boy who'd been attacked by dogs.



Levy

'00s

How much weight gain is healthy during pregnancy? Pitt's **Lisa Bodnar** (Reproductive Biology Fellow '04) has been studying that question since she served on an Institute



Bodnar

of Medicine (now the National Academy of Medicine) committee in 2009 that revised gestational weight gain guidelines. She realized there was still a lot to learn, so she is working to increase the evidence base for future guidelines. She has demonstrated that weight gain below national recommendations may not be adversely associated with poor outcomes for obese mothers or their babies. In January, she published charts for classifying maternal weight gain in twin pregnancies. Bodnar—vice chair of research in epidemiology and associate professor of obstetrics, gynecology, and reproductive sciences—says she loves being a researcher because you can “ask a research question, design a study, and then answer it for yourself.”

Patients with prostate cancer may require different treatments, depending on their biology, says **Nima Sharifi** (MD '01), director of the Center of Excellence for Prostate Cancer Research at the Cleveland Clinic. His team's January 2018 write-up in *Cell Reports* confirms there is a link between gene *HSD17B4* and treatment-resistant prostate cancer. He hopes that research will lead to personalized therapies. Sharifi, who holds the Kendrick Family Chair for Prostate Cancer Research, was named a 2017 Fellow of the American Association for the Advancement of Science. The recognition is encouragement to keep working, he says. “It's a long road. There's not a lot of immediate gratification in science.”

'10s As a Pitt student, **Julie Boiko** (MD '16) noticed something. Although half her peers were women, the composition of grand rounds speakers skewed toward men. She wondered: “Maybe the lack of women physically at the podium at these lectures sends the message to younger trainees that this isn't a place where my gender's presence is normative.” After looking at 200 grand rounds series at institutions nationwide, she reported in a 2017 *JAMA Internal Medicine* paper that women presented only 28 percent of the time, even though 36 percent of the faculty are women, as are 46 percent of residents. Now a pediatrics resident at UC San Francisco, she won the UC San Francisco Chancellor Award for Advancement of Women and is investigating factors that could increase the number of women at the podium.

—Charlotte Couch, Evan Bowen-Gaddy, Adrianna Moyer, and Sara Whitlock

ALUM INTEL

RACE, BIAS, AND OTHERNESS IN MEDICINE

The School of Medicine diversity office—over the decades led by William Wallace, Carolyn Carter, Nancy Washington, Paula Davis (who is now assistant vice chancellor for diversity), and, for the past several years, Chenits Pettigrew—has been home base for generations of students seeking friendship, guidance, and assurance that they belong. In April, *Pitt Med* hosted a dialogue between alumnae who are now diversity and inclusion officers at schools and hospitals around the country. Student **Nia James**, president of Pitt's Student National Medical Association, moderated the conversation that touched on the stakes of unconscious bias, student dilemmas, and what's working well at their institutions. Check out highlights here. You can read more of the conversation online at www.pittmed.health.pitt.edu/story/alum-intel.

Nia James: Is there a part of your job that surprises you?

Margaret Larkins-Pettigrew: I need to continue to check myself about where my bias lies.

Stephanie White: Lots of schools have made it pretty far being well-intentioned. To really continue to push issues forward, there need to be

SHERRI-ANN BURNETT-BOWIE

(MD '97), Endocrinology
Associate Director, Center for Diversity and Inclusion,
Massachusetts General Hospital
Faculty Assistant Dean, Student Affairs,
Assistant Director, Office of Recruitment and
Multicultural Affairs, Harvard Medical School



Burnett-Bowie

NIA JAMES

(Class of '21), President, Student National Medical
Association, University of Pittsburgh



James

MARGARET LARKINS-PETTIGREW

(MD '94, Res '98), Obstetrics and Gynecology
Director and Endowed Chair, Center for Clinical Excellence
and Diversity, University Hospitals Cleveland Medical Center



Larkins-Pettigrew

MIA MALLORY

(MD '94), Pediatric Emergency Medicine
Associate Dean of Diversity and Inclusion,
University of Cincinnati College of Medicine



Mallory

STEPHANIE WHITE

(MD '08), Pediatrics
Diversity Liaison for Student/Resident Advising,
Geisel School of Medicine at Dartmouth College



White

standardized ways of accomplishing things—and metrics for evaluation.

