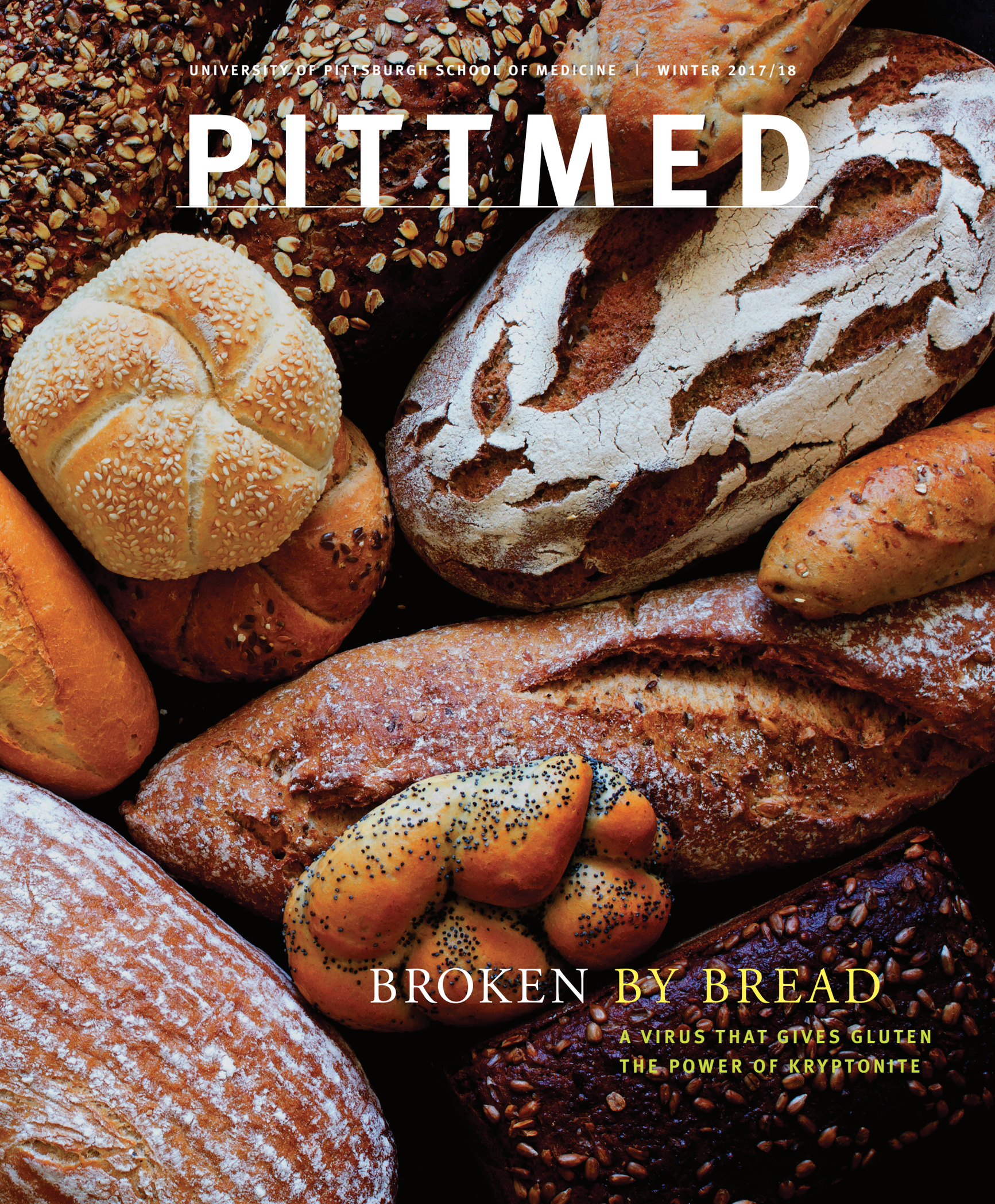
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | WINTER 2017/18

PITTMED



BROKEN BY BREAD

A VIRUS THAT GIVES GLUTEN THE POWER OF KRYPTONITE

KEEP ON KEEPIN' ON

I am 68, have been a physician for more than 30 years, and so love this profession that I'm dreading retirement, if and when it ever comes.

I practice anesthesia in rural Pennsylvania and, though I encounter many good clinicians, no one out here in the woods is on the frontier of science. This is not a pejorative comment, just a reality.

So imagine my hard-to-control elation every time I get *Pitt Med*. I devour it. It makes me feel so hopeful for the future of medicine, so proud of the research and its application to human disease and suffering. It never ceases to amaze me how some human brain, one of my contemporaries 110 miles away at Pitt, is bringing the unknown into the world of proof and known. The whole practice of medicine is being shifted by the proofs of research.

There is great hope for the next generation—and Pitt is branching out in so many areas. Bravo. Keep that magazine coming. I love every page.

Sharon Johnson (Fel '90)
Bedford, Pa.

CORRESPONDENCE

We gladly receive letters (which we may edit for length, style, and clarity).

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WINTERIZE YOURSELF

Feeling like a zombie now that temperatures are dropping? Put the fire back in your belly at the 13th annual Winter Academy, a day-long celebration of scientific discovery featuring Pitt's finest investigators in the biomedical realm.

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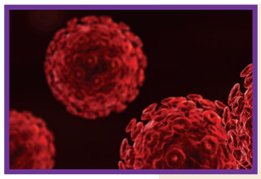
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FRANK HARRIS's ["We Are the Medicine Makers, We Are the Dreamers of Dreams"] artwork has been featured in *Vanity Fair*, *Harvard Magazine*, and *New Orleans Magazine*. Harris, originally from Youngstown, loves Pittsburgh. During a stint in New York City, "I always had these dreams at night, that someone was showing me around a part of New York I'd never seen. And it looked a lot like Pittsburgh," he says. Currently, Harris has a painting of Gilded Age model Evelyn Nesbit featured at the Heinz History Center as part of the Art of Facts exhibition. Harris has two sons; his partner, Teresa LaCaria, is a 2004 Pitt Med grad.

RACHEL WILKINSON's ["Radical Medicine," "Pivots," and more] passions lie in reporting on both the hard sciences and culture. Her essay "Her Hair" was featured in *Vela* and was long-listed for the 2015 Golden Giraffe awards for *The Browser*. A freelance writer based in Pittsburgh, she has published pieces in *The Atlantic*, *Smithsonian*, *Creative Nonfiction*, and *Slate*. Her MFA in nonfiction is from the University of Pittsburgh.

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COVER
Terence Dermody wonders why more people don't get celiac disease. (Cover: © Pepmiba/Getty Images)

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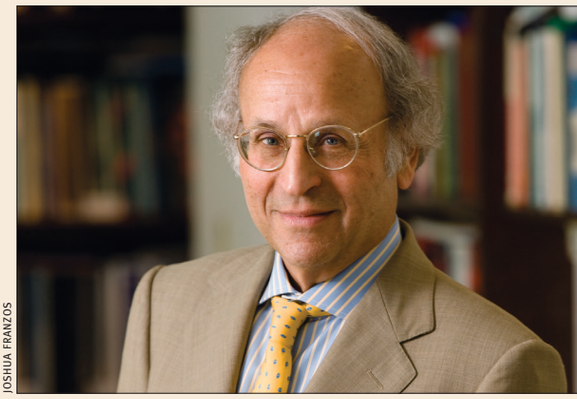
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Have you ever watched a crab on the shore crawling backward in search of the Atlantic Ocean, and missing? That's the way the mind of man operates.
—H.L. Mencken


JOSHUA FRANZOS

Imagine you have a heart attack. You are rushed to the hospital and treated immediately. You're given an aspirin; then the cardiologists remove the blockage and insert a stent to shore up your artery. You are also given a drug called clopidogrel (Plavix) or another anticoagulant. Here's the rub: For almost one-third of such patients, clopidogrel is not effective and fails to prevent another coronary artery clot—even one that may be lethal.

Philip Empey, a faculty member in our School of Pharmacy, was among the senior authors this October on a landmark paper from a multisite study demonstrating that patients carrying a certain gene allele will not respond to clopidogrel; the drug is not effectively metabolized. UPMC Presbyterian cardiologists have begun to assess which patients carry the allele by a simple test of their genomic DNA during hospital stays.These patients can then be given an alternative therapy. This is what precision medicine looks like. Can you imagine how many lives will be saved? How much waste in the health care economy will be avoided? As we harness the power of big data and also advance our knowledge of basic human biology and genomics, we will be able to achieve these kinds of results with drug after drug.

And Pittsburgh has, in short order, become a model for the nation—for many reasons that I don't have room to discuss here. Because we are positioned so well, the first enrollees of the National Institutes of Health's All of Us program, which will sequence the genomes of one million people, are coming through our medical center. (The Western Pennsylvania arm of the program is called PA Cares for Us—sign up to make history!) Pharmacogenomics, the area of precision medicine that gave us the clopidogrel insight, is the low-hanging fruit; approaching the chronic, complex illnesses, e.g., cancer and Alzheimer's disease, with genomics is considerably more challenging. Yet a recent case report shows what's possible: a boy cured of a lethal skin disorder, epidermolysis bullosa, which destroys the entire skin. Doctors in Europe harvested stem cells from the boy's marrow, genetically engineered the cells to correct the mutation that causes the disease, grew sheets of these corrected skin cells in the lab, and then grafted the sheets onto the boy.

Of course, there's more to who stays healthy than how our DNA sequences read. The World Health Organization breaks down causes of premature death this way: 30 percent of early deaths are attributed to genetics, 10 percent to what health care providers do (or don't do), 40 percent to individual behavior, and 20 percent to social, environmental, and economic factors. The latest generation of physicians is especially motivated to address that last component. Getting to the doctor on time, or at all, is a lot more difficult when it involves a 90-minute one-way bus ride with oxygen tanks in tow. Alumna Jodie Bryk and her colleagues are helping people navigate the labyrinth that poverty, psychologic make-up, policy, and other social and environmental circumstances erect to good health. (See p. 21,"Home Again.") Bryk et al. are mastering the high art of preventive care.

Assuring good health for all of us is work that requires great resolve, intent, and wisdom. My dear reader, each of us must contribute to that work if we are to have an enlightened society!

Arthur S. Levine, MD
Senior Vice Chancellor for the Health Sciences
John and Gertrude Petersen Dean, School of Medicine



Devoted to noteworthy happenings

at the medical school

A Severe Issue

A new study from the University of Pittsburgh shows that high doses of corticosteroids, used in some inhalers and in pill forms like prednisone, may be harming patients with severe asthma.

Researchers found that patients who used high doses of corticosteroids also had decreased lung function and high levels of an inflammatory protein called CXCL10 in their airways, says Anuradha Ray, the study's cosenior author and a PhD who holds the Endowed Chair in Lung Immunology at Pitt.

Low levels of CXCL10 can be detected in mild asthma. However, about 50 percent of patients with severe asthma show much higher levels of CXCL10 in their airways despite treatment with high-dose steroids. Although CXCL10 had been detected in mild asthma, it had never been studied in severe cases, says Marc Gauthier, MD clinical instructor and research associate as well as lead author. In contrast to severe asthma, CXCL10 levels are low enough that it is typically not a problem in patients with milder asthma.

Severe asthma affects five to 10 percent of the asthma population, contributing to substantial morbidity and even mortality, notes cosenior author Sally Wenzel, MD professor of medicine and director of Pitt's Asthma Institute. She adds there are adverse side effects related to prolonged use of high doses of steroids for patients with severe cases, including reduced bone mineral density and adrenal failure.

Worldwide, probably 300 million people suffer from asthma; that number is expected to jump to 400 million by 2025.

—Kate Benz

FOOTNOTE

Freddie Fu has examined more knees than you can shake a tendon at—tens of thousands, and not all human.

He's long been interested in ACL (anterior cruciate ligament) variants in his patients. And for years, every time the Pittsburgh Zoo anesthetized an animal for an exam, which was about once a week, he and former postdoc Sheila Ingham would stop by to examine its knee. They've observed rotations and flexions of monkeys, bears, lemurs, tree kangaroos, and then some—including one particularly helpful gorilla. (Helpful, at least, in terms of what its ACL revealed about the importance of bone morphology.) For his studies, Fu also has collected knee parts from the dearly departed among former residents of the zoo and other menageries throughout the world.



GORILLA: GETTY IMAGES



CAMI MESA

Overheard

Scott Maurer on Emotional Intel

For pediatrician Scott Maurer, work is a practice in empathy. Maurer, associate professor of pediatrics and chief of the Division of Palliative Medicine and Supportive Care at Children's Hospital of Pittsburgh of UPMC, serves families experiencing the pain of having a child with a chronic or terminal illness. His leadership in the classroom and in the hospital goes beyond teaching the nuts and bolts of patient care; he strives to model and teach emotional intelligence, which he says is necessary to the health of both patients and staff.

How do you and your colleagues maintain the stamina to witness and hold grief every day at work?

Sometimes I offer a kind word, or I pull someone aside when I know they have had a stressful day. I am a firm believer that the human experience is a shared experience. If something happens to you, it is helpful and cathartic if you can tell somebody about it. My colleagues and I are a family, and one person's experience affects the rest of [us]. I rely on my colleagues as they rely on me.

Is emotional intelligence something that can be learned?

Often people think of communication skills as something that is just part of one's natural ability, but communication is a teachable skill. I have the honor to be mentored by Bob Arnold, who is head of palliative medicine at Pitt and a cofounder of VitalTalk, a nonprofit dedicated to supporting emotional skills in medical professionals.

I teach students that when dealing with patients and their families, the first step is to expect an emotional response, and then to identify the present emotion, and lastly to follow that observation with an expression of support and understanding.

Why is emotional intelligence crucial to being a successful doctor?

Study after study shows that parents take your medical knowledge for granted, and the way they are going to judge your skills as a physician is how compassionate you are and how well you communicate with them. Medicine is one of those strange things in that you have to rapidly build rapport with somebody. I know if someone trusts me. I have become very good at reading body language and reading nonverbal cues. *—Interview by Nichole Faina*

Next Generation

When Lauren Goldschen (Class of '19) was an undergraduate, she witnessed several friends struggle with mental illness. She found that because of stigma, students were often afraid to disclose how they were doing to their friends and family and hesitated to access treatment off campus. While a third-year medical student, Goldschen has secured funding through the Roth Fellow Award to perform a qualitative study focused on how undergraduates cope with eating disorders. "This research experience has reinforced the importance of always treating patients' stories as a gift—not something to take for granted," Goldschen says.

Daniel Wonjae Chung is passionate about studying the neurobiology of schizophrenia with a focus on targeting the mechanisms of the disease. Chung is in the last year of the MD/PhD Pitt and Carnegie Mellon Medical Scientist Training Program. With David Lewis, MD Distinguished Professor of Psychiatry and Neuroscience and chair of psychiatry, Chung identified a novel synaptic pathology of schizophrenia resulting from an abnormal splicing mechanism. This mechanism could become a therapeutic target to prevent the onset or progression of schizophrenia. Chung has published papers in *Proceedings of the National Academy of Sciences* and the *American Journal of Psychiatry*.

Pitt Med's Sara Whitlock was picked to contribute a regular column to *STAT*, the health and science news publication, about her perspective as a grad student. Whitlock is a second-year student in the Molecular Biophysics and Structural Biology Graduate Program at Pitt and Carnegie Mellon University. One of her first *STAT* columns describes what she sees as a hurdle to American scientific excellence—young people being unwilling to fail. "By normalizing the experience of failure in the pursuit of science," she writes, "my hope is that we can keep American students in the field, so that we can remain competitive with other countries in uncertain times and in uncertain budgets." *—NF*

Liked and Lonely

Is social media making us lonely?

A recent study led by Brian Primack, MD/PhD director of Pitt's Center for Research on Media, Technology, and Health, suggests that increased time spent on platforms like Facebook and Instagram leads to heightened feelings of isolation in young adults.

Primack, who was recently named dean of Pitt's Honors College, says that as young people increasingly use social media to communicate, questions about the impact of the technology need to be addressed. His team studied the use of 11 platforms.

"We found that [the] more social media you used—whether it was defined in terms of time or frequency—related to more perceived social isolation," Primack says.

It may be that lonely teens are more likely to seek connection through these platforms, says Primack—a sort of self-medicating. Though it's unclear whether lots of Twitter-scrolling or Facebook-liking is the cause of the perceived isolation, it doesn't seem to be helping the problem.

Primack doesn't think that everyone should delete their accounts, but says: "I do think that these results might be a bit of a cautionary tale and help people to . . . make sure that the social media they use is making their lives better instead of inadvertently detracting from [them]." ***—Adrianna Moyer***



CATHERINE LAZURE

Another Paris Accord

With the intention of ending blindness, Pittsburghers and Parisians met at the French Embassy earlier this year.

How have the two cities become so closely aligned? José-Alain Sahel, chair of ophthalmology, joined the University of Pittsburgh last summer from Paris's Université Pierre-et-Marie Curie of the Sorbonne Universités (which happens to be abbreviated as UPMC). In Paris, Sahel built the world's leading research institute dedicated to halting and reversing diseases that cause blindness. He is expanding on that effort here in Pittsburgh.

Pitt's Arthur S. Levine, who is the John and Gertrude Petersen Dean of Medicine and senior vice chancellor for the health sciences, and Sahel, who maintains ties with Sorbonne UPMC, traveled to the French Embassy in Washington, D.C., in July. There, they met with the leaders of Sorbonne UPMC, as well as Inserm (the French equivalent of our National Institutes of Health) and CNRS (France's largest fundamental science agency) to sign an agreement focusing on research and education.

