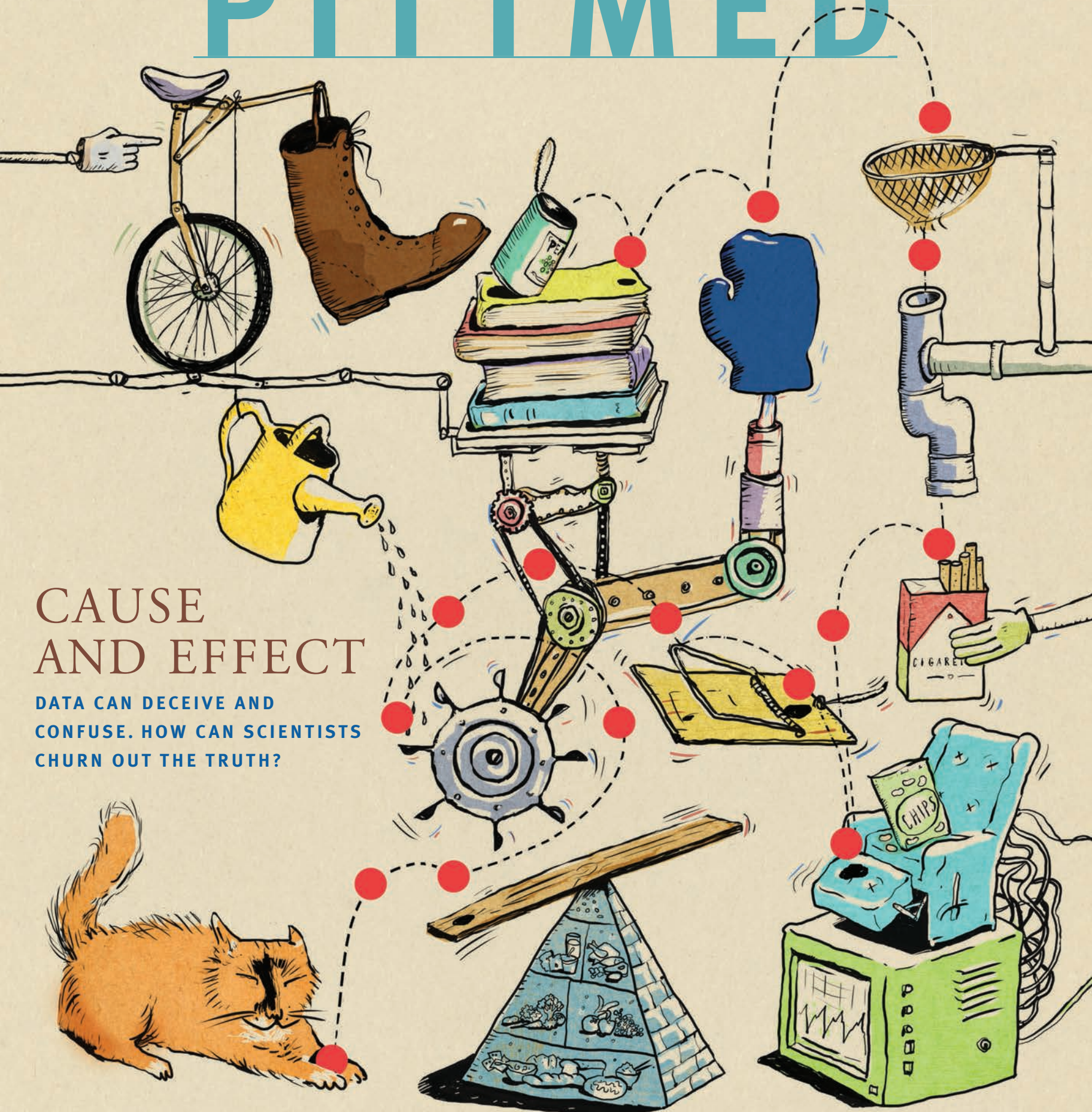
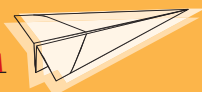


PITTMED

CAUSE AND EFFECT

DATA CAN DECEIVE AND
CONFUSE. HOW CAN SCIENTISTS
CHURN OUT THE TRUTH?





DARLING, IF ONLY . . .

Rarely are the images and words that land on our front cover the first we imagined. Now we are sharing a bit of our creative process—and some not-quite-ready-for-prime-time players—in a new Web section, Rejects Uncovered. There, you can eyeball would-be *Pitt Med* covers that never saw the light of the newsstand. For instance, you'll get a better look at this Lichtenstein-esque cover concept (rejected for this very issue). The thought balloon reads, "This is a meaningful relationship." And the superhero looking outside was proposed for our fall 2015 OCD cover. Tingling? You'll have to visit our Web site to find out more. Choose "Archives" on the home page, then "Rejects Uncovered," or go directly here: bit.ly/PMuncovered.