Mia Mallory: I am often surprised that not everyone believes in the importance of diversity in the health care workforce, especially given that the population of the patients that we are caring for is becoming increasingly diverse.

“There’s such empathy that’s inherent in the choice to provide relief of suffering. Sometimes people make the mistake of thinking, *I can’t be biased, because I’m in this pursuit.*”

NJ: What is trending in the world of diversity and inclusion offices?

Sherri-Ann Burnett-Bowie: There is a significant conversation that’s ongoing around supporting learners and faculty with disabilities. The idea that you have to be perfect is a real barrier to both seeking wellness and seeking accommodation.

SW: Students are coming in with more experience dealing with social justice. Think about the key events that took place in their formative years with Trayvon Martin and the inappropriate deaths of black males. This has been in their lives for as long as they remember, and it’s really hard as faculty to keep in mind that they do think about things differently. We’re going to have to bridge that gap, because they’re going to continue to want to talk about it.

MM: We’ve been seeing an uptick in patients who display biases against our students and physicians for a variety of reasons, whether it’s because they belong to a certain racial group, ethnic group, gender group, or sexual identity group. Now we are working to develop standards to educate and empower our students to combat the biases they are facing.

MLP: We just recently changed our patient bill of rights, because we had so many cases where our patients refused to have people, who are of the Jewish faith or African American, take care of them. We have decided to have a no-tolerance response. We say to a patient that we are all diverse, and this is a training institution, but if you are uncomfortable here we will transfer you at cost to another institution.

SW: If faculty members hear their students encountering something, they need to speak up for them at the time and not just ignore it, because that can be very demeaning. Students are in a difficult place, because in most situations, their grades and evaluations depend on their actions, and they don’t necessarily know what the attending would think if they verbalized their concerns.

NJ: Are there challenges that may be more significant than what you already listed?

MLP: I still feel that we can talk about all the “isms” that exist in our world today—as it relates to our LGBT population, our women—but at the end of the day, the people who are dying in my field [obstetrics and gynecology] are black women and black babies. Part of our responsibility is to recognize that unconscious bias does kill, and it can kill at the bedside.

SBB: Physicians and health care providers—not just physicians—sometimes need convincing that we have bias, because there’s such empathy that’s inherent in the choice to provide relief of suffering. Sometimes people make the mistake of thinking, *I can’t be biased, because I’m in this pursuit. . . .*

There is so much upheaval in our geopolitical context that it’s a hard time to be a student who is concerned about social justice. I have sent out e-mails about what

“Students really want change, like, yesterday. They are much more social-justice minded, and they’re pushing academic medicine educators to think about how we’re doing everything.”

I think are really heartbreaking national tragedies—after Charleston [church massacre], after Orlando [gay nightclub massacre]—where I share that I’m struggling with what has transpired, and that I would anticipate that they would be struggling as well, and that there are resources here to help them.

SW: Students really want change, like, yesterday. They are much more social-justice minded, and they’re pushing academic medicine educators to think about how we’re doing everything within the classroom, clinics, and medical school environment.

—Compiled by Cara Masset
Comments have been edited for length, style, and clarity.

HARVEY LINCOFF

AUG. 22, 1920—NOV. 25, 2017

Patching a bike tire is tedious—locating the hole, applying cement, praying the patch will hold. It's far easier to change the tire. Before the 1970s, ophthalmologists felt the same. Instead of finding and patching retinal tears, they treated the entire circumference of the eye.



Lincoff

Harvey Lincoff (MD '48), who died in November at 97, saw the damage this invasive approach caused his patients. "He was of the attitude," says his life partner Ingrid Kreissig, "not to do much surgery." He analyzed thousands of patients' retinal detachments, making precise drawings of each tear. These holes were "in the range of 1 to 2 millimeters," says fellow ophthalmologist Kreissig, noting "you have to look for hours" to find them. But Lincoff continued until he was able to define rules for finding retinal tears and published them in a landmark 1971 *JAMA Ophthalmology* paper, "Finding the Retinal Hole." He and Kreissig went on to develop a "minimal, atraumatic, localized retinal detachment surgery," she says, "by only treating the break." They had developed the retinal equivalent of patching a hole on a bike tire, and, to this day, ophthalmologists use Lincoff's rules to find retinal holes.