The accord encourages researchers of all four institutions to cooperate on fundamental research, development of novel therapeutics, and clinical trials, with an initial focus on vision and neuroscience. It also enables the exchange of resources, including personnel. "Taking on an immense challenge like the quest to cure blindness requires that we not only have bold ideas but also the brightest minds to work on them," says Levine. ***—Erica Lloyd***

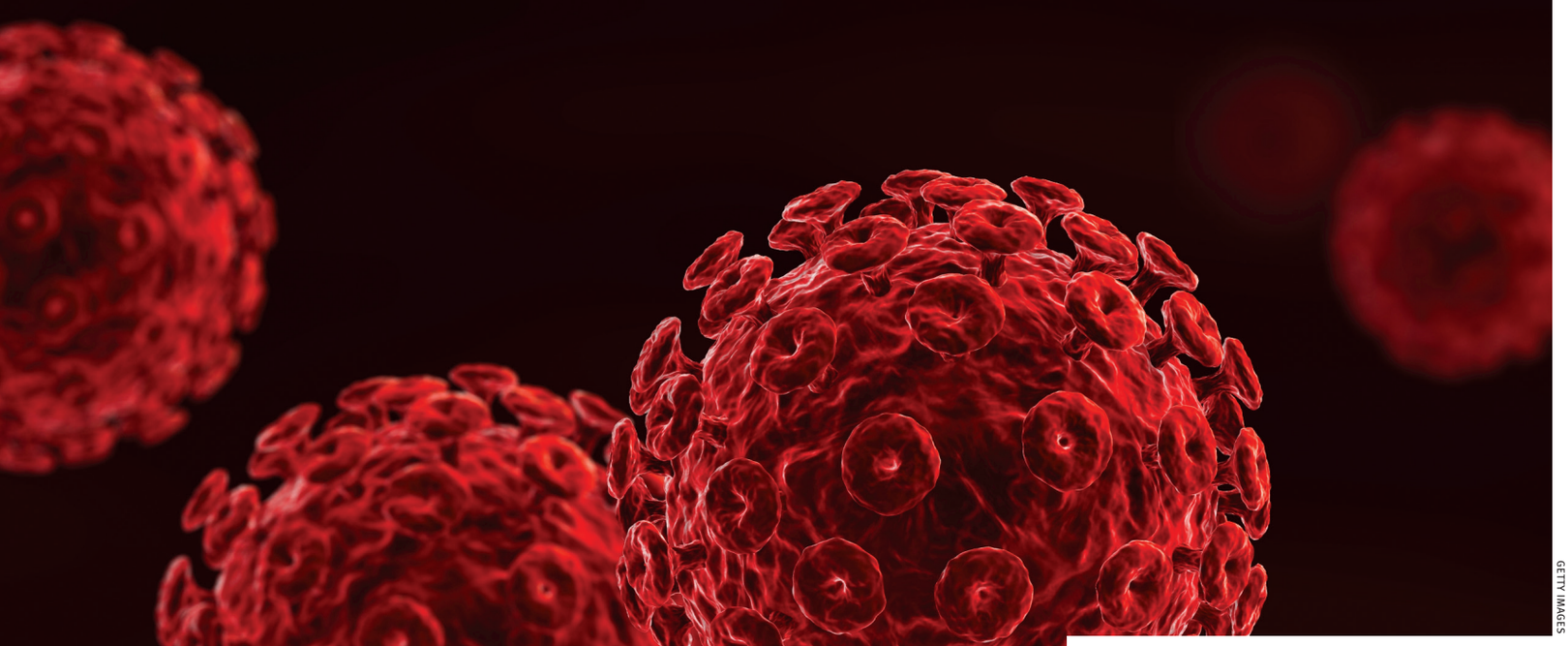
Class of 2021 Cheat Sheet

Take a look at who stands out among Pitt Med first-years:

Alexa Moreno became fascinated with obstetrics as a young girl, when her godmother was pregnant. She completed a bachelor's degree in nursing and a master's in nurse midwifery at the University of Miami. After eight years as a midwife, she realized that she could offer a higher level of care if she attended medical school. A marathon runner, beach volleyball player, and snowboarder, Moreno is always looking for a new physical or mental challenge. "If I fall, I get back up, bruised and injured but never dissuaded from learning, growing, and improving," she says.

Oluwaseun Ayoade began her career as a home health nurse in 2012 and found that she wanted to be more involved in care decisions. She began preparing for medical school, but took a detour in 2013 and enlisted in the U.S. Army. Working in physical therapy and rehabilitation, she was inspired by soldiers with training and overuse injuries who were determined to get back to doing what they loved. Those experiences continue to motivate her to not give up on her dreams.

South Hills natives Bryce and Travis Churilla didn't expect to attend the same medical school. The identical twins grew up in the same social circles and had many of the same interests—naturally, they became best friends. As undergraduates at Pitt, they continued to lean on each other for support. After these lifelong study partners were both accepted to Pitt Med, there was no question about where they would attend. Although the two plan to go into different specialties, they aren't sure how long that will last. ***—AM***



GETTY IMAGES

HIV is about 150 nanometers in diameter.

MEASURED APPROACH

Pitt researchers have figured out a new way to measure distances, as small as 3 nanometers, between proteins. Angela Gronenborn, a PhD, is Pitt's UPMC Rosalind Franklin Professor and chair of structural biology. With Elena Matei, a PhD research associate, she tagged proteins with fluorine during nuclear magnetic resonance (NMR) spectroscopy.

NMR spectroscopy can detect magnetic forces in certain atoms; researchers apply the technology to figure out the structure of molecules. Using fluorine, Gronenborn and Matei were able to eliminate interference normally associated with NMR spectroscopy when analyzing HIV (the virus is shown left). The technique results in highly accurate measurements and has broad implications for understanding a wide range of pathogens on a structural level. Gronenborn and Matei's proof-of-concept report in *Angewandte Chemie* was deemed a "hot paper." "It wasn't clear that it would work, and the fact that it works really well is gratifying," Gronenborn says.

—Elizabeth Hoover

Appointments

Kristin Davitt joins the University of Pittsburgh and UPMC as vice chancellor for development and alumni relations and president of the Medical and Health Sciences Foundation. Davitt has held leadership roles in multibillion dollar fund-raising campaigns at the University of Pennsylvania and Brown University. Chancellor Patrick Gallagher describes Davitt as an inspiring innovator and collaborator. In the newly created position, Davitt will lead institutional advancement for all of Pitt, including fund-raising to support Pitt's Schools of the Health Sciences and UPMC's efforts to "advance new discoveries and remake health care," says Jeffrey Romoff, CEO of UPMC.



Davitt

Pitt's **Robert Ferris**, a nationally known immunotherapy expert who was previously chief of the Division of Head and Neck Oncologic Surgery, was chosen as the UPMC Hillman Cancer Center's new director in June. The Hillman Cancer Center is one of the largest cancer treatment networks in the nation. "I am very excited to take on this role in an institution that has been a proven leader in cancer research and treatment," says Ferris, an MD/PhD and the Hillman Professor of Oncology.



Ferris

Earlier this year, **Rob Rutenbar**, a PhD, was named as Pitt's first senior vice chancellor for research. Previously a professor of engineering and head of the Department of Computer Science at the University of Illinois at Urbana-Champaign, Rutenbar is responsible for realizing a strategic plan for Pitt's research infrastructure and enhancing technology partnerships, including those at the medical school. "The landscape of science and technology is profoundly altered by big data," says Rutenbar. "I look forward to working with the medical school to connect its unique and enormous clinical data assets to the rest of the campus."

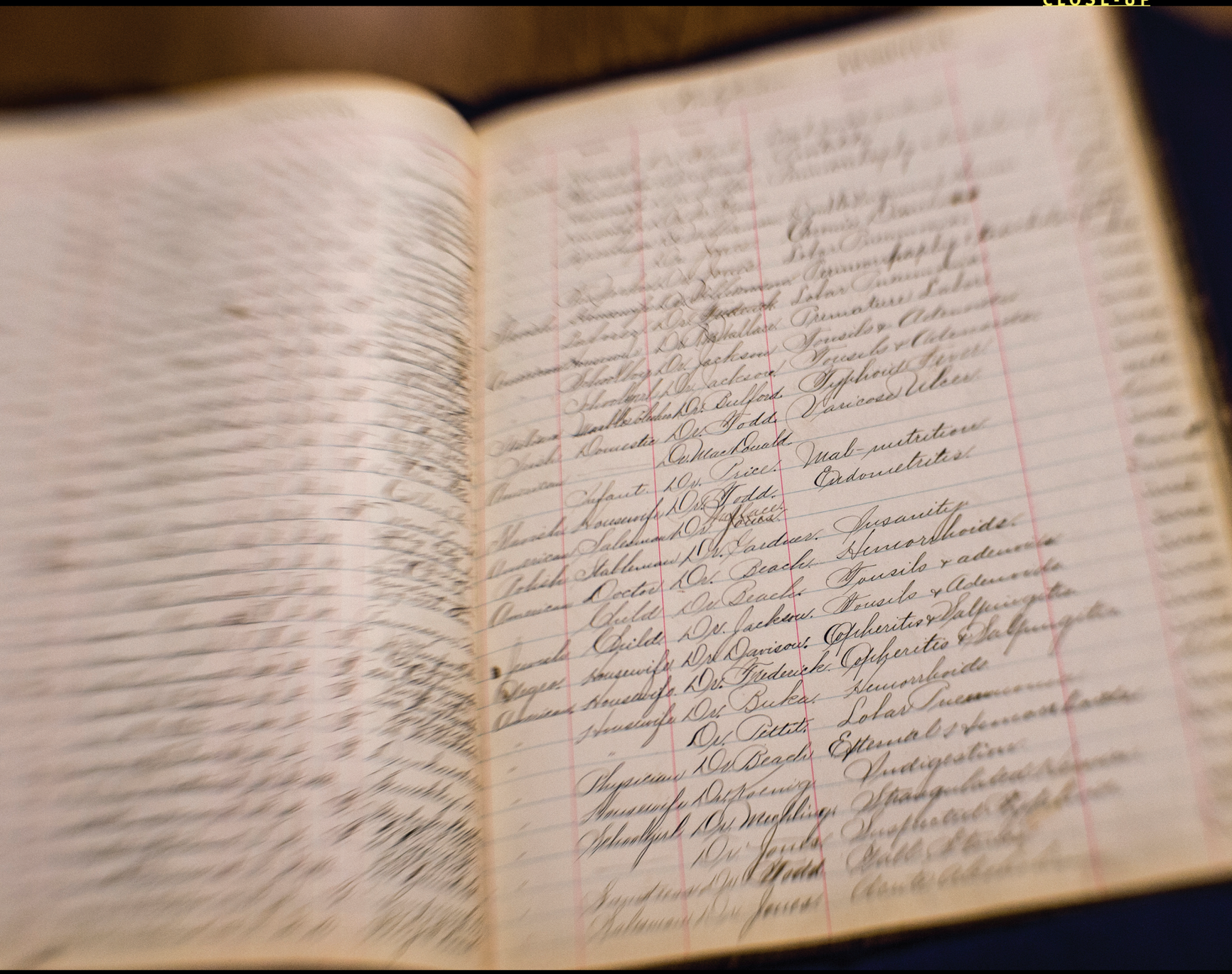


Rutenbar

Rocky Tuan, Distinguished Professor of Orthopaedic Surgery, will be the next vice chancellor and president of the Chinese University of Hong Kong. Tuan, a PhD, assumes the role in January 2018. While leading the Chinese institution, he will maintain ties to Pitt. Tuan's research focuses on stem cell science and tissue engineering. *—EH and AM*



Tuan



AN ELECTRONIC HEALTH RECORD

Behind wooden bookshelves in Pitt's Falk Library of the Health Sciences lay century-old patient ledgers from what was then called Presbyterian Hospital of Pittsburgh. The records date from 1895, the hospital's incorporation date, to 1924. The 10 ledgers themselves are about as large as an adult torso. Malgorzata Fort, head of Digital Resource Development for Falk, flips through the thick pages with care. In spiraled cursive, the entries tell of troubles from another time: *mal-nutrition, varicose ulcer, insanity, indigestion.*

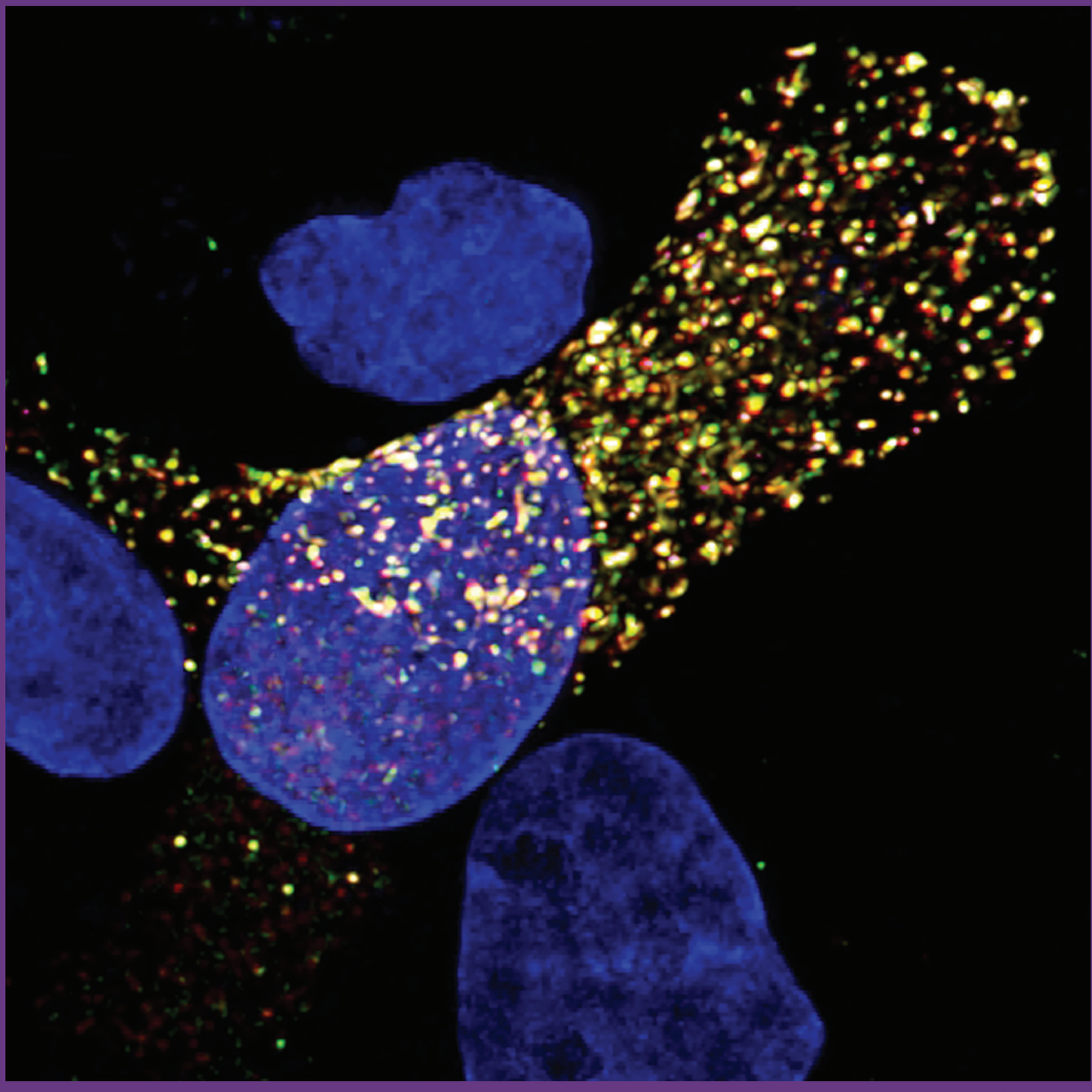
During a renovation project for Presbyterian several years ago, someone came across the ledgers in a closet. Falk director, Barbara Epstein, got a call: *Maybe you should have a look at these things.* Epstein has since had the ledgers incorporated into the library's History of Medicine Collection.

Each entry includes patient name, diagnosis, age, occupation, religion, ethnicity, nationality, treatment plan, and outcome. Once they are digitized, a historian might use the ledger data to pull together statistics on the 1918 influenza outbreak in Pittsburgh. Or an economist could see whether there was a correlation between birth rates and the religions of the mothers in 1900.

Fort, along with her colleagues Geoffrey Spear and Angie Zack, have been coordinating the digitization of these ledgers for about a decade now. Because of privacy concerns, access to information identifying patients will be limited. (Right now, a facsimile of one of the ledgers is on display on the 11th floor of Scaife Hall.)

Digitization hasn't been so straightforward. One difficulty in the endeavor is that the handwriting on the ledgers is often too ornate or sloppy to decipher with certainty. (Apparently, illegible handwriting is not a new issue in the medical field.) Another challenge has been funding. The project was even put on hold briefly in 2009. However, it has continued to make progress every year since. "At some point, this data will be available for researchers," Fort says, adding: "Slow but steady wins the race."

—Charlotte Couch
—Photography, Tom Altany



New insights into the structure of the influenza virus hold promise for better vaccines and antivirals.

WHAT'S NEW WITH FLU

A VIRUS MODEL MAKEOVER

BY ALLISON HYDZIK

The scientific textbook depiction of the flu virus is getting a facelift. A Pitt team has discovered that a model of the influenza genome architecture, untouched since the 1970s, isn't so perfect after all.

The discovery, reported in *Nucleic Acids Research* in July, reveals loopholes in the way the virus packages its genetic material. When one strain of flu comingles with another strain inside a cell, these loopholes allow the viruses to swap genetic material and give rise to new strains of flu. Knowing about these loopholes and how they interact with one another could give scientists the opportunity to better predict pandemics and find new ways to disrupt the flu virus.

"Although influenza has plagued mankind for hundreds of years and poses a substantial public health threat every winter, we know surprisingly little about flu pandemics," says senior author Seema Lakdawala, a PhD assistant professor of microbiology and molecular genetics. "Our discovery may give insight into how the flu virus continually evolves, opening the door to better vaccines and antivirals."

Influenza is a type of virus that uses single-stranded ribonucleic acid (RNA) to replicate, instead of double-stranded DNA. Influenza viruses are made up of eight RNA segments bound by a protective nucleoprotein. All eight RNA segments must come together inside a virus particle to make it fully infectious.

The classic model of the flu virus has these proteins coating the RNA like beads evenly spaced along a string. However, limitations of techniques used in the 1970s, when the model was developed, meant that unique features—like exposed RNA loops—were not apparent. Consequently, the universal depiction of influenza in textbooks is of a uniform random binding of proteins along the entire length of each RNA segment.

Lakdawala, who researches how viruses emerge and spread, teamed up with lead author Nara Lee, a PhD assistant professor of microbiology and molecular genetics, who specializes in RNA interactions. The two were curious whether there might be any areas along the influenza RNA strand that are more "open" and, therefore, more able to associate with other RNA segments. They used a process called "high-throughput sequencing of RNA by crosslinking immunoprecipitation" on two strains of influenza A, including the 2009 H1N1 pandemic (swine flu) strain, to get a better understanding of where the proteins bind to the RNA and to see if there were any areas of "naked" RNA.

"Honestly, we didn't expect to find any, since we had all learned the 'beads on a string' depiction of viral RNA," says Lakdawala. "But, amazingly, there are several stretches where the RNA was not bound by the nucleoprotein. This discovery opens up a whole new area of research."

Contrary to the classic model, Lakdawala and Lee found there are areas of RNA rich with protein coating and others that are exposed and presumably ripe for binding to other viral RNA during reassortment or to the swapping of genomic material between flu viruses. Evolutionary biology expert Vaughn Cooper, a PhD associate professor of microbiology and molecular genetics, guided the team to explore how these loops shape virus evolution in nature and during normal flu seasons.

The team is pursuing several potential research opportunities, including predicting the ways different influenza viruses could share genetic material to make new viruses. Knowing this could point scientists to the reassortments most likely to spark a flu pandemic and give public health agencies a leg up on creating targeted vaccines. There also could be ways to exploit the exposed RNA to make the virus less transmissible and deadly.

"It's really exciting to suddenly have all these research possibilities open up based on this one discovery," says Lakdawala. "The reason no one uncovered this [before] is because we all took for granted that 50-year-old research on the genome architecture, which looked really nice and had an easy explanation, was the full story. It shows that if we don't constantly resample and question scientific dogma, we could miss a big opportunity." ■

"We know surprisingly little about flu pandemics."

COURTESY SEEMA S. LAKDAWALA LAB



The top image shows typically developing heart ventricles in a mouse. The bottom shows the heart of a mouse with a mutation resulting in an underdeveloped left ventricle, as seen in a rare condition in newborns.

CHAMBER MADE

BETTER BEGINNINGS FOR HLHS BABIES

BY MARK ROTH

When a child is born with a condition known as hypoplastic left heart syndrome (HLHS), the family faces daunting challenges.

First, the baby must undergo a three-part surgery to correct life-threatening heart deformities. Then, if the heart still doesn't pump properly, the child goes on a heart transplant waiting list, and the family has to hope a donor will be found in time.