Two of our rejected covers. ABOVE: Lichtenstein-esque illustration concept by Stacy Innerst. RIGHT: OCD superhero photo by Cami Mesa. (We chose other covers by these same artists.)



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

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CARVING OUT TIME

To everything there is a season. But lately, doesn't it seem like you've got way too many things going on in the spring? There's your kids' graduations, grandkids' graduations. Well, your alma mater is right there with you, crunch-timing for every new crop of MDs, turning their tassels with all the pomp and circumstance they deserve.

So this year, **Medical Alumni Weekend is moving to the fall.**

We hope you'll find it easier to turn, turn, turn out for a little more relaxed time of year. So save the date!

Medical Alumni Weekend
September 23–25, 2016

For information:
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PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, WINTER 2016
VOL. 18, ISSUE 1



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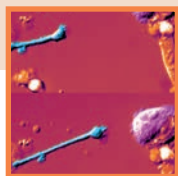
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Writing was "the only thing that spoke" to a young SARAH C. BALDWIN ["A Long Way to Go"]. Influenced by E.B. White, as a kid Baldwin wrote poems and stories about animals. When we spoke to her last, she was working on an essay about the death of her dog—it's not as sad as you might think. "What I thought was going to be a heartbreaking experience turned out to be heartbreakingly beautiful," Baldwin says. In addition to personal essays, she writes for magazines and organizations like the Watson Institute for International and Public Affairs at Brown University. Baldwin, who is based in Providence, R.I., is the former editor of *Brown Medicine*. She recently earned her MFA in creative writing.

ELAINE VITONE ["Pitt Medcast: Corneacopia"] is the voice of your favorite Pitt Medcasts, and her newest audiotale offers listeners something to chew on—namely, a potential method for curing blindness with teeth (okay, stem cells found in dental pulp). Vitone, an editor with *Pitt Med* for going on six years now, is cultivating progeny at home that are "easy on the eyes," too, she reports. Elaine, her husband, Dylan, and their daughter, Lena, welcomed fraternal twins, August and Walker, to the family this summer. Tune into Elaine's latest brainchild at bit.ly/PittMedcast.



COVER

The many variables inherent in big biomedical data can lead to spurious findings. A team of Pittsburghers is searching for true causal links. (Cover: Stacy Innerst. © 2016.)



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With training, mentorship, and seed funds from the Coulter@Pitt program, faculty inventions are going the distance, from innovation to commercialization.

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So correlation is not causation—then what is? Data can deceive and confuse.

Getting it to reveal meaningful relationships is the job at hand for a team of big thinkers in Pittsburgh. In the process, they are overhauling how modern science is done.

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Nathan Yates brings technologies to the table that allow scientists to step back and approach their studies as they never have before. For schizophrenia and cancer, he has helped colleagues present shortlists of important biological players, and he's just gaining steam.

BY NANCY AVERETT

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The more sand that has escaped from the hourglass of our life, the clearer we should see through it.
—Jean-Paul Sartre

It's true, old age ain't for sissies. Unless we are lucky, we may have cataracts, cancer, Alzheimer's disease, calcium in our coronary arteries. Our spines shrink, prostates enlarge, menopause takes its toll. Then, in our 70s, most of us die. It may be cold comfort, but we are learning more about the cellular-molecular biology of the limits on the life span.

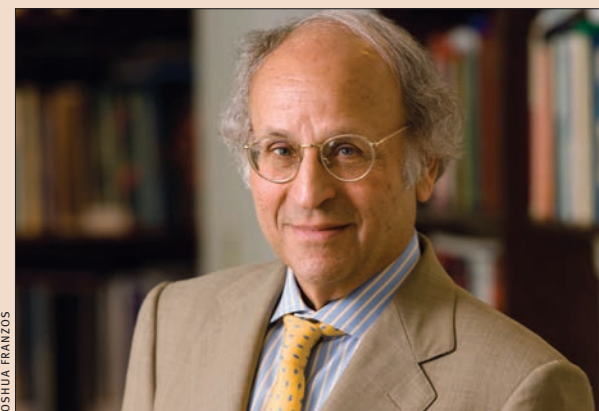
Plenty of it is genetics, as we see in the animal kingdom. A field mouse, for example, lives about two years, whereas a gray squirrel, so similar in its environment, diet, and metabolism, might see 20. If you'd like to make it to 100, you're most likely to get there if you have long-lived relatives on your mother's and father's sides. While surviving to your 70s is not very heritable, getting into the centenarian club is. For example, a variant of the gene *FOXO3* is found in most centenarians.