Lincoff's persistence extended beyond his work on the retina. Although his undergraduate career at Harvard was interrupted by WWII, Lincoff, a Pittsburgh native, completed his degree after serving in the navy and then received his MD from Pitt in 1948. He settled in New York, where he joined the faculty at Cornell University and remained for the duration of his career. While in New York, he met Kreissig, and—despite her living in Germany—the two sustained a transatlantic partnership for 48 years. She remembers him as a man of "impressive honesty and intellect. He was the most analytic ophthalmologist I have met." —Sara Whitlock

AVIVA L. KATZ

JULY 13, 1959—JAN. 17, 2018

Aviva L. Katz, an associate professor of surgery at Pitt known for her incisive analyses of ethical issues, including the ethical implications of the structure of medical education, died in January.

Raised in Brooklyn, the pediatric surgeon received her MD at Mount Sinai School of Medicine in New York and a Master of Arts in bioethics from Pitt. She joined the Pitt faculty in 2006 and also served as director of the ethics consultation service at Children's Hospital of Pittsburgh of UPMC, vice chair of Pitt's Internal Review Board, and director of the Consortium Ethics Program. Nationally, Katz chaired the committee on bioethics for the American Academy of Pediatrics (AAP), and was a member and chair of the ethics and advocacy committee for the American Pediatric Surgical Association. She was named a fellow of the American College of Surgeons and the AAP.

"Aviva was able to draw on her personal clinical experience and ethics expertise to

help draft important policy and position statements for the institution and the profession," says Lisa Parker, director of the University's Center for Bioethics and Health Law, with which Katz was affiliated. Parker recalls that Katz's faculty work "demonstrated keen insight into clinical ethics issues affecting pediatric patients and their families."

In a remembrance published by Katz's husband, Daniel Weiner, on the American Pediatric Surgical Association Web site, he notes: "She was active in the community as a mentor for women interested in medicine and a coach (for the Science Olympiad and Odyssey of the Mind) in her local community. She presented programs in her school district on issues related to medicine and ethics. And, she loved her family; was so proud of her children and their accomplishments. Finally, she loved to ice skate. She was so excited when she got medical clearance to return to skating." —Marty Levine