Recently, researchers at the University of Pittsburgh led by Cecilia Lo discovered a genetic cause of HLHS in mice, raising the possibility that there might one day be drugs that could at least partially correct the heart defect.

Lo, a PhD who holds the F. Sargent Cheever Chair of Developmental Biology, and her colleagues screened 100,000 mice with chemically mutated genes and looked for animals showing the classic signs of HLHS—a severely underdeveloped left ventricle, which normally pumps blood through the body, and a narrowed aorta, the largest artery in the body.

Of those 100,000 mice, eight fit the bill. The team then compared the genomes of these eight strains to those of healthy controls and found more than 300 mutations in the mice with heart defects. Further analysis showed HLHS was likely caused by combinations of many interacting genes.

The team soon zeroed in on one combination in particular, Sap130 and Pcdha9—in one of the mouse strains, mutations in both genes were required for all the hallmarks of HLHS to develop. Variants of Sap130 appeared to cause the small left ventricle and a weakness in heart metabolism, Lo says, while variants of Pcdha9 affected the aorta.

Lo's team collaborated with Stephen Murray and Kevin Peterson at the Jackson Laboratory in Maine, experts in the new genetic manipulation technique known as CRISPR-Cas9. Using this technique of altering genes in healthy mice, they were able to show these two mutations, once again, causing HLHS.

Working with colleagues at the University of Cincinnati and the University of California at San Diego, the team also examined a small sample of 68 patients with HLHS; one had Sap130 and Pcdha9 mutations, which are both rare.

The work, published in the May 22 issue of *Nature Genetics*, details what may be the first known genetic cause of HLHS, which affects about 2 to 3 of every 10,000 live births, or about 1,200 babies per year in the United States.

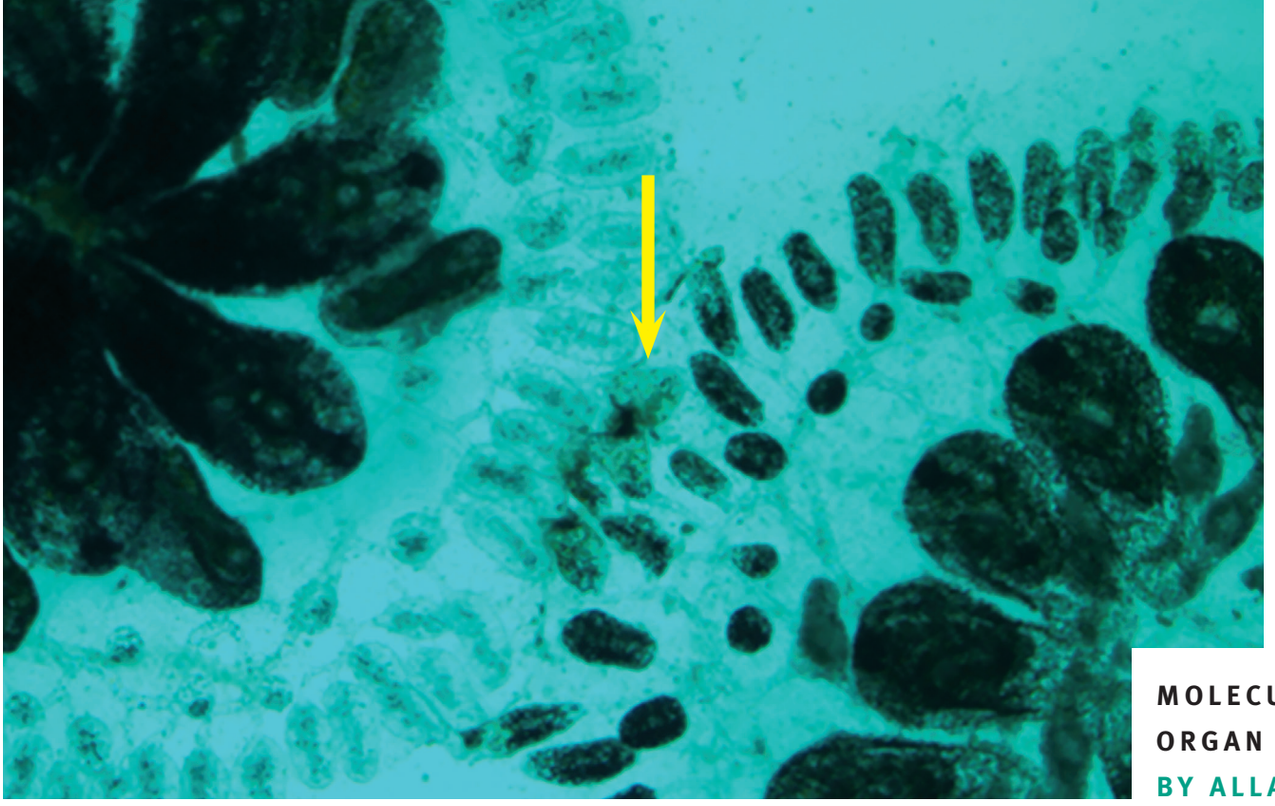
Eventually, Lo says, understanding the genetics of the syndrome might allow doctors to at least partially counteract the maldevelopment of an infant's heart with drug treatments. Most babies with HLHS are now identified in the womb, and it's possible that future therapies might reverse or reduce the severity of these malformations before the child is born.

"If we understand what causes this small left ventricle—and you can somehow treat that in utero—you can make the left ventricle grow . . . big enough that you can support biventricular physiology," says Lo. Then, doctors could do surgery after the babies are born and "still have two functional chambers [in the heart]. This would improve the patient's long-term prognosis."

The research also might allow doctors to one day determine which HLHS patients have abnormally weak heart muscles and therefore won't benefit from surgical repair; this would allow such children to get on the transplant list more quickly. "A number of studies have shown that the earlier you get a transplant, the better your outcome," she says.

It is likely that other combinations of mutations cause HLHS in the mouse strains the team worked with, Lo notes; so she is now seeking funding to search for other culprits responsible for this difficult congenital condition. ■

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RAFAEL D. ROSENGARTEN, MATTHEW L. NICOTRA, "MODEL SYSTEMS OF INVERTEBRATE ALLORECOGNITION," IN CURRENT BIOLOGY, VOLUME 21, ISSUE 2, 2011, © 2017. REPRINTED WITH PERMISSION FROM ELSEVIER

Even the immune systems of invertebrates, like these sea squirts (*Botryllus schlosseri*), can recognize when tissue is not their own.

MOLECULES THAT IGNITE ORGAN REJECTION

BY ALLA KATSNELSON

SELF-STARTER

Researchers had already figured out in great molecular detail how immune cells recognize and attack foreign tissue—a mechanism that leads the body to reject about half of all organ transplants. But one thing wasn't clear: What immune system signal kick-starts the process?

This summer, a *Science Immunology* paper by Fadi Lakkis provided an answer to this longstanding stumper. "What we've discovered is a very fundamental mechanism," says Lakkis, the Frank and Athena Sarris Professor of Transplantation Biology and of surgery, immunology, and medicine, as well as scientific director of the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh.

Mammalian immunity has two lines of defense: innate immunity, a primitive system consisting of tissue barriers and cells that are permanently mobilized to fight whatever toxins and pathogens they encounter, and adaptive immunity, the more recently evolved system that deploys a dragnet of T lymphocytes and other cells that search out and destroy specific interlopers when the innate immune response can't do the job.

It's the adaptive immune system that engineers transplant rejection. Unless a patient receives heavy doses of immune-suppressing drugs, the adaptive immune system identifies replaced organs as foreign tissue. But the adaptive immune system's marching orders come from the innate immune system, which hasn't generally been thought to be able to distinguish self from nonself tissue. Historically, researchers have assumed that generalized inflammation was sparked when a failing organ was removed and a new one plopped into its place, bringing T cells to attention.

But Lakkis was bothered by one truth of biology that holds up across species: Only vertebrates have adaptive immune systems, and yet invertebrates—which evolved earlier—can also distinguish their own tissues from foreign ones. "This was a very strong hint," he says, that perhaps the innate immune system had some nonself recognition chops that had gone underappreciated.

Lakkis teamed up with Matthew Nicotra, the PhD assistant professor of surgery and immunology at Pitt whose work had illuminated this ability to distinguish self from foreign matter, called allorecognition, in invertebrates. The duo searched for similar signals in the innate immune systems of mice. Using a genetic technique called positional cloning, they homed in on a molecule called SIRP-alpha and a receptor it binds to called CD47. SIRP-alpha is an ideal nonself marker because different people have slightly different versions of it. The researchers conducted a series of transplant experiments in mice and found that when a slightly divergent SIRP-alpha in donor tissue engaged with the host's CD47, the innate immune system revved up.

The team's first priority is to make sure the finding extends to humans. If so, then the signaling system might explain why, even years after a successful transplant, an organ is still at risk of rejection. "To us, it indicates that something is constantly waking up the innate system," Lakkis says, "and then the innate system turns around and wakes up the adaptive immune system."

Interfering with this signaling could help prevent rejection, Lakkis says, though he speculates that the system comprises much more than what they've found so far. "My guess is that we have just discovered the tip of the iceberg," he says. "There may be many other molecules that are activating the immune system in a similar fashion." ■



BROKEN

BY BREAD

A VIRUS THAT TURNS GLUTEN INTO KRYPTONITE

BY SHARON TREGASKIS

When you have celiac disease, your immune system goes berserk in the presence of gluten, the protein that gives bread its stretch. The resulting blitzkrieg turns the villi—the microscopic, finger-like protrusions within the small intestine that absorb nutrients and fluids—into the targets of a search-and-destroy mission.

You can't feel anything as the villi flatten and atrophy, but the resulting dysfunction—gas, bloating, diarrhea, constipation—takes its toll. And that's just for starters. As the damage spreads, the symptoms intensify: malnutrition, behavioral and mental health problems, joint and muscle issues, reproductive dysfunction, even increased risk for some forms of cancer.

There is no cure. But for many people with celiac, in the absence of gluten the attacks subside, and eventually the villi can heal—like skin slowly repairing itself after a burn. Yet probably less than 20 percent of people with celiac get an accurate diagnosis.

As for eliminating gluten, that's no easy task with this darling of the food-processing industry. Some things are obvious—bread products and anything that contains wheat or a half-dozen related grains. But gluten also lurks in the shadows—in condiments, spice mixes, thickeners, even the coating that gives french fries their crunch. When you have celiac, eating away from home turns into an exercise in Russian roulette, and reading ingredient lists becomes a matter of survival.

PEPMIBA/GETTY IMAGES

Approximately one in 130 people worldwide will develop celiac over the course of their lifetimes. "That sounds like long odds," says the University of Pittsburgh's Vira I. Heinz Professor of Pediatrics Terence Dermody, an MD, "but it's not." These days, everyone knows someone who has it.

The puzzling thing, says Dermody, who is chair of pediatrics, is the disparity between the prevalence of the gene variants that confer the risk of developing celiac and the relative rarity of the disease itself.



JOSHUA FRANZOS

Terence Dermody

Between 40 and 50 percent of us have the gene variants for celiac. They're ticking time bombs. Even as we happily make like Eric Carle's very hungry caterpillar—swilling beer and blissfully, ignorantly noshing our way through the Super Bowl buffet—the switch is poised to flip, ready to turn a benign foodstuff into kryptonite.

"So what gives?" says Dermody. "Why isn't celiac more common?"

In April 2017, *Science* published results of a series of experiments by Dermody and colleagues at the University of Chicago that begin to offer an answer: a combination of wrong-time-wrong-place factors that converge around reovirus, a bug so innocuous that most of us have had it and never even noticed. Even its name—an acronym conferred in 1959 by live-oral polio vaccine developer Albert Sabin—evokes its presumptively benign role in human health. Isolated from the respiratory (r) and enteric (e) tracts, or intestines, of human patients, it was an orphan (o) to which scientists at the time couldn't tie a single human disease.

Board certified in infectious disease, Dermody has spent more than three decades studying reoviruses; he is becoming one of the world's leading experts in the field. Reovirus is the fruit fly of virology—ubiquitous, inexpensive to maintain in a laboratory setting, and possessed of a relatively simple genome. That combination makes this virus family the perfect model for basic virology. In the 60 years since reoviruses were first isolated, scientists have built an extensive body of knowledge describing and manipulating their RNA, developing corresponding mouse models, and digging into just how viruses leverage host biology to perpetuate their own genomes. And reoviruses are pretty much harmless.

"I can look in the eyes of the mothers of my students and postdocs and tell them the virus isn't going to hurt them, and they've already been infected," says Dermody. He has supervised more than 90 aspiring physicians and scientists in his laboratories at Harvard, Vanderbilt, and, since January 2016, the University of Pittsburgh.

Although human exposure to reovirus doesn't cause any symptoms of disease or leave a trail of damage in its wake, the virus can't just skate past the immune system. At some point, probably early in life, reovirus makes its way through our guts, and our adaptive immune system generates antibodies that stay with us for life. That's how we know most of us have been infected.

Like a kid learning to read by sounding out new words, the adaptive immune system—housed, among other places, within the lining of our small intestine—learns by exposure, screening for the molecules, known as antigens, that our white blood cells use to distinguish proteins and assess threats.

"We eat really complex things every day," says Dermody, who is also physician-in-chief and scientific director at Children's Hospital of Pittsburgh of UPMC.

"If salmonella comes in, our immune system sees it as a foreign invader, and tries to clear the infection. But that doesn't happen when you eat a potato, or yogurt, or chicken."

That's because the adaptive immune system treats those antigens with a delicate balance of vigilance and tolerance. We encounter novelty throughout our life spans, and we live in a soup of hazards—aerosolized flu particles in the air at work, trace *E. coli* on a piece of spinach, a veritable zoo of microbes in a home-brewed bottle of kombucha.

So instead of launching a reaction in response to every unfamiliar antigen we encounter, the adaptive immune system preserves homeostasis, tolerating commensal microbes and the vast majority of foods we ingest, while mounting a defense against pathogenic invaders. Like the cordoned off entrances at an exclusive Manhattan nightclub, the lining of the intestine has its own protocol for deciding who's waved in, who gets stuck in the queue, and who is sent back to Jersey.

The gut actually sorts out what's coming at it with dedicated virus-detection centers known as Peyer's patches, as well as screening stations where food antigens are processed (the mesenteric lymph nodes and the lamina propria).

That compartmentalized approach "reduces the risk of responding to food antigens in the context of pathogens," says immunologist Bana Jabri. Jabri is an MD/PhD, director of research for the University of Chicago Celiac Disease Center, and Dermody's collaborator and the senior author on the *Science* paper.

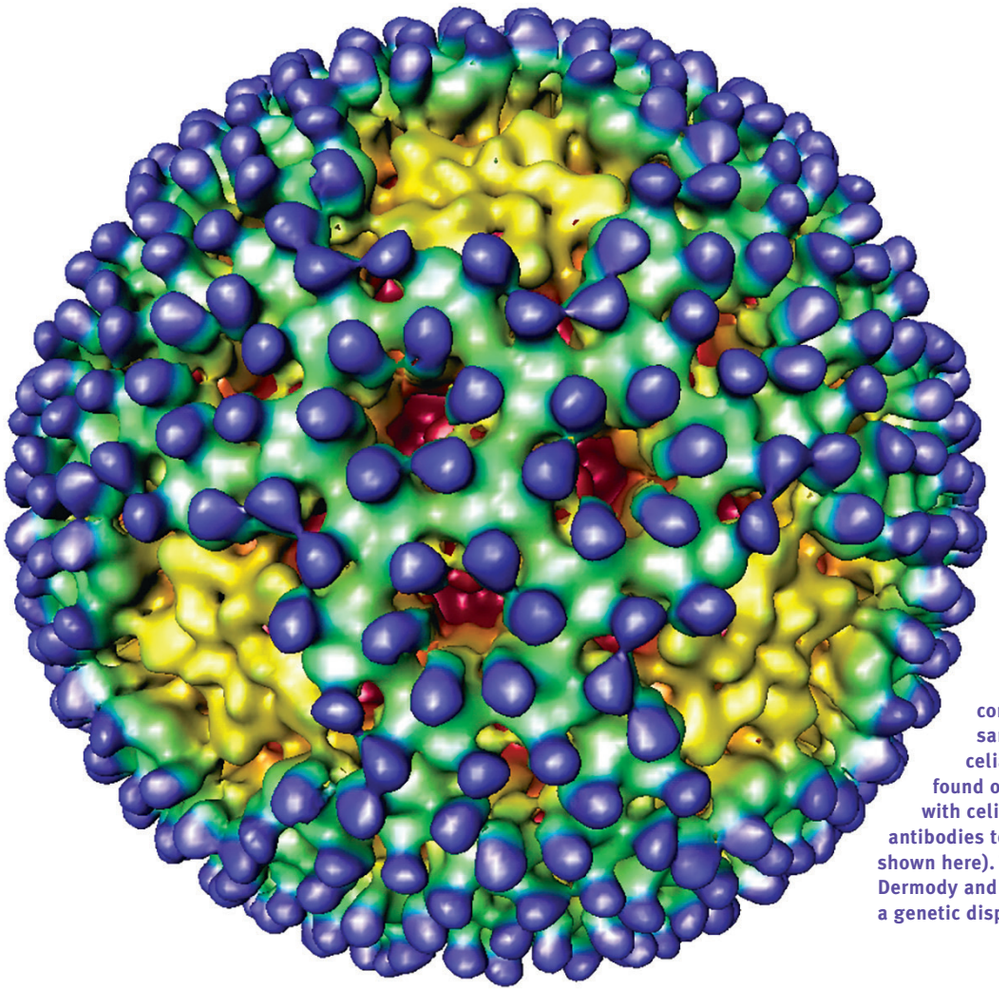
Still somehow, with celiac, the body forgets that gluten has a VIP pass to the intestinal club. And the whole system goes haywire, causing a debilitating inflammatory response.

Scientists have long suspected that viral infection might be to blame.

Yet, "it's really difficult to establish cause and effect, the mechanisms that underlie how viruses could trigger celiac or autoimmunity," says Jabri. "That means it's really important to have a good model system, like the mouse."

And a virus. When Dermody gave an invited lecture at the University of Chicago in 2010, his host, who knew of Jabri's interest in viral triggers, introduced her to Dermody. At the time, he was working with UT Southwestern collaborators to put the

JOURNAL OF VIROLOGY, JULY 2001, 75:14, 6625-6634. "A MONOCLONAL ANTIBODY SPECIFIC FOR REOVIRUS OUTER-CAPSID PROTEIN σ3 INHIBITS σ1-MEDIATED HEMAGGLUTINATION BY STERIC HINDRANCE" EMMA L. NASON, ET AL. REPRODUCED WITH PERMISSION FROM AMERICAN SOCIETY FOR MICROBIOLOGY.



When researchers combed through blood samples of people with celiac against controls, they found one thing linking people with celiac: higher levels of antibodies to reovirus (virus model shown here). This confirmed what Dermody and Jabri found in mice with a genetic disposition to celiac.

finishing touches on a manuscript for *Science* about how viruses exploit the bacteria within the intestinal microbiome to speed their own replication and transmission. Previously, he'd worked with a team detailing the biochemical choreography of reovirus infection and immunity within Peyer's patches and identified host receptors that reoviruses leverage for their own gain. "One of the key elements [virologists] are studying is what's required in order to defend ourselves against a virus and get rid of it," says Jabri. "As an immunologist working on autoimmune disorders, I want to know why the immune system starts recognizing self and other antigens as dangerous."