And then there's the passage of time and the damage it brings—free radicals ravaging our DNA, RNA, proteins, telomeres. The latter—protective “shoelace caps” that keep our DNA from unraveling—vary in length from one person to another, and the length of these caps is tied to longevity. As telomeres shorten over time, they become less protective, thus our immune cells become compromised, our risk of cancer increases, cardiovascular disease occurs, etc.

But perhaps there's good news here. There is evidence that stress can influence telomere length, so to the degree that our environment can affect longevity, sometimes it's ours to influence.

Humans number among a very short list of nonsissy species that live decades past the ability to reproduce (in good company with certain whales and Asian elephants), and you have to wonder why. One answer is that age confers a lifetime of experience, judgment, and wisdom that is our charge to pass on to younger people—certainly an evolutionary plus for our juniors. An older brain, though often not as fast in cognitive processing, is not only more knowledgeable, but also more adept at certain experience-dependent cognitive tasks and more skilled at reading emotions in others.

Once you've lived long enough, you're done fighting the good fight, competing in your career and, yes, in reproduction—your very reason for being, from one evolutionary standpoint. But from another, this age of battles long ago fought and, hopefully, of equanimity, is ripe with promise. One variant of the gene *CD33* that in older people suppresses the buildup of beta amyloid, either a cause or a biomarker of Alzheimer's disease, is thought to have emerged at the point in primate evolution when intact and wise brains became an evolutionary advantage. Our closest living cousins—chimps, bonobos, and gorillas—who do not outlive their fertility, largely lack this gene variant. These findings, published in *PNAS* this January, give new clout to the debated “grandmother hypothesis”—the nana as crucial caregiver. The elders, invested in babes' success and experienced at ensuring it, are so important that we evolved genes to protect their minds, the researchers suggest. There's certainly room for more investigation here, yet it seems that our longevity and transmissible wisdom are not independent of each other.



JOSHUA FRANZOS

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*

Ebola Lives in Wastewater

An Ebola patient can excrete up to 10 liters of liquid waste each day. During the recent Ebola outbreak, experts at the World Health Organization and U.S. Centers for Disease Control and Prevention advised affected countries to dispose of that waste into latrines and sewage systems without disinfection, believing the virus wouldn't remain active long in such an environment.

In a study published in the August *Environmental Science & Technology Letters*, Pitt's Kyle Bibby found that the virus persists for up to eight days in wastewater. The issue is "far more complex and more poorly understood than scientists previously thought," says Bibby, a PhD and assistant professor of civil and environmental engineering and of computational and systems biology. He adds that, although there's never been a documented case of waterborne Ebola transmission, "the results emphasize the value of a precautionary approach and the development of wastewater protocols for epidemic situations." —Nancy Averett

COURTESY NUSOM. ILLUSTRATION BY FRANK HARRIS.



Nazarbayev's first class of med students.

KAZAKHSTAN SCHOOL OPENS WITH PITT HELP

It's a universal truth. Whether in Kazakhstan or the United States, new medical students look the same—nervous.

This August, the republic's Nazarbayev University School of Medicine (NUSOM) welcomed its inaugural class of 20 students to begin a U.S.-style, English-language curriculum taught by faculty from Kazakhstan and other parts of the world. The university had tapped Pitt for help in developing its medical school in the capital city of Astana in 2013, and progress has been rapid.

NUSOM opened under the guidance of its founding dean, Massimo Pignatelli, an MD/PhD, Pitt clinical professor of pathology, and former head of the School of Medicine at the University of Glasgow in Scotland. Students were welcomed with an official White Coat Ceremony in an auditorium not so different from the crimson-seated lecture room in Scaife Hall.

"The University of Pittsburgh School of Medicine is both honored and humbled to be Nazarbayev University's strategic academic partner in this bold experiment," noted Maggie McDonald, a PhD and Pitt associate vice chancellor for academic affairs, health sciences, at the opening ceremonies. —Lori Ferguson

FOOTNOTE

A five-year review of U.S. neurosurgical residency programs published in the *Journal of Neurosurgery* last year ranked Pitt's program third of 103 accredited residencies—notably, ahead of Brigham & Women's and Johns Hopkins. Publishing prowess and citations informed the rankings. In other noggin news: Pitt researchers are also #1 for publications on traumatic brain injury.



Overheard

Bolstering Clinical Research Careers

Physician-scientists—docs who work in the clinic and also pursue research—are invaluable in translating insights from the bench to patient care. Yet, physicians with this double expertise are an endangered species, says **Wishwa Kapoor** (above), an MD/MPH and director of the Institute for Clinical Research Education at the University of Pittsburgh.