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Katz

IN MEMORIAM

'40s

GEORGE R. SENITA
RES '47, RES '58
JAN. 30, 2018

'50s

ROBERT E. SANDY
MD '53
FEB. 20, 2018

ERNEST E. REIGH
MD '54
OCT. 1, 2017

JAMES S. ROSS
MD '54
FEB. 12, 2018

JAMES V. BONESSI
MD '56
FEB. 28, 2018

CHARLES C. HOHING
MD '56
FEB. 20, 2018

CHARLES L. PIFER
MD '56
FEB. 14, 2018

JOHN C. SCARAMUCCI
MD '57
JAN. 29, 2018

HERBERT H. ANDERSON
MD '59
FEB. 7, 2018

CHARLES ROBERT WOLF
MD '59
FEB. 26, 2018

'60s

DAVID H. ROSENSTEIN
MD '60
APRIL 10, 2018

FREDERICK G. BROWN
MD '61
FEB. 24, 2018

HARVEY SLATER
RES '66
FEB. 5, 2018

JOHN S. KENNERDELL
RES '68
AUG. 11, 2017

'70s

CHARLES C. WILLIAMS JR.
MD '73
MARCH 28, 2018

CLINTON N. CORDER
RES '75
APRIL 1, 2018

'80s

DANIEL B. LEVINE
MD '87
JAN. 25, 2018

'10s

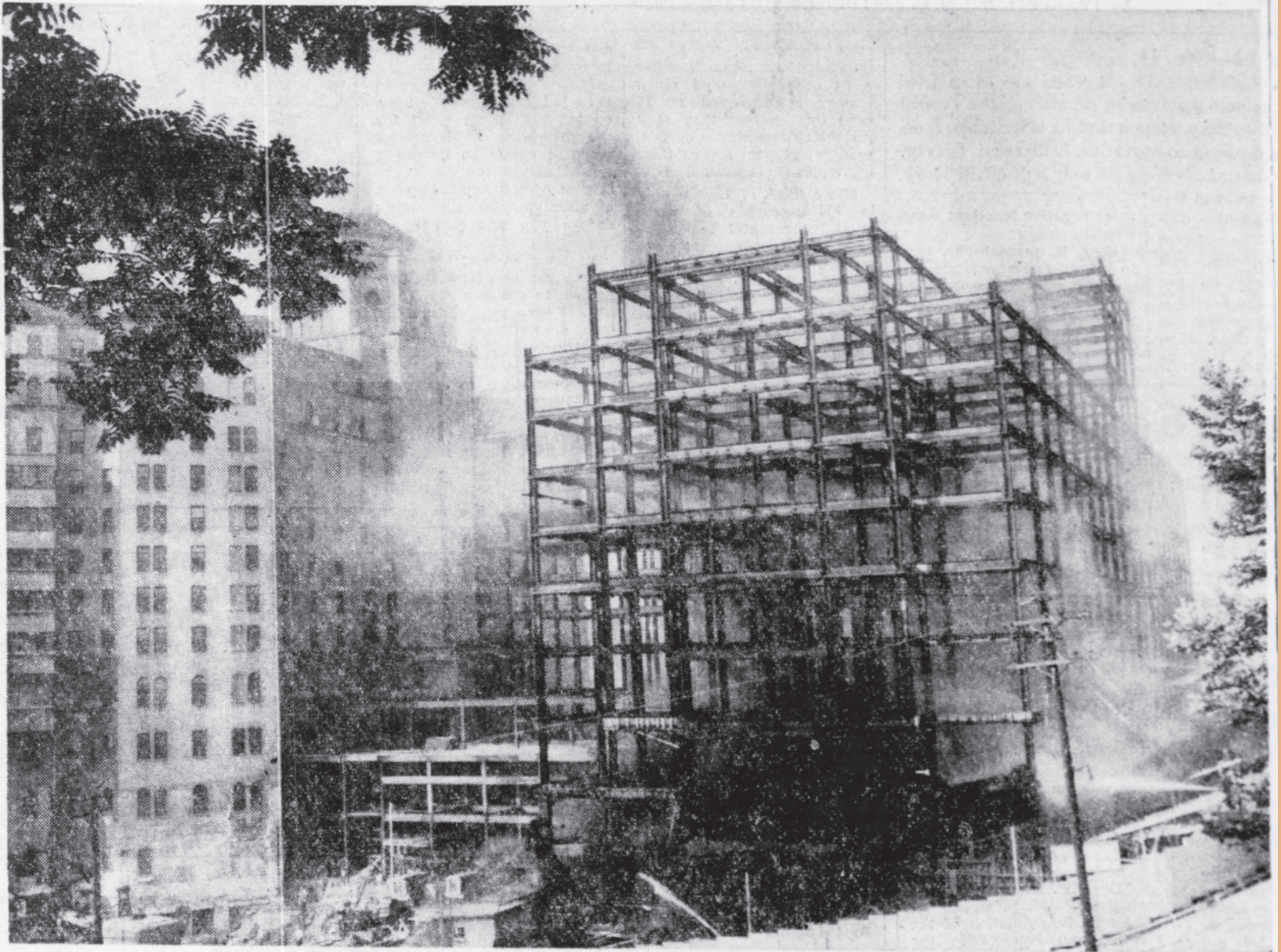
ALESSANDRA M.
BARREIRO-YANCEY
MD '12
FEB. 27, 2018

FACULTY

JOHN F. BOARDMAN
RES '01
MARCH 16, 2018

CHARLENE S. DEZZUTTI
MARCH 15, 2018

Flames Sweep \$15,000,000 Structure at Pitt



Presbyterian Hospital is shown behind the steel frame of Pitt's Health Professions Building as firemen battle to control flames.