Together with funding from the National Institutes of Health—a $3.2 million, four-year grant awarded in 2014—they got down to business. Their first task was for Dermody's group to create two genetically engineered reoviruses that would each infect the mouse intestine and precipitate viral antibody production, without causing physical symptoms or tissue damage. Strains labeled T3D-RV and T1L fit the bill. Although T3D-RV-infected mice developed lower reovirus antibody levels than those exposed to T1L, the two strains had a similar effect on Peyer's patches—security was summoned (i.e., antigens appeared), but little else happened. That's what the researchers expected.

Next, Dermody and Jabri turned their attention to food antigens, looking for differences in immune function among mice infected with each strain. Scientists have long used egg protein as a way to study food tolerance and allergies in mice, so the team fed its T3D-RV- and T1L-infected mice the egg protein ovalbumin. Those exposed to T3D-RV were unaffected. But in the T1L-infected mice, immune system signals got crossed, and they promptly developed an egg allergy.

"What really made this a good science day was that we had two closely related strains of reovirus," says Dermody, "one that blocked tolerance and the other that didn't. We could investigate the underlying immune response to food as a dangerous substance, as opposed to an innocuous substance."

In their third set of experiments, the team subbed in a line of mice engineered with a genetic predisposition to celiac and infected them with one of the two reoviruses. Instead of the egg protein, they fed the mice a big dose of gluten. Again, the T3D-RV mice sailed through. The mice infected with T1L experienced an inflammatory response that looked a lot like celiac. Somehow the mouse's food and virus recognition complex had been turned around. Gluten not only fell off the A list—it was suddenly seen, not as food, but as a dangerous viral pathogen. A gut-wrenching case of mistaken identity.

Dermody and Jabri want to explicate the pathways by which T1L triggers intolerance of food antigens.

First, however, they tackled a question too intriguing to ignore: Do *people* with celiac have heightened antibodies to particular viruses?

Jabri and a colleague, University of Chicago gastroenterologist Carol Semrad, had blood samples from patients with celiac, as well as gender- and age-matched controls with and without the celiac genes. The researchers combed through all of the samples measuring titer—the level of antibodies to a given antigen—for reovirus, rotavirus, herpes simplex, and even tetanus. (Basically everyone these days gets a tetanus vaccination, so tetanus served as an extra control to reveal whether folks with celiac just exhibit amplified anti-

body levels across the board.)

People with celiac stood out in only one regard—they had higher reovirus antibody levels than those without a diagnosis, and they were significantly overrepresented among those with very high reovirus titers. Otherwise, their titers were unremarkable. Apparently, certain forms of reovirus can profoundly confuse the biochemical signaling within the part of our adaptive immune system dedicated to food antigens.

The work is far from complete.

"We understand, immunologically, the switch that is thrown that leads food to be tolerated or not," Dermody says, "and we have a clue about reovirus and celiac." But more investigation is required to understand timing and causal elements of the relationship.

Somehow, with celiac, the body forgets that gluten has a VIP pass to the intestinal club.

Dermody and Jabri have studies under way to test whether a reovirus vaccination can keep mice with the celiac gene from developing the disease. If it works, they'll have made the case that for people at high risk, a vaccine might prevent full-blown celiac. They're also designing a prospective study to follow children with a genetic predisposition, monitoring their viral antibodies, weaning, and solid food introduction for better clues about when and how celiac manifests. The work also has the potential to reveal other viruses that can derange the same delicate signaling pathways reovirus affects. Meanwhile, both Dermody and Jabri have a host of questions about the role of the microbiome, as well as the effect of the timing of a viral infection on subsequent immunity dysfunction.

Michele Dorfsman, an MD associate professor of emergency medicine at Pitt, and her children were diagnosed with celiac in 2015, when her youngest was 9 and the oldest was 14. Various digestive issues had plagued the four for as long as they could remember. Then Maria, the youngest, developed severe tummy aches and anxiety. She started seeing a therapist, and her pediatrician treated her for constipation. Her symptoms escalated, however, and she was finally admitted to the hospital. As part of her inpatient bloodwork, the lab checked for gluten antibodies. A biopsy of her villi confirmed celiac. "Now that I quit eating gluten," says the sixth grader, "I feel amazing. I feel really happy, not sad anymore."

The transformation was incredible, says Dorfsman. "Maria jokes that she had to go to a therapist because of her celiac."

At the time, however, it was no joking matter. Celiac genes run in families, so Dorfsman and the older children were screened, as well. The elder, Elena, had a positive biopsy though her endoscopy looked normal. Fourteen-year-old Oscar, however, had ulcers. The severity of his presentation also helped to explain a mystery that had confounded the family since his infancy. "When Oscar was 1, he weighed 22 pounds," says Dorfsman, who notes that her son hovered in the third percentile for height and weight throughout his childhood. "When he was 2, he weighed 20 pounds." A failure-to-thrive workup at the time yielded no insight.

Then the family eliminated gluten. Oscar grew four inches in two months, and Dorfsman, who is the program director for Pitt's emergency medicine residency, discovered that her very long list of food intolerances evaporated. The renewed ability to enjoy avocado, broccoli, cantaloupe, cauliflower, pineapple, and zucchini has more than made up for the pizza she foregoes at resident events.

"My GI tract was just so messed up that I was reacting to a lot of different things," she says.

Dorfsman's family says the boost in overall health has been well worth the hassles of going gluten free.

That said, each would happily have opted for a vaccine, if one had been available, to preserve their gluten tolerance.

"Couscous," says Maria.

"Chicken nuggets," adds Elena.

"Pizza and hamburgers with real buns," says Oscar. "Sourdough bread. Baguettes. Bread bowls."

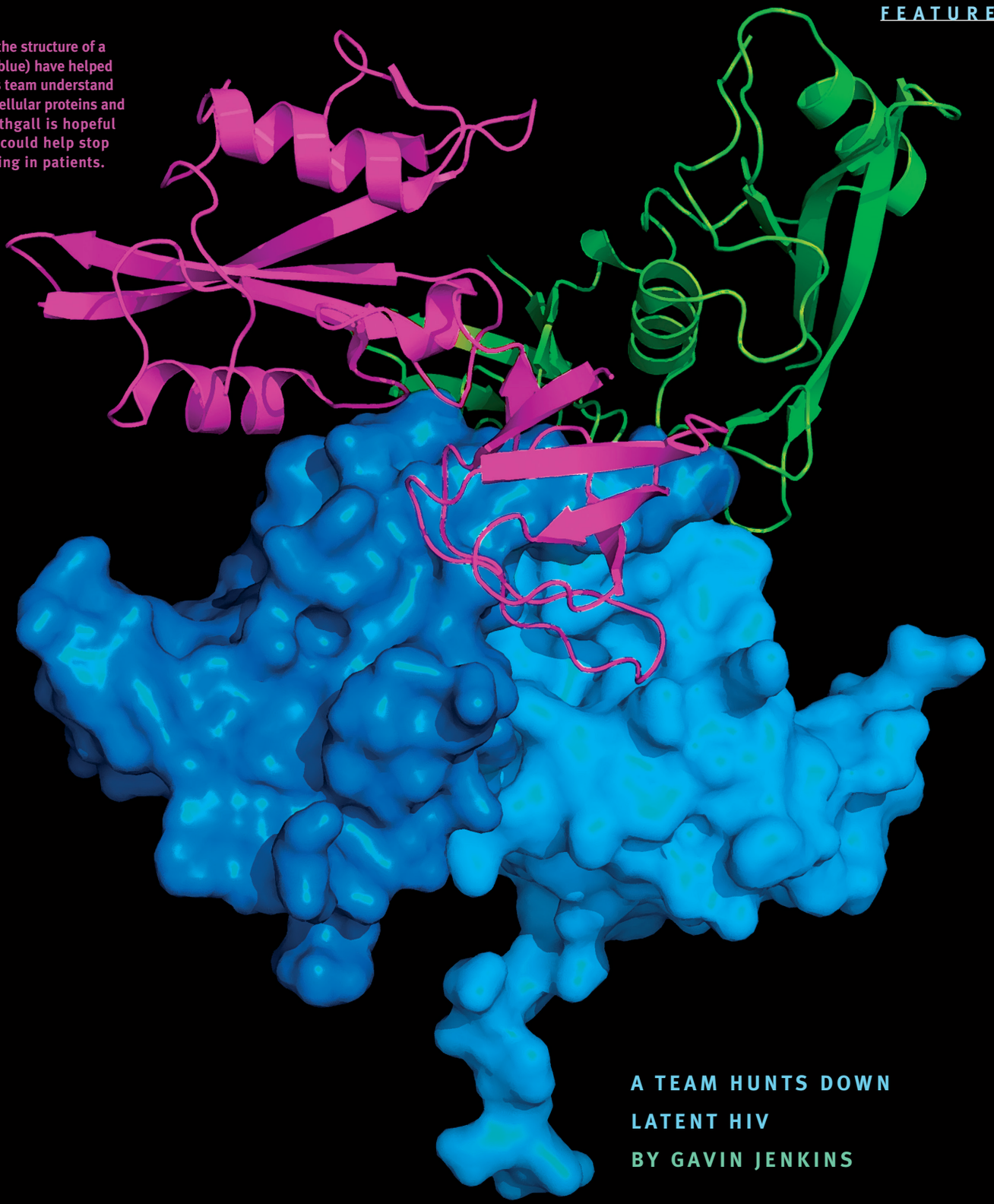
As passionate as Terry Dermody is about exploring reovirus, he's equally intent on training aspiring scientists. With ever increasing numbers of his trainees launching their own labs—often leveraging the projects they started under his tutelage—the field has been getting crowded. "I wanted my postdocs to be able to take their reovirus scholarship and use it as the foundation for their own independent careers," he says. "I wanted to be out of their way." So even as the work with Jabri continues, Dermody is increasingly focused on chikungunya, a mosquito-borne virus common in Africa, Asia, and the Indian subcontinent.

Most people clear chikungunya. But a select few develop severe, lifelong arthritis. Understanding how a blood-borne virus makes its way to the joints could offer insight about how viral invaders circumvent human host barriers to affect a particular system or organ, whether the liver (as in hepatitis), the brain (encephalitis), or the joints (chikungunya). "What's the beacon calling the virus to that spot?" Dermody wonders. "And once it lands, how does it initiate an infectious cycle and destroy the cell?"

A rewarding career, Dermody frequently tells students, is at the intersection of three circles inscribing personal talents, personal passions, and things the world needs. Find the space where those three overlap, he says, and you can change the world.

Yet for Dermody, who leads a major Pitt department as well as both the clinical and research programs at Children's, the idea that his basic inquiries into the biology of an innocuous virus could actually reduce human suffering in his own lifetime is still a thrill: "I couldn't have imagined in the spring of 2010 that we would ever get to the point where we might alleviate a condition that is prevalent in one in 130 Americans.

"To be able to help in that way, with our very basic research studies, learn new things about pathogenesis and preventatives, is pretty gratifying." ■



Insights regarding the structure of a protein called Nef (blue) have helped Thomas Smithgall's team understand how it attaches to cellular proteins and turns them on. Smithgall is hopeful that blocking Nef could help stop HIV from reemerging in patients.

IMAGE: AMY SMITHGALL

A TEAM HUNTS DOWN LATENT HIV

BY GAVIN JENKINS

NEF BUSTERS

John Alvarado is pretty good at scooping up salt grain–size Nef protein crystals. This task is like fishing out leaves from a swimming pool—except, well, a lot harder. Alvarado's "skimmer" is a metal rod, about as big as a pen, with a 20-micrometer diameter hoop attached; he needs to magnify the tip to even see his hoop. Alvarado is a PhD research assistant professor of microbiology and molecular genetics at the University of Pittsburgh and an x-ray crystallographer. When he was a grad student at Purdue University, he made his own tool by supergluing nylon loops to rods.

This meticulous and usually grueling approach to studying proteins is not a job for over-caffeinated scientists with jittery hands. The crystalline nuggets can stick to the bottom of the slide or slip around in the solution.

Even with more than 15 years of experience, Alvarado might take eight hours to capture 20 crystals. He estimates that 10 percent of the crystals he harvests are physically damaged and not suitable for the next step—shooting x-rays though the crystals to see the diffraction patterns.

X-ray crystallography gives scientists a picture that offers clues to an atomic protein structure. Imagine, you aren't shown a prism, but you are shown the pattern of light that emerges after a lightbeam is shone through the prism. From that pattern, you are expected to figure out the shape of the prism. That's akin to what x-ray crystallographers do as they solve the structure of proteins.

The outermost surface of a protein creates an electron cloud that diffracts or scatters x-rays. (The more ordered the protein molecules packed inside the crystal, the higher the resolution of the diffracted rays—and that means more structural clues are revealed.) By applying the diffraction data, scientists can connect the dots about protein structure by determining where each amino acid must be.

Alvarado's expertise in this field has made him a key member of Thomas Smithgall's laboratory team, a group that's applying newly found knowledge about Nef to figure out how to stop HIV from hiding from the immune system.

In 2016, Smithgall's lab landed a spot on the BELIEVE (Bench to Bed Enhanced Lymphocyte Infusions to Engineer Viral Eradication) project. Funded by the National Institutes of Health (NIH) with a five-year, $28 million grant, this 18-center consortium aims to find ways to eliminate hidden HIV reservoirs through a cell therapy approach that will focus on augmenting natural immunity specific to each patient.

This tactic has been borrowed from breakthroughs in cancer treatment showing how the immune system can fight back when strengthened. Smithgall, the William S. McEllroy Professor and chair of microbiology and molecular genetics, notes that, like cancer, HIV can come back. Because of hidden viral reservoirs, HIV will reemerge if a patient stops taking antiretrovirals—even after years of treatment.

"It's fair to say this is a big part of what AIDS research is right now: defining the so-called latent viral reservoir and then coming up with approaches to wipe it out," Smithgall says.

To figure out how to eradicate these reservoirs, Smithgall says that his team has taken on an "agonizingly slow process" of experimentation. One morning this summer, Smithgall, Alvarado, and Haibin Shi, a PhD research assistant professor who moved to Pittsburgh from Tianjin, China, gathered in a corner of the lab and laughed about how "extremely interesting and frustrating" it is to search for a cure that has eluded scientists for more than 30 years.

But Alvarado later adds that driving to the lab, located off Technology Drive along the Monongahela River bank, can feel like "going to playtime every day. … It's always exciting, and it's never the same."

And despite the vexation and intrigue inherent in his work, Smithgall, 57, always seems to be smiling. (He's a native of Reading, Pa., who studied and trained at the University of Pennsylvania and the NIH.) In his large corner office, the size of which he likes to joke about, there's a bookcase filled with gifts from PhD students who have worked with him through the years. One student drew a portrait of him; others have added to his growing Penguins and Pirates bobblehead collection; some Chinese students have presented him with bottles of baijiu, a grain alcohol.

One of his favorite gifts to show off is on a shelf near the floor. On an August morning, he's laughing before he can slide out the book: a former PhD student's bound thesis with a yellow and black cover that reads, *Nef for Dummies*.

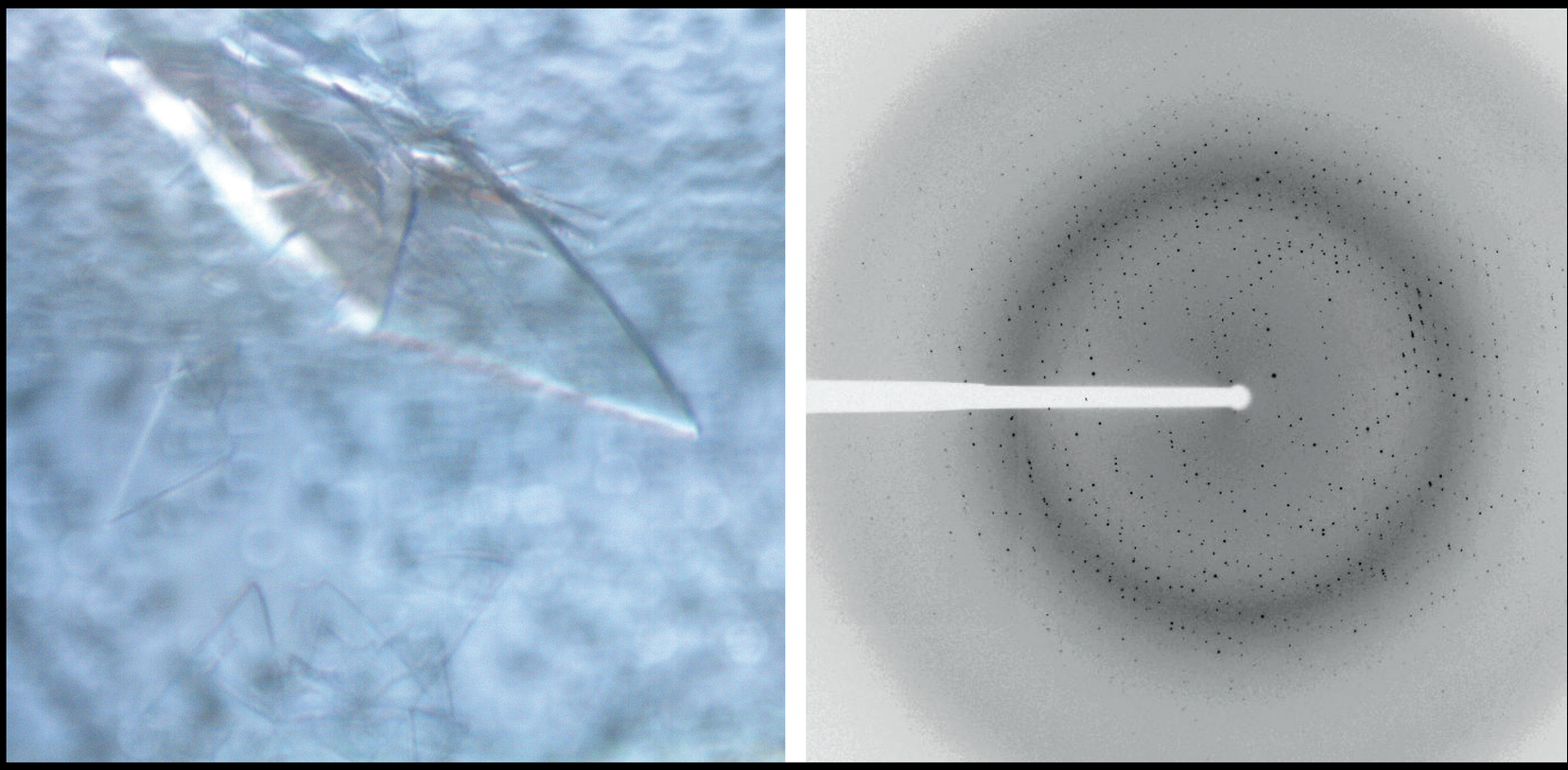
For Dummies is a series of textbooks that takes a complex subject and explains it in a digestible way for a common reader to understand. Like *Auto Repair for Dummies*.

Nef (negative regulatory factor) is an HIV accessory protein that helps the virus block the host cell's communication with the body's immune system. Smithgall has been examining Nef since Pitt recruited him in 1998; and earlier this year, his team reported on a synthetic molecular compound that, during lab tests, inhibits Nef and reestablishes communication between the infected cell and the immune system. With Nef inhibited, the immune system was able to kill the HIV-infected cell. Smithgall's group tested 250,000 compounds over an 18-month period before finding one that seems to stop HIV from hiding from the immune system. The lab's role in BELIEVE centers on Nef.

Unfortunately, *Nef for Dummies* doesn't actually exist, but Smithgall would probably enjoy writing such a text.

He explains that after HIV infects an immune cell known as a CD4 T cell, Nef removes a molecule called MHC-1 from

J.J. ALVARADO AND T. SMITHGALL



LEFT: These crystals took more than three months to grow. They are crystallized versions of the Nef protein as it binds to a kinase in the immune system of its host. Nef is an HIV-1 accessory protein that shuts down the immune response to HIV-1. Inhibiting Nef may help patients use their own immune systems to fight latent HIV reservoirs. RIGHT: The high quality of the crystal and the diffraction patterns it created on this x-ray crystallograph allowed John Alvarado in Smithgall's lab to figure out Nef's structure as it binds to the kinase.

the cell's surface in a process called immune escape. Typically, the immune system has a mechanism to recognize virally infected cells and ignore uninfected ones; but Nef eliminates this line of communication, preventing the immune system from being activated despite the presence of HIV.

"The promise of developing drugs or inhibitors for Nef is that they could restore, or perhaps prevent Nef from downregulating, MHC-1," says Smithgall. And once viral antigens have been restored to the cell surface, the body's immune system could wipe out the virally infected cells.

After reporting the first drug leads for Nef in 2013, Smithgall's lab garnered attention from researchers who wanted to team up. Smithgall credits Douglas Nixon, chair of microbiology, immunology, and tropical medicine at George Washington University, with putting together the BELIEVE project. The partnerships are already paying off.

Earlier this fall, Smithgall and Lori Emert-Sedlak, a PhD in pharmacology and a research assistant professor in his lab, coauthored a paper in the *Journal of Clinical Investigation* with Mario Ostrowski at the University of Toronto. The paper shows that Nef inhibitors discovered by the Smithgall team can indeed reverse Nef-mediated immune escape by HIV-infected cells from patients.

Emert-Sedlak coordinated the screening campaign with Paul Johnston in the School of Pharmacy, and she estimates that they tested 50 to 70 plates of 300 compounds each day. The process took 18 months because they had to continually make and test new protein batches and then perform follow-up tests for promising compounds to be sure the results could be replicated.

As exciting as their discoveries are, it's a long road from a proof of concept inhibitor to something that can go into a pill, notes Smithgall. The team found compounds with useful inhibiting properties. But that doesn't mean the compounds can be absorbed orally, get along with the liver, or meet other stringent requirements of a new drug.

Emert-Sedlak and Shi, together with research technologist Li Chen, make up the frontline team that conducts the first phases of testing potential drugs, or analogs, for Nef inhibition. (Analog synthesis is done in partnership with the Fox Chase Chemical Diversity Center, in Doylestown, Pa., and is funded through an NIH Small Business Technology Transfer Research Grant directed

by Smithgall.) Emert-Sedlak also developed many of the assays that the lab is using now to assess drug candidates. The team had been conducting experiments from cells easily grown in culture and infected with HIV. It's now testing cells derived from blood from both healthy donors and HIV patients.

"These cells are as relevant as we can get before going into animal models," Emert-Sedlak says. (She notes the CD4+ T cells from patients can be difficult to work with since they have a "very defined and short life span.")

Shi manages a new surface plasmon resonance (SPR) detector, which gives real-time data on the interaction of each analog with Nef. The team is looking for an inhibitor that binds quickly and remains bound to Nef.

Compounds that show promise move to a second phase where they are crystalized and x-rayed by Alvarado. At the same time, they are tested on mouse models by Sherry Shu, a PhD research assistant professor.

Smithgall wants the members of his team to understand and appreciate how much HIV/AIDS research has changed. He encourages everyone who works in his lab to read David France's book, *How to Survive a Plague*, about the epidemic's early years, so they don't lose sight of the groundwork that came before them or the devastating number of deaths attributed to HIV—about 35 million people. Now his lab may help lead the way to a cure.

"This is what we're working for," he says.

Advancements in technology have accelerated progress in HIV research, and there are reminders of this throughout Smithgall's lab. Some seem subtle, like the SPR detector that Shi excitedly points out during a tour.

Other signs are more obvious, like the "nice robot," as Alvarado calls it. To make protein crystals, Alvarado mixes 200 nanoliters of crystallization solution with 200 nanoliters of purified protein. In just five minutes, the robot drops the mixture into 96 wells. Alvarado used to do this part by hand—that task alone would take him a full eight-hour day.

Later, he'll sit down at a microscope and look at the drops for crystal nuggets to scoop for x-ray experiments. Crystals might form overnight or take weeks or months to grow.

While at Purdue in the 1990s, Alvarado didn't think his x-ray crystallography skill set translated well to where HIV/AIDS research was then. He says no one studied HIV or any other retroviruses at Purdue at the time, and, unlike other viruses that interested him, not much was known about the structure of HIV. Alvarado notes that the HIV envelope protein structure was only just determined in 2012.

"I did not want to study HIV because it was too complicated," Alvarado says.

After graduating from Purdue, Alvarado landed a postdoc position at Albert Einstein College of Medicine, where he analyzed proteins in a herpes virus. In 2009, when he accepted a job in Smithgall's lab, Alvarado still considered HIV to be a daunting field. But he was confident in his level of expertise, and with good reason. His insights regarding the structure of Nef have helped Smithgall's team understand how it attaches to cellular proteins and turns them on.

Now Alvarado is working on determining the three-dimensional structure of Nef when it is bound to an inhibitor. Smithgall says that figuring this out will offer unprecedented insight regarding how their compounds work. He adds that solving this structure would also give his team a clearer path to developing a generation of compounds that can be tested in animal models and ultimately in people.

Alvarado is optimistic about where the team is headed, saying, "We're close." ■

TICK SPIT FOR THE TICKER

Even when they are on antiretroviral therapy, people living with HIV are almost twice as likely to suffer from cardiovascular disease than those without the virus. However, researchers from Pitt and the National Institute of Allergy and Infectious Diseases (NIAID) report that a chemical in tick saliva may help these patients.

The researchers found that HIV patients had an elevated number of immune cells called monocytes; these cells were producing high levels of a protein called tissue factor, which is linked to inflammation and blood clotting. The monocytes were present regardless of how well a patient's HIV was being controlled with antiretroviral therapy.

A team led by Irini Sereti, an MD at the Laboratory of Immunoregulation at the NIAID, exposed blood samples to Ixolaris, an experimental drug based on an anticoagulant found in tick saliva. Sereti's group found that the compound shut off tissue factor activity in monocytes.

Pitt's team, led by Ivona Pandrea, MD/PhD professor of pathology, focused on the causes of inflammation in HIV patients and primate models, a topic Pandrea has been examining for a decade. The cause isn't the same with each patient, but Pandrea says one of the most common explanations for inflammation stems from what happens in the gut shortly after infection. The virus destroys immune and epithelial cells there, allowing bacteria to spread through the bloodstream.

"Of course this bacteria stimulates a lot of immune cells and creates a vicious cycle, because stimulating more cells [creates] more targets for the virus, more virus replication, then more gut problems," says Pandrea.

Hypercoagulation (too much clotting) also causes inflammation, and Pandrea notes that this is often misinterpreted to mean problems in pulmonary arteries. But it's a tissue problem as well as a peripheral one, she says. Microscopic clotting can show up in small blood vessels in the kidney, lung, gut, or brain.

"When we see these problems, we don't know if they have a common cause or if they occur independently," Pandrea says. "I think hypercoagulation may be a good explanation for connecting these comorbidities." *—GJ*



Pitt Med alum Jodie Bryk (at the wheel) en route to a patient's home with Jeanette Valentine

HOME AGAIN

HUDDLING UP AROUND HIGH-NEEDS PATIENTS

BY ELAINE VITONE

PHOTOGRAPHY BY JOHN ALTDORFER



Seven women circle a conference table on the sixth floor of UPMC Montefiore, running down their patient roster and wrapping their collective hivemind around no fewer than 140 names. It's a primary care practice—but on steroids. Both MDs, all three RNs, the staff social worker, and the administrative assistant all sit down together for this morning meeting five days a week.

Each patient's case is the kind most primary care docs would call their most challenging. At 8:30 a.m., they're just halfway through the list, and they've already covered: a trauma survivor who is so terrified of her (male) orthopaedist that someone she trusts has to go with her; a man who's working two jobs so his girlfriend, who's in a federal prison, can buy palatable food from the commissary; and a mother of two who, since her husband's deployment, has been too depressed to take her antidepressants, let alone keep up with her pulmonary rehab.

Welcome to the "huddle meeting."

This morning ritual is a staple of the UPMC Enhanced Care Program (ECP), a suite of services based out of Montefiore's General Internal Medicine Clinic. The brainchild of a University of Pittsburgh faculty member, ECP was designed for people with complex medical and psychosocial needs—"super utilizers," as they're known in the literature for their frequent visits to the emergency department. These patients' advocates often cite that 5 percent of Medicaid enrollees account for half of all Medicaid spending.

Among these advocates is Jodie Bryk (MD '09, Res '12, Fel '14), medical director and architect of ECP, and clinical instructor of medicine at the University of Pittsburgh. She sees her unique patient load as a window into issues that affect public health on a grand scale.

Bryk ticks through the list of names. Some are a quick mention ("*Audrey Lane… Jack Lee* …"). Others become the focus for several minutes' worth of round-tabling. (We've changed patient names and details.)

"*Cheryl Leyden*," Bryk says—a woman in her 50s, I later learn, who has severe chronic obstructive pulmonary disease (COPD), among other illnesses. "She was doing excellent yesterday." Bryk adds that she gave Leyden tips for quitting smoking, like switching to an e-cigarette first. "And I told her husband on the phone that he has to do it, too."

"I mean, Cheryl *gets* it," says social worker Jeanette Valentine. "She repeats it back to you! It really seems like she's gonna do it."

Everyone agrees.

"*Wayne Lowe*," says Bryk.

"He just got discharged yesterday," says Patricia Englert, an RN. She knew the moment this patient left the hospital, thanks to Augr, an app that UPMC developed to buzz the ECP staff every time one of their patients checks in or out. Augr makes timely follow-up—which keeps readmissions down—much easier. It's helpful when patients are admitted, too. For example, Bryk once had a patient who was so petrified of having a second heart attack that he went to the hospital every time he sneezed—267 emergency department visits in one year. So she started

OPPOSITE PAGE: **Bryk designed ECP three years ago for UPMC patients with complex medical and psychosocial needs.** BELOW: **On day one, each new ECP patient's prescriptions are sent to ACORx, a pharmacy based in Carnegie, Pa., that pre-sorts and labels medication doses and delivers these "med packs" to the patient's door.**



intercepting him in the waiting area and bringing him upstairs for an EKG in the clinic instead. It took a few months to reassure him—but it worked.

"*Dana Moore*," says Bryk. "She did great yesterday. All her health maintenance is up to date: mammogram, colonoscopy …"

"That's *my* patient," says Theresa Goldston, a BSN and RN.

Everyone laughs.

"*Danny Newman*!" Bryk practically sings.

"Yaaaay Danny!" says Engler—he's *her* patient. But everyone at the table knows what a big deal it is that his blood pressure is stable. And that's the whole point of the huddle. If a team member is out sick or on vacation, patients don't lose ground.

"*Stephanie Nowak*," says Bryk.

Across the table, Kim Kunkle, an RN, takes a deep breath. Yesterday, she says, she was reviewing paperwork and, after a little investigating, figured out that the 30-something-year-old had finagled a way to double-dip opioid scrips.

The room tenses.

"I had a long talk with her on the phone yesterday," says Bryk. "These were the options I gave her: Self-taper—and I'll give you those instructions; or detox at Mercy; or rehab at Western Psych. She voted none of the above and said she *needs* the medication."

Anita Leon-Jhong, an MD, laments, "Chronic opioids are not shown to improve chronic pain. They *don't work*. They [can] make you tolerant and more sensitive to pain, and then some people get really addicted."

Bryk continues. "Stephanie was like, *You gotta understand, I didn't know what to do*. I said, 'Hey, we gave you a whole *plan* for what to do: physical therapy, behavioral health.' And she hasn't followed through."

"What did she say to that?" asks Kunkle.

"She got really quiet," says Bryk. "She said she wanted to come in. I told her I'm not dismissing her. I'll still treat her, but on the *right* treatment. And then she asked to move up her appointment. So if you want to be there…"

"Absolutely, I do," Kunkle says.

"Because I think I'm gonna get different stories," Bryk says.

"Absolutely, you will," Kunkle says. "Because her parents! They mean well, but they're making excuses for her!"

And the whole room answers in chorus, "*Yeah*!"

This is a team that notices things: Which patient has a dad with a cancer diagnosis and just might be diverting his painkillers. Whose housing just fell through because now the landlord suddenly wants more money up front. Who is grieving. Who has gone back to her abusive boyfriend—again—and needs to hear that the safety net is still here for her. Who always sounds like he's at death's door, but 9 times out of 10 is just calling because he's having a bad day. Who is still in the ICU and, in the professional opinion of her nurse (Englert), "needs a hug."

The team knows, because in addition to scheduled clinic visits—which can be arranged same-day, as needed—they regularly see patients in their homes. Because patients are able to reach them directly, 24/7. Because every new ECP enrollee gets a 90-minute intake, a detailed medical-history report dating all the way back to the earliest appointment on record, and a comprehensive plan for the way forward. And because the whole hivemind huddles up and downloads around the status of that plan every day.

At this moment, Stephanie Nowak is on the precipice of falling headlong into opioid addiction. The ECP team will put everything they've got into saving her from this modern epidemic, but the approach they use looks surprisingly … old school. It's not a battery of tests, a clinical trial, a new pill, a million data points, (though statistical tools certainly help—more on those later). Most of all, it's building relationships, noticing things, and following up. It's a throwback to the very start of Western medicine:

The house call.

Bryk speaks with a Cleveland accent, but she grew up on a dairy farm 50 miles outside of the city. Her dad, who trained as both a veterinarian and an MD, and her mom, an RN, did outreach in rural areas and convinced Amish bishops to implement vaccination programs. After that, families who'd never felt comfortable going to a hospital would buggy up to the Bryk farm with sawed-off fingers. "My dad would suture them up and stabilize them to get them to the right place," she says. "It was kind of fun."

Bryk learned to work with people's belief systems: *Yes, you should pray—for the surgeon who is going to operate on you*. She came to see trust as something that did not come easy—but it was absolutely worth the ride.

Bryk found a comfortable fit at Pitt, where the medical school and its clinical partner,



Valentine, a social worker, is part of a multidisciplinary team providing wraparound services for ECP patients.

UPMC, have a long and storied history of rooting the biology of the brain firmly in human health. She completed her MD and internal medicine residency, then stayed for concurrent fellowships in Psychiatry for the Internist and Public Service Psychiatry.

Around this time, a new movement was gaining steam. Atul Gawande wrote a *New Yorker* piece about Jeffrey Brenner, a Camden, N.J., physician who studied billing data and found that high-cost care tended to "hot spot" in geographic areas. Brenner created wraparound services for high-needs patients. Health care systems across the country have since noted the promise of this approach and done the same.

Three years ago, Bryk designed ECP for patients caught in a revolving door of emergency department visits and hospital stays that are largely preventable. (Patients with complex needs in end-of-life care are outside of the program's scope, Bryk notes, adding that for those patients, UPMC's Advanced Illness Program is a better fit.) ECP patients are often contending with what experts call the social determinants of health: childhood trauma, domestic violence, financial strain, hunger, functional illiteracy, transportation difficulty, language barriers, inadequate housing, and homelessness.

With conditions like renal disease, emphysema, and heart disease on top of those difficulties, diagnoses multiply. Specialists enter the picture. One hand doesn't know what the other is doing. And cruelly, "the system" proves most complicated for those who have the most barriers to navigating it.

So ECP helps break those barriers down.

"They'll have 15 meds on the table," says Bryk, "and I'm like, '*I* could not reliably take all these!'" On day one, ECP switches each new patient's scrips to a single, centralized pharmacy that presorts the doses and delivers "med packs" to the patient's door. The ECP team also helps patients manage the cost: by switching to generics, hunting down coupons, calling the pharmacy to ask if they'll waive the copays Medicaid won't cover.

If a patient has diabetes, for example, ECP staff can make a house call to watch him run through his glucose-monitoring and insulin-injection routine to ensure he's got it down pat. They can bring a podiatrist to perform a foot exam. They can even use a telemedicine-enabled camera to have an eye doc back in Oakland perform a retinal exam remotely.

On a recent fall morning, as Bryk and I drive to a patient's home, she tells me about other needs that don't typically make it onto a medical chart. ECP team members have packed up and loaded moving boxes. They've reconnected patients with long-lost loved ones. They've held patients' hands as they've made the first unsteady steps outside after a long illness. For Cheryl Leyden—the woman we're on the way to see now—her nurse once made a trip for the express purpose of taking her, finally, back to church. And then, to bingo.

We arrive at a brick house with a flower bed full of toys. "Hi! Have a seat if you can find one!" Leyden says, standing to greet us, tethered by tubes pumping oxygen into her nostrils via an air compressor that hums loudly from the back of the house. Apart from the fleet of oxygen tanks in the corner, it's a typical old Pittsburgh home: hardwood floors, a piano in the front room. Leyden's grown daughter curls up on the couch with her own preschool-age girl, brushing her hair; the youngest, 15 months old and wearing a Minnie Mouse shirt, toddles at our feet.

"You're walking already!" says Bryk, and the moms talk milestones. Bryk has a little girl, too.

It's been a week since the huddle meeting with the encouraging progress report from Bryk regarding Leyden. Then, three days later, Leyden had a scare: severe headache, hand tremors, spikes in her blood pressure. Most emergency physicians would've admitted her on the spot, but Bryk was able to rule out worst-case scenarios with lab work in the clinic. Those tests also showed a possible explanation for the symptoms: Leyden's phosphorus level was low.

Bryk explains she's here to draw some blood to check it again and to administer a flu shot, in addition to the usual home-visit routine: a chat on the couch about nutrition and other behavioral factors, and a check-in on how well Leyden is keeping up with her pulmonary rehab and medications. Bryk can see the latter at a glance, simply by looking at the med packs. These kinds of preventive and vitals monitoring visits are crucial to keeping Leyden in the clear—but it's not easy for Leyden to get to the clinic at Montefiore. From Leyden's home, it's 90 minutes on the bus each way; and that's with oxygen in tow.

"How's that tremor?" Bryk asks.

"I've still got it," Leyden says, showing us her shaking hands.

"We're setting up an appointment with the neurologist at UPMC. I mean, it could be from the steroids you're on; but we should definitely get that checked out, because it's getting worse."

"It is, it is," says Leyden.

"And how are you doing on the smoking?" Bryk says.

"About five to seven" cigarettes per day, she says—an improvement.

"I'm telling everyone: the e-cigarette!" says Bryk. "You don't miss the habit, because it's not like you don't have anything in your hand anymore. And it's gonna be cheaper. We've gotta get your husband to do it, too."

Leyden nods "yes" and says it all back—she

really *does* seem like she's going to do it.

We watch the baby play as Bryk gets to work with her blood pressure cuff, stethoscope, and syringes. Leyden's blood pressure is much better today, *whew*, and no signs of new trouble in her lungs, either. After last week's scare, Bryk is relieved, she says—and so happy with how things are going.