A SIX-ALARM fire, starting at 6:30 a. m. yesterday, devastated the steel framework of Pitt's new Health Professions building, and forced the

evacuation of 250 patients at next-door Presbyterian Hospital. The fire twisted steel beams and one city official indicated the entire framework may

have to be torn down before construction can resume. Total damage will not be known for several weeks. The building was to be ready by late 1956.

WITHOUT FUSS OR PANIC

Found in the June 29, 1955 *Pittsburgh Post-Gazette*: the above news item on a six-alarm fire at Scaife Hall, which was then still a work in progress. A follow-up in the next day's *Post-Gazette* described how the blaze spread next door to adjoining Presbyterian Hospital. George Knarr, chief chef and a former firefighter, helped put out the fire at the hour he normally would have been preparing breakfast. *When the flames had been doused ... Mr. Knarr, aided by many other hospital employees [sic], cleaned things up, and breakfast was only an hour late. Lunch was served on schedule.*

And so it went throughout the hospital ... Within 30 minutes after smoke had begun to pour into the hospital and alarms had been sounded, nurses and doctors and other employees had completed evacuation of every patient without fuss or panic. Employees who were off duty heard of the fire and hurried to the hospital to be of service.

We like happy endings. Have a peek at Scaife Hall's shiny new look on p. 7. —Erica Lloyd

CALENDAR

FOR ALUMNI & FRIENDS

Unless otherwise noted, for information: Ashley Knoch at 412-648-9059, akk57@pitt.edu

PITT NETWORKING DAY JUNE 7

Find an event in your area:
www.alumni.pitt.edu/news-events/pitt-networking-day/

HEALTH SCIENCES NETWORKING NIGHT JUNE 15, 6–8 P.M.

Lemieux Sports Complex
Cranberry Township, Pa.

WHITE COAT CEREMONY AUGUST 12, 11 A.M.

Carnegie Music Hall
Reception immediately following.

MEDICAL ALUMNI ASSOCIATION REUNION WEEKEND OCTOBER 5–6

Reunion Classes:

1958, 1963, 1968, 1973, 1978, 1983,
1988, 1993, 1998, 2003, 2008, 2013

HEALTH SCIENCES ALUMNI & FRIENDS RECEPTIONS DATES TBA

Atlanta, Ga.

Philadelphia, Pa.

For information:

Sarah McMullen at 412-647-5307 or
msarah@pmhsf.org

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

GETTY IMAGES



FOR REAL! TWEEN SCIENCE

Why do we weep? It seems to have to do with how long *Homo sapiens* children depend on adults to survive, says Pitt's Lauren Bylsma, an assistant professor of psychiatry who has studied crying. We humans depend on adult caregivers longer than any other animal does. So, we need a surefire way to let others know when we need their help: Tears do the trick.

I know what you're thinking, *Don't other animals make tears?* Yes, pretty much any creature with eyelids produces them to keep eyes moist and free of dirt. But, although it's hard to prove, tearing up for emotional reasons seems to be uniquely human.

When we're born, we often wail to attract the attention and care of another person, much like a hungry baby bird calls for its mother to feed it. A few months after birth, babies start to replace loud cries with tears to express a need or emotion. As we grow older, we slowly start to rely on other humans less for survival and more for emotional support. During this time, tears tend to completely replace vocal cries, accompanying complex states of mind like relief, anxiety, frustration, and joy.

Why the shift from vocal to tearful crying? One theory is that it allows us to more discreetly direct our desire for support toward specific people. We can avoid attracting the attention of people we don't find comforting or who might harm us.

So the next time your floodgates open, for crying out loud, don't get down on yourself about it. Remember, tears may have helped early humans survive, and thrive. —Susan Wiedel

Is there a topic you'd like us to explore? Drop us a line: medmag@pitt.edu



New Yorkers are getting schooled on how **Pitt is it**. This spring, a Times Square jumbotron spot featured some juicy brag points, including these:

#1 Public University in the Northeast
—*Wall Street Journal*

Top 5% Universities Globally
—*U.S. News and World Report*

See for yourself at www.pittmed.health.pitt.edu/bonus.