"I remember when you first started the program, you had that swelling in your legs," says Bryk. Back then, Leyden was in and out of the emergency department every month. "They were telling you that you had to go to a nursing home. You showed them. You worked *hard*."

"Sure did. They said I'm gonna be on this oxygen for the rest of my life. I said, 'No, I'm not! God is gonna heal my lungs. I'm gonna get off this oxygen!'"

"I think if anybody is able to do it, it's you," Bryk says, smiling. "I think you've got what it takes." But the hardest part will be the smoking, she says—pray for the strength to quit smoking.

In a paper published in *Population Health Management* in September, the ECP team shows that in the program's first 30 months, their patients' emergency department visits decreased by half, and unplanned care overall significantly decreased. The program has also shown improvements in quality metrics for diabetes and hypertension care, cancer screenings, connection with mental health providers, and weaning off opioids.

Supporting the old-school house calls is a wealth of data, courtesy of UPMC's services division, which funds ECP. They're in constant cross-talk with the team, brainstorming new services. As an academic health care center and one of the largest payer/providers in the country, UPMC Health Plan has a treasure trove of population data—a powerful complement to the on-the-ground insights of Bryk's team, says Marion McGowan, the division's chief clinical officer and senior vice president for population health. By comparing patients who share similarities, for example, "we can see who tends to respond when we give them a call or when we offer a coaching opportunity," she says.

ECP is going so well, says James Schuster, an MD and chief medical officer for behavioral and Medicaid services at UPMC Health Plan, that they're now working to grow the program to include people who have other primary care providers. Recently, UPMC announced a forthcoming study comparing the effectiveness of two approaches for high-needs patients: home visits from nurses and social workers versus Web-based health tools. A $3.8 million grant from the Patient-Centered Outcomes Research Institute will fund the study.

Though ECP patients' emergency department admissions are down, other costs are up, like medications and screenings. Some preliminary data show inklings of programs like ECP saving money in the long run, notes Thuy Bui, the Pitt associate professor of medicine who approached UPMC with an idea for the ECP program back in 2013. But really, cost was beside the point.

"We thought, *How can we bring it all together and provide the best possible primary care to patients with high needs?*" Bui says, adding that her dream is to bring this level of high-touch to primary care overall. What patients really value, she says, is "seeing the same person, having a relationship with them, and having them know who you are. … They want to walk into a clinic and feel like they're at home."

Back at Montefiore, Bryk and Kunkle, the RN who spotted the coming storm in Nowak's opioid use, sit down for a heart-to-heart with Nowak and her father.

Taking controlled medications in an unauthorized manner is serious—the risk of overdose is high, Bryk says. "I'm no longer comfortable prescribing them." And then she takes it from the top one more time: self-taper, detox, or rehab. Bryk strongly recommends detox.

Nowak is scared—of a lot of things. But right now, mostly the stigma of addiction, and the looming threat of pain, which was once a constant companion. She doesn't want to go back to it.

So they make a compromise.

Bryk reaches out to a pharmacist and comes up with a plan to taper down the painkillers, as well as alleviate the racing heart and wrenching anxiety that might follow. Then she calls the UPMC Pain Medicine Program and gets Nowak an appointment that very day.

Nowak's dad pulls Bryk aside. "Thank you for doing this," he says, and fesses up—this has been an intervention for him, too. "I try to advocate for her," he says, "but I know what I'm really doing is *enabling* her."

One week in, Nowak calls Bryk and says she's doing well. Granted, these are early days yet, and the future is far from certain. Still, there's plenty to celebrate at the next huddle. Nowak didn't simply fire Bryk and look for another doc, another scrip. This patient is putting in the work.

And actually, she feels better off the opioids, she says. Finally clear again, and *here* again. Back to her real life, and family, and home. ■



"I think there's a really thin line between mental health and physical health," says Bryk. "I got interested in creating a clinic where we look at all of these things."

WE ARE THE MEDICINE MAKERS, AND WE ARE THE DREAMERS OF DREAMS



DREAMERS, DRUGS,

INSPIRED MEDICINE

BY RACHEL WILKINSON AND HEATHER BOERNER, WITH ERICA LLOYD AND MICHELE BAUM | ILLUSTRATION BY FRANK HARRIS

For a second consecutive year, the University of Pittsburgh has broken its patent record. The end of the fiscal year on June 30 saw a total of 102 patents issued, topping last year's record of 80. That puts Pitt in the top third of universities granted utility patents worldwide; many of the University's patents are in biomedicine and biotech. Last year, Pitt also spawned 29 start-ups (14 of which are student run).

This didn't just happen overnight, of course. To understand what's going on, you have to go back to 1980. That year saw the passage of the Bayh-Dole Act, cosponsored by Senators Birch Bayh and Robert Dole. The legislation allowed nonprofit institutions to own, patent, and commercialize inventions developed with federal research monies.

Before Bayh-Dole, any products of federally funded research were strictly owned by the government and difficult to gain the rights to. Potential advances often languished in labs with no clear path to get to the marketplace—or to the clinic.

Since 1980, more than 5,000 new companies have been launched from federally funded university research, contributing about $30 billion to the U.S. economy annually. In a 2002 op-ed called "Innovation's Golden Goose," *The Economist* argued that Bayh-Dole resulted in a "sudden reversal of fortunes" for a then-sluggish U.S. economy, bringing about "a flowering of innovation unlike anything seen before."

In the past couple of decades, people have been dreaming big around here. Chancellor Patrick Gallagher recently wrote in *Science*: "The [Pittsburgh] region clawed back from its economic breakdown by refocusing on technology innovation fueled by federally funded research at its major universities. . . . It is no accident that the top of the city's tallest building now advertises the University of Pittsburgh Medical Center—not U.S. Steel." Gallagher, who previously served as director of the National Institute for Standards and Technology, has strengthened Pitt's commitment to commercialization.

When Pitt people apply their ingenuity to human health, things get really inspiring. We've devoted the next several pages to showing you what their dreams are made of.

THOSE BLASTED KIDS

Pitt students are teeming with idealism and great ideas. The Blast Furnace was founded in 2015 to support the entrepreneurs among them.

9 weeks of intensive classes and mentorship

32 mentors in the program's history

6 cohorts of student entrepreneurs

13 health care concepts to go through the program

36 projects total to make it to market



OPEN-CONCEPT WEB SPACE

Ray Funahashi hasn't even finished medical school, and he's already seeking funding for his first start-up. "Problem-solving and innovation is what I love," says Funahashi, who is in his third year at Pitt Med. "I'm an idea person at heart."

His big idea? Remove the walls that researchers and students build around themselves and make it possible for them to find one another and collaborate for better science and better care. Think of the project, an academic portal dubbed LabKind (a play on "humankind"), as the open-concept work space of the Internet.

"Even in a lab two doors down from you, you don't know what they're working on," Funahashi says. "Some labs don't have a Web page at all."

LabKind is conceived of as a portal that consolidates and delivers information researchers, students, and faculty seek on a daily basis. The portal helps them share what they are working on in an easily navigated space.

Through the Blast Furnace, Funahashi met undergrad business student Drew Brumbaugh and **Luca Calzoni**, an MD/PhD student in bioinformatics, to create LabKind. The team graduated from Blast Furnace in summer 2016 and received second prize from the Innovation Institute at the Startup PittBlitz Competition. They also nabbed fourth place in the Randall Family Big Idea Competition. Now the team is looking for funding to complete its prototype and run a pilot program at Pitt. *—HB*



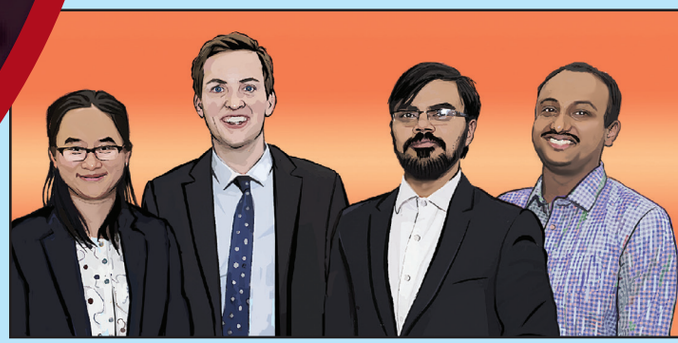
O_2 REDO

"Oxygen was discovered by Joseph Priestley in 1774. … It is therefore remarkable that oxygen treatment is still not widely available in low- and middle-income settings."

—International Journal of Tuberculosis and Lung Disease, 2010

The Problem: In areas without regular electricity or that have been hit by natural disasters, lack of access to supplemental oxygen can cause needless death.

The Promise: Access to supplemental oxygen can reduce the rate of children dying from pneumonia by 35 percent.



Solution, Take One: A portable hand pump that concentrates oxygen without the need for electricity, conceived by **James Newton**, a second-year Pitt Med student (shown above, in tie), along with (from left) Johns Hopkins neuroscientist Wendy Zhang, Pitt bioengineer Sushrut Bhalerao, and Carnegie Mellon engineer Ashwin Prabhu. That idea netted the team $500 for further development as third-place winner of the Blast Furnace Demo Day 2017.

But the students tried their prototype in Malawi and determined that the approach wasn't efficient in a real-world setting.

Solution, Take Two: A new design. The new idea? A solar-powered system to fill oxygen tanks at medical centers. "We are seeking funding to install the system in a health center in Malawi," Newton says, "to make observations and begin to work through logistical details." *—HB*

GOOD FOR MOM, TOO



"I guarantee you will think differently about the world once you witness the birth of a new life," says **Alysia Tucker**, a former doula (a professional who educates and assists women before, during, and after pregnancy). She birthed an app to make this blessed, though typically overwhelming, time a bit easier.

Tucker, a Graduate School of Public Health student, wants "to make sure women get connected to what they need." Hence Best4Baby, which links expectant mothers with doulas. Tucker won first place and $2,500 for the app at the spring 2017 Blast Furnace Demo Day. *—HB*

LAUNCHPADS

Pitt's Innovation Institute and other organizations at the University offer a number of programs to help biomed and biotech dreamers get their ideas off the ground.

BLAST FURNACE

Students on fire! (See p. 28.)

CHANCELLOR'S INNOVATION COMMERCIALIZATION FUNDS

Helps faculty investigators through the "derisking" stages between concept and market.

COULTER TRANSLATIONAL RESEARCH PARTNERS II PROGRAM

Each year, five $100,000 Coulter grants go to Pitt clinician-engineer teams focusing on biomedical interventions to address unmet needs. The Swanson School of Engineering–based program gets faculty boardroom ready.

MICHAEL G. WELLS ENTREPRENEURIAL SCHOLARS FUND

Awards up to $20,000 to Pitt students with ideas that could fundamentally change health care.

PITT INNOVATION CHALLENGE

A program of Pitt's Clinical and Translational Science Institute. (See "Pinch Us," right.)

PITT VENTURES FIRST GEAR

Often the first stop for students looking to figure out whether an idea has start-up potential. Pairs students with business mentors and provides $3,000 of exploratory funding via the National Science Foundation's I-Corps Site Program.

UP AND COMERS

Pitt Med students eager to contribute new ideas to medicine can now pursue the Area of Concentration in Bioengineering, Biotechnology, and Innovation.

PINCH US

The Pitt Innovation Challenge (PInCh) has been driving and rewarding innovation since 2014, granting more than half a million dollars a year to Pitt faculty and their teams to advance all manner of medical and scientific innovation.

In PInCh's very first year, Med Guardian, codeveloped by James Kaus (MD '15), won a $25,000 prize. The cell phone app is now known as Take Meds Now; it seeks to increase patient adherence to medications and to prevent some of the tens of thousands of accidental poisonings each year resulting from mismanaged medication. Take Meds Now went to market in June 2017.

These more recent PInCh hitters are also hoping to knock one out of the park.

TREATED IN UTERO

Imagine a way to prevent cerebral palsy and seizures, all in the womb and all without requiring a cesarean section of the mother at birth. That's the future Pitt's Stephanie Greene and Stephen Emery are working toward. Greene is an assistant professor of neurological surgery and a pediatric neurosurgeon at Children's Hospital of Pittsburgh of UPMC, and Emery is an associate professor of obstetrics, gynecology, and reproductive sciences and director of the Center for Innovative Fetal Intervention at Magee-Womens Hospital of UPMC.

Using technology developed to treat spina bifida in utero, they have designed a low-profile shunt that can be inserted in a fetus to drain fluid from the brain, preventing damage and, potentially, resulting conditions. It will likely be five years before they can test the shunt, called a ventriculo-amniotic shunt for fetal aqueductal stenosis (VASFAS), in humans.

NOW FEEL THIS

In his time as a neurosurgeon, Paul Gardner (MD '01), associate professor of neurological surgery, says he's "never seen anything that truly amplifies nerve healing." Mostly, he says, surgeons reconnect the nerves and hope for the best. Usually, incomplete nerve regrowth means a loss of motor control, selective weakness, and, potentially, pain.

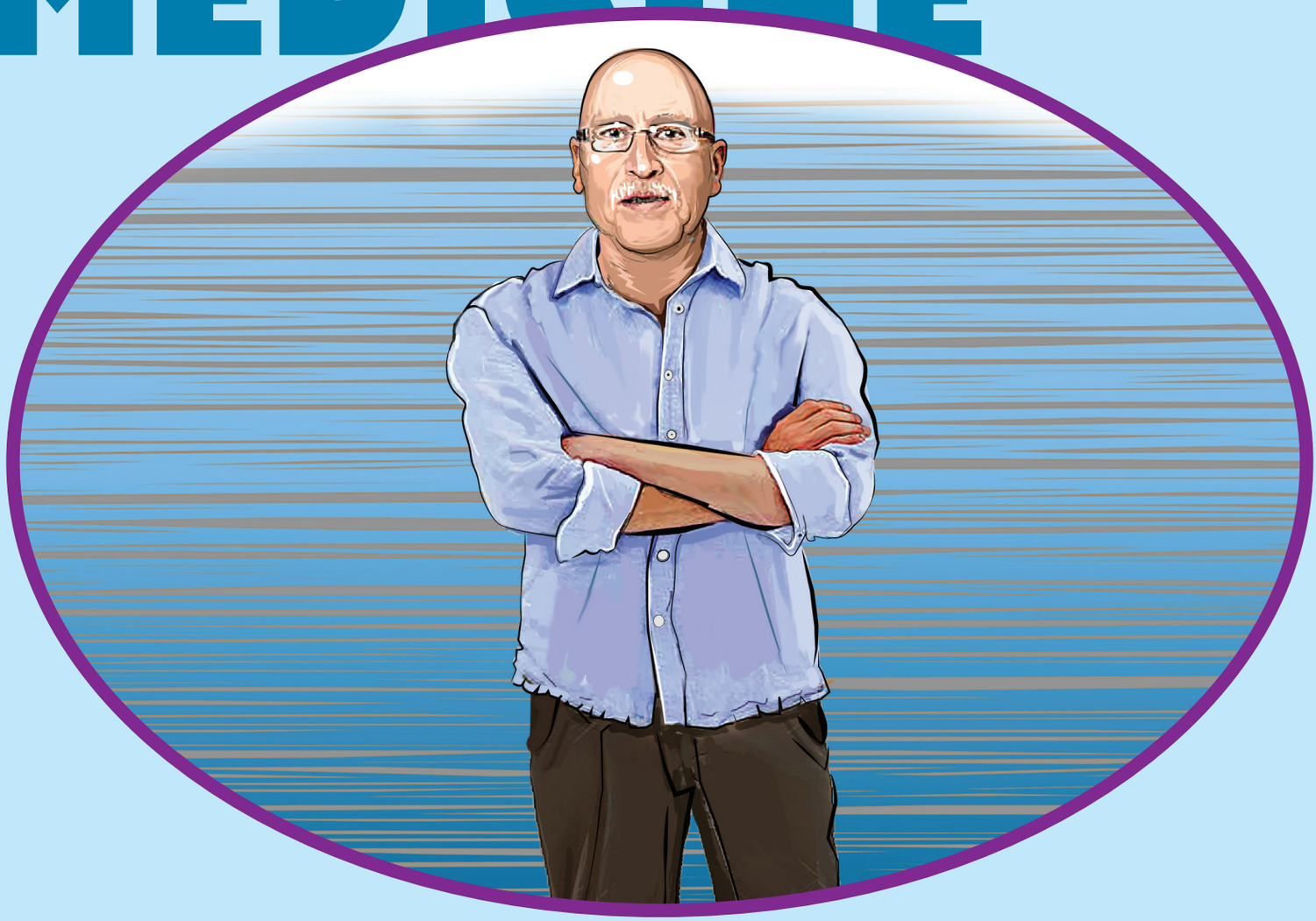
That is, Gardner never saw such a thing until he saw the solution created by Bryan Brown, PhD assistant professor of bioengineering. Brown has created a gel from porcine nerve tissue that provides scaffolding for human nerve tissue to regrow around. The gel is designed to be injected.

Brown's creation, Neurogel, won $100,000 in 2016 in the PInCh competition. Gardner and Brown have been working with the Food and Drug Administration with an eye on clinical trials.

Gardner says the PInCh prize allowed them to take their idea to the next level; a new company called Renerva is developing the technology. "To bring this to patients is a huge process that involves more studies to understand where this can be used best and a lot of regulatory work," says Gardner. *—HB*

DREAMERS

RADICAL MEDICINE



In the 1980s, Bruce Freeman, a PhD biochemist and pharmacologist, was giving a lecture in Buenos Aires; afterward, on a whim, he went to play a soccer game with a few graduate students. On his team was Rafael Radi, an MD and biochemist, who would become the first Uruguayan to be elected to the U.S. National Academy of Sciences. But back then, Radi was a new PhD student with few resources. He shared Freeman's interest in oxidants and free radicals—small, chemically reactive molecules that can start chains of dangerous reactions in the body, disrupting living cells and damaging DNA.

Freeman began to mail Radi chemicals with which to experiment. They struck up a friendship, and Radi completed a postdoctoral fellowship with Freeman in the United States (from 1989 to 1992). In 1994, Freeman returned to South America as a Fulbright Scholar at Universidad de la República in Montevideo, Uruguay.

Freeman and Radi's team was interested in a free radical called nitric oxide (NO). The molecule presented something of a puzzle to scientists, as it had contradictory properties: it was a combustion product and could react to form another molecule, nitrogen dioxide, which is "the brown gas you see in photochemical air pollution," explains Freeman, a Distinguished Professor and the UPMC-Irwin Fridovich Professor who chairs the Department of Pharmacology and Chemical Biology at the University of Pittsburgh.

High concentrations of NO also exist in blood vessels and in tissue during inflammation. Yet the gas is a critical player for the health of the immune system and for the normal functioning of the heart, lung, brain, pancreas, uterus, and liver, among other organs. NO was named "Molecule of the Year" by *Science* in 1992. It was the subject of the 1998 Nobel Prize for Physiology or Medicine; the Nobelists were honored for advancing the understanding of NO's key signaling roles in the cardiovascular system. (Many Pitt faculty, especially scientists in the Departments of Surgery and Medicine, know the molecule well. Among other things, they've helped lay out the role NO plays in organ rejection and sepsis.)

While studying NO in the late 1990s, Freeman's team deduced that the molecule transforms into nitrogen dioxide (NO_2). They found that NO_2 chemically reacts with fats and produces nitro-fatty acid derivatives with unique chemical properties—this molecule group is now called nitro-fatty acids (NO_2-FAs or NFAs). This was a wholly original discovery.

"Long story short, these nitro-fatty acids are found in insects, plants, and mammals and appear to play a central role in regulating inflammation and stress responses," says Freeman. "[They're] profoundly tissue protective and anti-inflammatory."

In the nearly 25 years since their discovery, nitro-fatty acids have been a focus in Freeman's lab. They form the basis of Complexa, a clinical-stage biopharmaceutical company that raised $62 million in its most recent funding round. Freeman is a Complexa scientific advisor and cofounder.

Nitro-fatty acids' progression from a scientific discovery to a commercial venture has been a slow burn. Freeman says it took another decade to grasp the vast potential for clinical application and for the right environment and development team to coalesce.

After the initial detection of nitro-fatty acids, Freeman and his team, anchored by Francisco Schopfer (who is a PhD and an associate professor in Freeman's group), were able to further their knowledge of the acids' molecular structure and ability to regulate gene expression. They discovered that nitro-fatty acids make up a key constituent of the Mediterranean diet—long known to be heart-healthy—rich in vegetables, legumes, fish, and other foods high in "good" unsaturated fats.

Freeman's team demystified why such a high-fat diet is beneficial. When you eat a salad doused with olive oil, for example, you increase concentrations of molecules that regulate cell behavior, including nitro-fatty acids, making your cells better able to adapt to stress and resist inflammation. (Research from Pitt's chair of medicine, Mark Gladwin, MD and Jack D. Myers Professor, has also played a key role in understanding how nitrate from foodstuffs can react to form tissue-protective fatty acids.)

Freeman began to wonder: If synthesized in their purest form, could the molecules be therapeutic? If a healthy person could reap the benefits of simply eating a nitrate-rich diet, perhaps high concentrations of nitro-fatty acids could help treat acute inflammation, even protect against it.

"In a state of delusion, I said to myself, *These could be potentially important as drugs*," says Freeman.

In 2002, while at the University of Alabama, Birmingham, Freeman began filing patents for the nitro-fatty acid class of molecules, receiving one of only four U.S. patents ever to "protect the composition of matter and methods of use" of a biomolecule, says Freeman. Ultimately, the intellectual property surrounding nitro-fatty acids make up a patent tree; the patents apply to any other molecule that has similar signaling activity. This means, essentially, no one else can patent a similar class of drug, because these patents "cover every possible atom that could be put on any possible structure to confer similar reactivity."

Freeman imagined starting a biotech company around the technology—though the overarching goal, he notes, was always to "translate [knowledge] into treating disease."

Christmas 2005: Freeman was named Pitt's pharmacology and chemical biology department chair and moved to Pittsburgh with his wife, Margaret Tarpey, MD and recently retired professor of anesthesiology. A few Christmases later, they wrote a $40,000 check out of their own pockets to synthesize the first 40 grams of CXA-10—Complexa's lead compound—and cofound the company.

"In its early years, Complexa needed to evolve, as it had encouraging lab-based data

THEY PERSISTED

It takes more than brilliance to turn a laboratory breakthrough into a new therapy. The secret formula includes inspiration, serendipity, teamwork, funding, and persistence.

1 in 10 drugs entering industry-sponsored phase 1 clinical trials between 2006 and 2015 advanced to FDA approval.

Drugs with the highest likelihood of advancing from phase 1 trials to FDA approval were in the fields of hematology, 26%, and infectious disease, 19%.

Cancer and psychiatric drugs entering phase 1 trials had the lowest likelihood of getting to patients, at 5% and 6%, respectively.

but only had a murky development and business plan," Freeman says. "We did things on our own early on just to find out if this was a crazy fantasy or if there was some substance to these molecules being truly efficacious as drug candidates."

Complexa earned its first early stage funding through local investors like the Pittsburgh Life Sciences Greenhouse (PLSG) and Innovation Works. Freeman and Schopfer took entrepreneurship classes through Pitt's Office of Technology Management (now part of the Innovation Institute). Schopfer ended up getting an MBA from Pitt's Katz School. Initially, the company was fund-raising amidst a deep recession in 2008 and 2009, when start-up investments were difficult to come by. But with help from the PLSG, Complexa was able to hire Josh Tarnoff in 2011 as its director, president, and chief executive officer.

"It was the [Pittsburgh] community coupled with the University that really enabled and gave the chance to this technology," Tarnoff says. "Without that, we would've never gotten off the launchpad."

Tarnoff and Freeman attribute both the challenges and successes of Complexa and CXA-10 to the fact that its effects are many and its applications are so broad. In Freeman's vision, nitro-fatty acids' "profound" anti-inflammatory effects could represent a new drug class because the fatty acids both *stop* acute inflammation and also *reverse* its effects in diseases like fibrosis and diabetes. Or, as Tarnoff put it, CXA-10 is a "stop and repair" technology.

"It's absolutely remarkable technology, because basically Freeman's team discovered this major reparative technology that also blocks key inflammatory mechanisms in the body," says Tarnoff.

The complexities of signaling pathway technology were less understood as recently as five years ago. Complexa produces its "stop and repair" effect by inhibiting the biological pathway NFkB, stopping inflammation, then upregulating the protective and reparative pathway Nrf2. Another Pitt pharmacology professor, Thomas Kensler, a PhD, has spent decades researching Nrf2 and the possible therapeutic effects of another molecule, sulforaphane. Found in broccoli and cruciferous vegetables, the molecule plays a cancer-preventive, detoxifying role by activating Nrf2.

One of the Freeman Lab's first animal studies gave nitro-fatty acids to obese, diabetic mice. The molecules not only lowered blood-glucose levels, helping manage diabetes, but also restored sensitivity to insulin, beginning to lessen or undo the disease's progression. The drug also produced an anti-inflammatory effect in fat cells, which could be therapeutic for obesity-related diseases. Hitting multiple targets, the molecule works through what's termed a pleiotropic signaling mechanism. (*Pleiotropy* translates to "more ways" in Greek.)

Tarnoff and Freeman say a major hurdle to CXA-10's commercialization has been pitching such a multifaceted drug to both investors and the pharmaceutical industry. "Their mindset is they like the concept of one drug, one target, one response," says Freeman. "And we've had to change their psychology."

Now, CXA-10 is on the eve of phase 2 clinical trials, scheduled to start in early 2018. After five phase 1 trials to determine safety and dosing, Complexa's leadership hopes to solidly prove efficacy. The company's strategy centers on treating two orphan diseases: focal segmental glomerulosclerosis, a renal disease affecting about 40,000 people in the United States, and pulmonary arterial hypertension, a type of high blood pressure afflicting 20,000 Americans. There's no cure or effective long-term treatment for either of these diseases.

Tarnoff predicts Complexa's approach will be a "game-changer."

Success treating these orphan diseases, Freeman hopes, would allow Complexa to go after more widespread diseases. Because so many diseases induce harmful inflammatory responses, Freeman's lab is exploring even broader applications of nitro-fatty acids: the potential to treat asthma, sickle-cell anemia ("fundamentally a vascular inflammatory condition," says Freeman), even acute lung injury from viral infections.

Funders in Complexa's most recent round included international investors like NEA and Edmond de Rothschild Investment Partners, two of the world's largest financial advisory groups, and JAFCO, a Japanese venture firm, as well as U.S.-based Pfizer. And there's interest in Complexa among several other major pharmaceutical companies.

Successful phase 2 trials may lead to a buy-out by a pharmaceutical company, an initial public offering (IPO), or another round of fund-raising for phase 3 trials.

Freeman likens seeing Complexa take off to watching a child go off to college. But his goal was always larger than starting a company. He estimates even with a small marketplace penetration, CXA-10 could save tens of thousands of lives.

"My team and I want to make a transformative difference," he says. *—RW*

VIRUSES FOR GOOD

Among the 102 patents issued to Pitt inventors in the past fiscal year, one was based on the work of Joseph Glorioso, a PhD professor of microbiology and molecular genetics, and Paola Grandi, PhD assistant professor of neurological surgery and of microbiology and molecular genetics. The researchers modified the herpes simplex virus to target highly malignant forms of cancer, including the most aggressive brain cancer, glioblastoma, by activating the body's immune response. This experimental approach is known as an "oncolytic virus."

The herpes technology was partially licensed from Glorioso and Grandi by Cambridge, Mass.–based Oncorus. In July 2016, Oncorus raised $61.4 million to support phase 1 clinical trials. The company was featured in the *Wall Street Journal*, and the industry site BioSpace put Oncorus among the "Top 20 Life Science Startups to Watch in 2017."

"As far as an unmet medical need, it's gigantic," says Glorioso.

Another oncolytic virus, invented by Pitt's Stephen Thorne, a PhD assistant professor of cell biology, immunology, and surgery, has also resulted in a spin-off company, Western Oncolytics. The company struck a deal with Pfizer to codevelop the virus WO-12. In mouse models, WO-12 cleared several types of solid tumors up to 100 percent of the time. The technology will soon go into clinical trials. *—RW*

DATA, IT'S BIG

• In fall 2012, UPMC announced it would invest $100 million throughout the next five years in a data warehousing, integration, and analysis project that would bring together clinical, financial, genomic, and other information to improve patient care. UPMC is partnering with Oracle, IBM, Informatica, and dbMotion to make this happen. Pitt faculty lead the research efforts.

• In January 2014, Pitt established its Institute for Precision Medicine, which harnesses the power of data analytics to understand complex biology at the level of the individual.

• In 2014, the National Institutes of Health awarded Pitt's School of Medicine $11 million to lead the Big Data to Knowledge Center of Excellence.

• In 2015, Pitt, UPMC Enterprises, and Carnegie Mellon partnered to create the Pittsburgh Health Data Alliance to move knowledge acquired from data into solutions for patients. The Alliance expects to attract hundreds of companies and entrepreneurs to Pittsburgh.

• In June 2017, NIH and Pitt announced the initial recruitment phase for the All of Us campaign to inform advances in precision medicine. In Western Pennsylvania the study is called PA Cares for Us; and over five years, Pitt will recruit 150,000 participants of the expected 1 million total nationwide. Pitt's was the first site to open nationally.

• Just this year, Dean Arthur S. Levine, senior vice chancellor for the health sciences, was asked by the National Library of Medicine to chair a working group charged with determining how to advance biomedical discovery and translational research in this data-driven era.

SAVING THE THYROID

1 in 4 thyroid cancer screens come up inconclusive.

20% of inconclusive nodules turn out to be cancer.

Old standard of care: If any suspicious nodules were found, the whole, or part of, the thyroid was removed, necessitating lifelong thyroid hormone replacement therapy for many.

Current approach: Pitt-developed molecular marker panel, ThryoSeq, helps UPMC doctors be more accurate and judicious in evaluating nodules. ThyroSeq was developed by **Yuri Nikiforov**, MD/PhD professor and vice chair of pathology.

Better yet: A new two-year trial includes patients who have a biopsy that is positive or suspicious for cancer. Some patients may be adequately treated with partial removal of the thyroid and not require follow-up medication. The current trial will see if ThryoSeq can offer doctors that important preoperative information.

"We want to do the right operation the first time around," says **Linwah Yip**, MD associate professor of surgery and principal investigator on the trial. *—HB*

DRIVER, ID PLEASE

Excuse me, cell. Do you know how fast you were multiplying? You're going to need to show me some ID.

"Cells accumulate genetic mutations every time they divide," **Xinghua Lu**, MD/PhD professor of biomedical informatics, says. "Some of these drive cells into uncontrolled proliferation and migration and eventually lead to cancer. And some are nonconsequential events. We need to differentiate between the driver and the passenger."

Hence the Tumor-specific Driver Identification (TDI) algorithm and software being developed and tested at Pitt by Lu and **Gregory Cooper**, MD/PhD professor and vice chair of biomedical informatics. TDI is designed to reveal, in a given tumor, mutations that might cause cancer.

At this point, Lu and colleagues are still sorting out the mutational noise from the significant events and fine-tuning parameters. "Most others are working out this issue from the population level—watching for mutations in a cohort of, say, 10,000 people," he says. "We are doing it at an individual tumor level." *—HB*

CRASHES PREDICTED, COURSE CORRECTED

Your blood pressure can keep going up and still stay in the normal range.

So when is that safe and when should it raise a red flag? That's what **Ricardo Muñoz**, MD professor of critical care medicine, pediatrics, and surgery, found himself wondering after witnessing cardiac events in children.

"We don't want to treat an event; by then, it's too late," he says. "You've already crashed. . . . When a plane crashes, and you have survivors, that's lucky. It's preventing it before it happens" that's the real trick, he says.

To do that, Muñoz is harnessing retrospective data from Children's Hospital to train a computer algorithm to recognize and flag warning signs of cardiac events before they happen.

That's where **Rich Tsui**, PhD associate professor of biomedical informatics, comes into the picture. Tsui had already been working on predictive technology to identify whether patients were likely to be readmitted to a hospital after discharge when he met Muñoz. Then the two men started brainstorming how to teach a computer to identify negative trends and flag them so providers can take action. And, ideally, they would prevent crashes.

The resulting algorithm, now being tested in a partnership between Pitt and Children's, has shown that, using retrospective data, it can predict cardiac events in patients. The next step is to sift through real-time hospital data and identify trends. That part of the project should begin in 2018, says Muñoz. If successful, it could be rolled out beyond UPMC to other hospital systems.

And while the team has already applied for a patent for their system, Muñoz said that's not the point. "My interest isn't in money," he says. "If we can make a really effective machine, it could make a tremendous difference for patients and for health care spending." *—HB*

PIVOTS



While an undergrad at Carnegie Mellon University, Shivdev Rao was a skateboarder and social history major, interested in philosophy and headed toward an academic career in the humanities.

Then he went to a lecture by architect William McDonough.

McDonough told the story of Govindappa Venkataswamy, an Indian eye doctor who founded one of the largest ophthalmology hospital networks in the world and restored more than two million people's sight for free. Venkataswamy achieved this by designing a swiveling surgical room resembling an assembly line, where he and his team could perform a cataract operation in 10 to 20 minutes, then quickly move to the next prepped patient.

McDonough's philosophy, that "design is the first signal of human intention," spoke deeply to Rao."He inspired me to think about how I want to impact people," says Rao, who then "pivoted" toward medicine. Rao (MD '07) is now a clinical instructor of medicine at Pitt and executive vice president for UPMC Enterprises, the commercialization arm of the medical center.

Rao carries his ethos of influencing the world through design to his work at UPMC Enterprises. The unit invests in and builds technologies that do what Rao calls the "three As": assist, augment, or automate aspects of health care delivery, with an immediate focus on UPMC's $16 billion health care system.

This mission is newly evolved, says Rao. Enterprises—which has its colorful open-concept offices in Bakery Square—was originally called the Technology Development Center and focused largely on software-centered solutions for UPMC and elsewhere. The vision has broadened in recent years to include solutions based on everything from basic science to advanced analytics.

Rao says Enterprises' "secret sauce" is access to UPMC's more than 30 hospitals, 600 doctor offices, and 3,800 physicians, as well as its insurance plan; UPMC's massive system constantly generates data and can function as a real-time feedback mechanism.

Still a practicing cardiologist, Rao takes weekly appointments at Magee-Womens Hospital of UPMC and performs rounds at UPMC Presbyterian.

"Seeing patients always . . . informs me about some new nuance that I can bring here [to Enterprises]," he says.

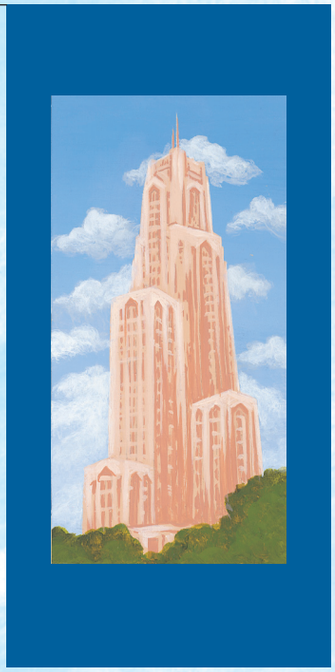
At Enterprises, Rao focuses on solutions that "work backwards" from patient care. Rao says the goal is to embrace higher-level ideas that would affect patient and provider experiences. These include artificial intelligence and its subsets like deep learning (wherein networks, with designs inspired by the structure of the brain, are capable of learning and sometimes making decisions from large datasets).

"Deep learning really sings in the imaging space, more than any other domain. Radiology, pathology, aspects of ophthalmology and cardiology" will all benefit, says Rao.

For instance, a pathology system might filter for images with abnormalities and even make diagnostic suggestions based on the data to create an entirely new workflow. For perpetually overworked clinicians, Rao believes such technology would improve efficiency and help with decision-making. He emphasizes he doesn't believe in "push-button" technology for diagnosis in the near future. Instead, he believes that "we can help doctors do better." Through a partnership with Microsoft's artificial intelligence labs, he envisions leveraging "technology to transform clinicians from overwhelmed and time scarce, to nearly omniscient and omnipresent healers."

He says Enterprises is walking a path toward wholly person-centered health care, where every patient controls his or her own data over vastly interconnected systems.

"We're far from that," says Rao. "But we have all the ingredients." —*RW*



CLASS NOTES

'80s

When **Lee Shapiro** (Internal Medicine Resident '80, Rheumatology Fellow '82) came to Pittsburgh for residency, the first patient he saw had scleroderma, an autoimmune disease that hardens skin and connective tissues. Shapiro ultimately centered his practice on helping people like that first patient. Now, in Albany, N.Y., he directs the Steffens Scleroderma Center, which conducts clinical trials for scleroderma and Degos disease, a similar but little-known vascular condition that is often fatal. The center is now cosponsoring a bench research project in collaboration with the National Institutes of Health and the Ottawa Hospital Research Institute to learn more about Degos disease and underlying pathways. "Not many talk about these diseases. I think that needs to change," he says. "That's one of our main goals here."

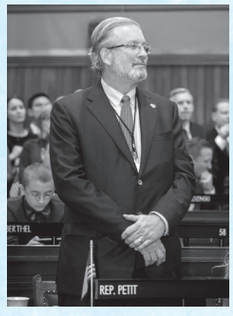


Boretsky

Karen Boretsky's (MD '84) daughter reached into the trash and pulled out a flier for Operation Smile, a charity for children with facial deformities. Boretsky had dismissed the flier when she saw it in the mail, but her daughter challenged her to take action. Soon, she was in China helping patients to manage pain. Boretsky, then a Pitt Med faculty member and now assistant professor of anesthesiology at Harvard, was thankful for her daughter's prod. Boretsky has since taken residents on similar missions to Guatemala, Zambia, Ethiopia, and Bhutan through Surgicorps International. They learn the basic necessities of anesthesia, like how a ventilator may run mechanically rather than electronically. "There's a lot of information to be gained by holding a breathing bag and feeling it," she says. Stateside, Boretsky guides trainees through pediatric regional anesthesia at Boston Children's Hospital.

During his early days at Pitt Med, **David Peace** (MD '80, Internal Medicine Resident '83) was inspired by his mentor Thomas Gill (now professor emeritus) to look beyond conventional cancer therapies to immunotherapy, the targeting of malignant tumors with one's own immune system. Peace, professor of medicine and training program director at the University of Illinois, now focuses on CAR T-cell therapy, a method that enlists engineered human T-cells to seek and destroy malignant tumors. The first CAR T-cell therapy was approved in August for use in a select pediatric population; other uses are under review. Peace says, "I've watched my lightbulb moment from back in my early days go forward to clinical development and successful achievement. We have a long way to go, but the door is now open."

When we talked to **William Petit Jr.** (MD '82) three years ago, he shared news of the Petit Family Foundation, created in memory of his wife, Jennifer, and children, Michaela and Hayley, who were murdered during a home invasion in 2007. The foundation has awarded approximately $2.5 million in grant support for shelters and other programs for those affected by violence in Connecticut. As the foundation marked its 10th anniversary this fall, Petit added a new title to his accomplishments: legislator. He was elected in 2016 to the Connecticut House of Representatives. "I thought it was time to try and create change," says Petit. He follows several of his family members into government service.



Petit

'90s

After **Jeffrey Quinlan** (MD '92) graduated from Pitt Med, he joined the navy as part of the Health Professions Scholarship Program. He has since been deployed three times in support of Operation Enduring Freedom. Stationed at the Uniformed Services University in Bethesda, Md., Quinlan holds the rank of captain and serves as chair of family medicine. He recently received a $1.1 million grant to develop interventions to reduce unwanted pregnancies and STIs in service members. He also serves on the editorial board of the Advanced Life Support in Obstetrics program, an effort to train maternity care providers in the United States and 55 other countries to effectively manage obstetric emergencies.

From her second-year neuroscience class at Pitt Med, **Anahita Deboo**'s (MD '97) fascination with the intricacies of the nervous system only grew. She pursued a neurology residency at the University of Pennsylvania and further specialized in clinical neurophysiology and neuromuscular medicine. Then she joined the faculty at Drexel University, where she directed the clinical neurophysiology fellowship program. Recently, she moved to Temple University as associate professor of clinical neurology. Deboo is involved in clinical trials for amyotrophic lateral sclerosis (ALS) treatments and codirects Temple's MDA/ALS Center of Hope clinic. Among the center's many ongoing projects are tissue collection, phase III clinical trials, cognitive behavioral studies, and brain-computer interface studies designed to help ALS patients communicate. "Right now is a very exciting time for ALS because of all the new therapeutics that are on the horizon," she says.



Deboo

'00s

The brain is like a battery, says **Jed Hartings** (PhD '00), associate professor of neurosurgery at the University of Cincinnati. As a founding member of the Co-Operative Studies on Brain Injury Depolarizations (COSBID) research consortium, Hartings studies how that battery loses its charge after a traumatic brain injury. "We're discovering how the brain dies," he says. Doctors in the field have nicknamed this spreading loss of charge a "brain tsunami." In March, COSBID held an international conference on brain tsunamis in Berlin, where scientists from Asia, Europe, and the Americas presented their latest research. Hartings studies the brain tsunami mechanism with Pitt's own David Okonkwo, clinical director at the Brain Trauma Research Center.



Hartings



Bonfield

While working in the OR during a mission to Tanzania, neurosurgeon **Christopher Bonfield** (MD '07, Neurological Surgery Residency '14) realized that the electric drill normally used to remove portions of the skull

was not working. "We had to use hand tools and other techniques to get the bone off. Working on that mission abroad taught me different ways of looking at problems … and it also showed me the disease process at a much more advanced stage," says Bonfield, assistant professor of neurological surgery at Vanderbilt. His research focuses on spinal deformities and craniofacial surgery outcomes and encompasses often-overlooked aspects of spinal problems like pregnancy, social well-being, and psychological issues associated with scoliosis.

—Rachel Mennies, Rajiv Reddy, and Evan Bowen-Gaddy

TOAST WITH THE MOST

On Friday, Sept. 8, the medical school and the UPMC Physician Services Division hosted A Toast to Diversity and Call to Action at the Heinz History Center. Pitt Med students, faculty, and staff attended the event. PICTURED LEFT: Kia Washington (Fel '08, Res '11, Fel '12), assistant professor of plastic surgery (who investigates whole eye transplants), was among the speakers. BELOW: Paula Davis, assistant vice chancellor for health sciences diversity, poses for a photo with Esa Davis (no relation!), associate professor of medicine and of clinical and translational science.





TRIALS AND CELEBRATIONS

Pitt emergency medicine professor Susan Dunmire (MD '85, Emergency Medicine Resident '88) and Samuel A. Tisherman (MD '85, Surgery Resident '93, Critical Care Fellow '94), a University of Maryland surgery prof, with their son Robert Tisherman (MD '17) at the luncheon for his graduating class. Last fall, Sam's clinical trials on the effectiveness of extreme hypothermia as a way to buy more time for cardiac arrest patients—a project that started here at Pitt, with Peter Safar—made ink in *The New Yorker*.



HENRY SHOENTHAL

PASTORAL ROUNDING



Shoenthal in his apple orchard.

In a borrowed van, 13 Pitt Med students bumped along the back roads of a 120-acre apple orchard last spring. "The funniest moment was figuring out who was going to sit on whose lap," says Henry Shoenthal (MD '72). "We didn't have enough room for everyone to have a seat."

That kind of community spirit is the reason Shoenthal, a family physician in his hometown of New Paris, Pa., loves what he does and where he does it. Having practiced in this area for 45 years, he's now on a mission to entice more physicians to greener pastures. Or to pastures at least.

Of his practice, he says,"I usually don't have to ask for a family history because, in many cases, I already know it," he explains. The population of New Paris is less than 200 people. Many of his patients have roots in the region that date back decades or even centuries. Shoenthal's own family has been here since 1868.

Shoenthal speaks of a vibrant social life at a more relaxed pace and a comparable salary to his urban peers. "People think they can make more money in the city, but to recruit people here, you have to pay the same as in urban centers."

Lifestyle benefits aside, Shoenthal says there's an urgency for more physicians in the countryside. "Rural America is suffering. Right here in Bedford County, there are only about 15 of us practicing pediatrics, family practice, and internal medicine—and half are over 55." Part of his outreach this year involved hosting Pitt's student-run Rural Medicine Interest Group, which included the orchard tour, as well as a visit to his office.

Grace Lisius, second-year med student and coordinator of the spring field trip, was attracted by the prospect of a rural practice. "I have a healthy appreciation for the outdoors that doesn't always go together with medical school. It seemed like Dr. Shoenthal had a really great setup, owning land and being part of a community that he [has followed] for generations."

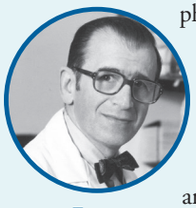
Drawing on the students' enthusiasm, Shoenthal established an endowed fund to offer perpetual support for rural health education. Shoenthal tells students, "Don't give up on rural areas. Think about it."

—Kristin Bundy

PHILIP TROEN

NOV. 24, 1925–SEPT. 1, 2017

Philip Troen was left-handed, but when he got in front of a classroom to teach, he'd hold the chalk with his right hand, says his son, Bruce Troen, chief of geriatrics and palliative medicine at the University at Buffalo. "If you write with your left hand at the board, you're often covering what you've written," Troen had explained to his son. It was just one example of the practical, deliberate nature of the Pitt retired assistant dean and physician-in-chief emeritus. Philip Troen died in September.



Troen

Born in Portland, Maine, Troen left his hometown at age 15 to attend Harvard College for his undergraduate studies and medical education. He joined Pitt Med in 1964 as professor of medicine and chief of medicine at what's now UPMC Montefiore, beginning a 50-year career in which he shaped medical education at Pitt.

One of Troen's Montefiore interns from 1975, E.J. Donnelly (Res '78), now a retired internist, remembers the "morning report," when they'd sit at a round table and present cases. "That was a great learning experience. … He asked excellent questions."

Troen copiloted the integrated case studies course at Pitt Med in 1992, introducing students to mock patient cases. Paula Clemens—professor of neurology, microbiology and molecular genetics, pediatrics, and human genetics—led the course with Troen and says his commitment to the scholarly process stuck with her as a teacher of med students. "He had a willingness to accept all that it took to develop clinicians."

After becoming assistant dean of medicine in 2004, Troen led the design and implementation of the Scholarly Research Project, now a model for medical schools seeking to integrate research into their curricula.

Arthur Levine, senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the University of Pittsburgh School of Medicine, says Troen was a skilled educator with an "infectious" passion for science. The med school's Philip Troen, MD, Excellence in Medical Student Research Mentoring Award recognizes a faculty advisor who excels at leading students through their Scholarly Research Projects.

—Evan Bowen-Gaddy

ROBERT WILKINS

AUG. 18, 1934–MARCH 31, 2017

When Robert Wilkins (MD '59) got married over Christmas break in 1957, he asked Pitt Med classmate Robert Horsch (MD '59) to stand beside him. Horsch was proud to serve as the best man for a friend with "a great mind" and "keen sense of humor that would pop out every once in a while." The bride, Gloria, remembers Wilkins's humor a bit differently. "He liked a bad pun better than good pun," she quips.



Wilkins

After Robert and Gloria (EDUC '58) earned their Pitt degrees, they moved near Duke University, where Wilkins completed his internship and residency. He later became professor and chief of neurosurgery there, a post he held for 20 years.

Wilkins started a new journal for the Congress of Neurological Surgeons in 1977. He and Gloria worked together in their North Carolina bedroom—Wilkins editing, Gloria typing—to put together *Neurosurgery*, what, today, is the top-rated journal in the field, says Allan Friedman, Duke's Guy L. Odom Professor of Neurological Surgery. Wilkins was internationally known for his scholarship, Friedman notes, publishing more than 300 papers and the three-volume textbook *Neurosurgery*. Gloria was "clearly a partner" in his medical career, Friedman adds.

After Wilkins's 50th Pitt Med reunion, the duo established the Robert and Gloria Kohl Wilkins Student Resource Fund at Pitt.

"There's no one [else] in our class … that achieved what he achieved academically in the field of neurosurgery," says Horsch.

—EBG

IN MEMORIAM

'40s

CALVIN C. RUSH
MD '44
OCT. 4, 2017

ROBERT S. MCKNIGHT
MD '45
SEPT. 30, 2017

SALEEM J. ANTOON JR.
MD '49
SEPT. 18, 2017

'50s

CLARENCE E. DIEHL JR.
MD '50
JULY 6, 2017

ERNEST E. REIGH
MD '54, RES '59
OCT. 1, 2017

JOSEPH A. DECENZO
MD '55
SEPT. 19, 2017

HAROLD C. MORGAN
MD '55
OCT. 8, 2017

HUGH H. HARKINS
MD '59
DEC. 27, 2016

JOSEPH J. JACKLINE JR.
MD '59
AUG. 18, 2017

JAMES S. THOMPSON
MD '59
SEPT. 29, 2017

'60s

ARNOLD J. SNITZER
MD '60
SEPT. 7, 2017

ROBERT C. MILSOVIC
MD '63
AUG. 15, 2017

ALAN L. ITSKOWITZ
RES '68
OCT. 10, 2017

SANFORD F. TOLCHIN
MD '66, RES '67,
RES '71, FEL '73
JULY 24, 2017

STEVEN L. TAUBE
MD '67
AUG. 26, 2017

'70s

ROBERT C. SNYDER
MD '71
JULY 9, 2017

JOSEPH S. SALIPANTE
MD '74
JUNE 28, 2017

FACULTY

JOHN F. MOYER JR.
RES '62
OCT. 11, 2017

WILLIAM PRIN
JULY 12, 2017

RAUL RUIZ
DOOR TO DOOR

BY SHARON TREGASKIS

COURTESY R. RUIZ



Ruiz (left) was elected to the U.S. House of Representatives in 2012.

Raul Ruiz (Res '06) was 17 when he banged out a contract on a manual typewriter, polished his dress shoes, borrowed a briefcase, and bought an itchy navy suit two sizes too big. "I wanted one to grow into as an investment for medical school interviews," he explains.

Then he proceeded to walk door-to-door in the hot desert sun, talking to business owners and store clerks alike. In exchange for his neighbors' financial support, Ruiz stipulated that he would earn an MD and return to his underserved Southern California community. "This was my life goal and mission," says Ruiz, now 44. "I was inviting people to invest in their future."

Ruiz and his neighbors have continued building on that youthful bond. A board-certified emergency doc, Ruiz was elected to the U.S. House of Representatives in 2012, when the political neophyte unseated seven-term incumbent Mary Bono.

Ruiz never aspired to elected office, but for a kid raised in a trailer and coached to offer solutions, not complaints, the trajectory seems inevitable. Born in Mexico, Ruiz was reared by an aunt and uncle, migrant farm laborers who worked the fields of California's Coachella Valley. The family couldn't afford health insurance, yet that wasn't the biggest obstacle to accessing medical care. The region had just one doctor for every 9,000 residents. No matter where Ruiz turned, it was hard to miss the desperate medical needs of his neighbors in the low-income, predominantly agricultural, and increasingly Latino community.

With pledges of support from his neighbors plus $2,000 in hand, Ruiz attended UCLA, graduated magna cum laude, and earned three graduate degrees from Harvard (an MD, as well as master's degrees in public policy and public health). He did a few stints abroad as a public health worker in Mexico, El Salvador, and Serbia; trained in emergency medicine at Pitt; and returned home in 2007.

On his first overnight shift in the Coachella Valley's Eisenhower Medical Center emergency department, he had six patients in respiratory distress, all of whom had to be intubated and stabilized. "I was so thankful that night for my Pitt mentors and professors," he says. "I chose emergency medicine because the emergency department is the true safety net of our nation—it's open 24/7 and required by law to take care of anyone with a life-threatening illness or severe emergency, regardless of their ability to pay, where they're from, or their background."

He kept busy off-hours, too. He rose to the rank of senior associate dean of community engagement and partnerships at the University of California, Riverside School of Medicine, and founded the Coachella Valley Healthcare Initiative. He also founded a pre-med mentorship program, Future Physician Leaders, for aspiring docs intent on practicing in their underserved home communities. He helped open a free primary care clinic and served with the nonprofit Flying Doctors of America. "My heart and soul was in the community," he says, "with my patients, with the people in the greatest need for health care and facing the greatest barriers."

Having long grappled with the profound effects of factors like income, race, and educational status on his patients' health outcomes, Ruiz felt that a run for Congress seemed the best next step. A member of the House Energy and Commerce Committee, he's made affordable health care, veterans' services, and transparency his priorities.

"When we live in a society that is healthy and productive, we all benefit," he says. "The bottom line of a health care system is to produce a healthy population. That's how we should measure our success in health care." ■



DRAWING BY STEENLINK FROM A PAINTING BY THE 17TH CENTURY DUTCH PAINTER ADRIAEN BACKER/GETTY IMAGES

Reforming Healthcare

I try to think of what I'm thankful for.
Parade of misery comes through my door:

dysuria, depression, hemorrhoids,
a lung mass that proved to be carcinoid,

low back pain that I've tried to diagnose,
strange tingling sensations in the nose

that honestly I haven't. What I do
so often seems frankly contrary to

my vision of myself as healer, noble
if undervalued shepherd to the feeble.

I try to think of what I'm thankful for.
As I examine someone's painful sore,

I wonder if I'm thankful I'm not him.
Adderall, Oxycontin, Valium:

I wonder if I'm thankful that relief
might yet be possible, that in this life

there is suffering, yes, but there is peace.
The classic rash of lupus marks the face

the beautiful young woman I see next
has tried to cover with a scarf as best

she can. It's not shaped like a butterfly,
I see when she reveals it; when she cries,

I don't pretend it's sweet music, or bleed
from some wound I can't trade for hers. Instead,

I grasp at last what I'm still thankful for:
not the disease that lets me comfort her,

or my unexceptional abilities
however insufficient they might be,

but in the final absence of a cure,
the need in all of us for someone's care.

—Rafael Campo

POET AMALGAMATE

Standing in front of the crowd in Scaife Hall, Rafael Campo poses the question, "To which community do I belong?" Campo is a Harvard-educated physician and an award-winning poet, a son of America and of Cuba. As a doctor, he is a member of a highly respected profession; as a gay man, he is a member of a socially disregarded community. He reminds us: just as a person cannot be easily categorized, neither can health nor illness be simply defined.

As a visiting lecturer in the Medical Humanities series of Pitt's Center for Bioethics and Health Law earlier this year, Campo shared some of his poems with the campus community. Through his poetry, the reader steps away from health as hard science and toward health informed by the broader human experience. Campo struggles with questions of identity and ethics until, through verse, he ultimately arrives at empathy. He has been doing so since he was a medical student.

Poetry, according to Campo, is "the purest, clearest drug of all, the essence and distillation of the process of living itself." *—Susan Wiedel*

CALENDAR

FOR ALUMNI & FRIENDS

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

MARSHALL S. LEVY MEMORIAL LECTURE
November 17
9 a.m.
Scaife Hall Conference Center, Room 1105 A&B
Gary Gilkeson, Speaker
For information: 412-303-8123 or sadej@pitt.edu

WINTER ACADEMY
February 16
10:45 a.m., Registration
The Ritz-Carlton, Naples, Fla.
(See inside front cover.)

PITT DAY OF GIVING
February 28

MARSHALL S. LEVY MEMORIAL LECTURE
March 12
9 a.m.
Scaife Hall Conference Center, Room 1105 A&B
Alan Steere, Speaker
For information: 412-303-8123 or sadej@pitt.edu

MATCH DAY 2018
March 16
12 p.m.



WESTEND61/GETTY IMAGES



FOR REAL! TWEEN SCIENCE

Have you ever built a complicated Lego sculpture and thought: *I wish I had three hands?* In 1998, two Pitt Med psychiatrists created an experiment that let people experience having an extra mitt.

In the experiment, subjects hid one of their hands. The researchers stroked it, and also a rubber hand the subjects could see, with paintbrushes. After 2 minutes, the subjects reported that they felt the paintbrush touching the rubber hand!

How is this possible?

Your sensory systems—in this case, touch and sight, as well as the system for figuring out your body position (called proprioception)—tell you what's going on based on what's happened to you before. If your real hand is blocked from view, your brain "fills in" information. It tells you the rubber hand that you can see is attached to you, even though you know that's not rational.

Pitt prof Julie Fiez says that such illusions show that "we are always trying to make sense of the world in the face of incomplete, and sometimes contradictory, information."

And that can get a bit freaky. The rubber hand illusion also messes with our sense of "self." In other words, if your brain can't recognize a fake hand from your own, how do you know what's you and what's something else? And how does your body process that kind of information? Some scientists and philosophers spend a lot of time delving into these questions.

There are all kinds of tricks you can play on yourself. For instance, you could make two adjacent fingers feel like one. If you tape them together, your brain would reorganize so you couldn't tell the difference between a touch on one finger and a touch on the other. The only problem is this illusion takes several months to pull off. So, it's probably better not to try this at home. *—Lela Nargi*

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

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STEVEN ERRICO/GETTY IMAGES

LOCATION, LOCATION, DONATION

Ah, the joys and pains of fixer-upping: Painting your very own ceiling! The suspense of finally finding out what's hiding under that shag carpet!

If the appeal of renovation has seriously curbed, your house-flip is a flop, or you're just plain fed up and ready to downsize, consider a real-estate gift to Pitt.

Whether it's a home, a lot, a rental property, or a vacation spot, your asset can provide you or your loved one with an income stream for life. It can also help make tax time less taxing. You can even designate a specific area that your gift will benefit—say, Scaife Hall's own renovation, now under way, or a researcher who's hammering out promising new cures.

To learn more, contact:
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