According to a comprehensive assessment by the National Institutes of Health last year, the average age of physician-scientists is rising, and pressures in today's funding climate create additional challenges for young trainees. Kapoor notes that many programs at Pitt are attempting to address the shortage: from summer institutes for kids to seminars on work-life balance for junior faculty.

What are some of the factors contributing to the leaky pipeline?

Becoming a physician-scientist requires more training, and you often start out with more debt; research salaries are also lower than clinical salaries at the start.

Also, in my view, these careers are a lot harder than being a physician in practice. Not that being a physician is easy, but the path is relatively straightforward: You join a practice and, generally, patients keep coming. As a physician-scientist, though, you have to take the reins and guide your career in a creative way—ask the right questions, develop your research program, get the grants. There's a significant degree of burnout because of the stress of trying to get funding.

How can institutions help trainees succeed?

We need to make this track more accessible to younger researchers and to train and retain more women and minorities. There is no magic-bullet solution. The focus must be not just on recruitment, but on sustaining and supporting these investigators. But I think the most important component of success is mentorship. Young investigators need mentors who can devote time to them and who are committed to promoting their careers—both at the home institution and with outside colleagues.

What mentors from early in your career stand out?

I had a couple of excellent mentors [like Pitt's former chair of medicine Gerald Levey and former chief of general internal medicine Michael Karpf] who spent a lot of time with me. English is a second language for me, so I was a terrible writer. They helped me with study design, and they helped me learn to write—that's what really made the difference. —Interview by Alla Katsnelson

Faculty Snapshots

Juan Fernandez-Miranda has secured a five-year, \$1.8 million grant to continue his research in language deficits and neuroplasticity in aphasic stroke patients. Fernandez-Miranda, an MD, associate professor of neurological surgery, and director of the Fiber Tractography Lab, is working with speech-language pathologist William Hula, a PhD at the VA Pittsburgh Healthcare System, to understand whether targeted behavior therapy structurally alters the brain and results in speech recovery. The award is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute on Deafness and Other Communication Disorders.



Fernandez-Miranda

In the past 10 years, a team at Pitt's Center for Medical Countermeasures Against Radiation (CMCR) has patented two drugs that mitigate the effect of radiation on the body, specifically radiation emitted during emergencies like terrorist attacks or reactor meltdowns. (These drugs have also been effective in treating patients with head and neck cancer who have undergone radiation.) Led by Joel Greenberger, an MD and chair of the Department of Radiation Oncology, the team received its third renewal of a five-year, \$18.4 million grant from the National Institute of Allergy and Infectious Diseases. Next, CMCR's research will focus on the discovery of drug-delivery systems for these medications, as well as treatment options for radiation-triggered disease.



Greenberger

Can bioactive molecules in broccoli lower the risk of cancer from environmental toxins? Thomas Kensler and colleagues are about to dig deeper for answers, thanks to funding from the National Cancer Institute (NCI). Kensler, a PhD, professor of pharmacology and chemical biology, and coleader for the Cancer Epidemiology and Prevention Program at the University of Pittsburgh Cancer Institute, received a \$6.3 million Outstanding Investigator Award—created this year by NCI.



Kensler

Lori Shutter and Gabriella Gosman have been selected for the Executive Leadership in Academic Medicine (ELAM) fellowship program at Drexel University College of Medicine. ELAM prepares its fellows for senior leadership roles. Shutter, an MD, is vice chair of critical care medicine education, professor of critical care medicine, neurology, and neurological surgery, and medical director of the neurovascular and neurotrauma ICUs at UPMC Presbyterian. Gosman, an MD, is vice chair for education and associate professor of obstetrics, gynecology, and reproductive sciences. She is also program director of the ob/gyn residency and associate designated institutional official of UPMC Graduate Medical Education. —Kristin Bundy



Shutter



Gosman

Cheat Sheet on the Class of 2019

Allow us to introduce a few members of the Class of '19 now roaming the hallowed halls of Scaife:

While in the Peace Corps, **Matthew Allen** educated Fijians on the importance of healthful eating and physical activity and on the dangers of smoking. "What I really liked was the intersection [of] medicine and psychology, the behavior-change aspect of things," says Allen, a psych grad from the University of Virginia. Allen aims to become a primary care physician, incorporating the community health models he learned in Fiji into patient care.

Before enrolling in the School of Medicine, **Claire Becker** studied Spanish and English at Pomona College, taught visually impaired high school students, and earned her master of fine arts in creative writing. "Studying literature has helped in the way I am able to communicate," she says.

During his undergrad years at Pitt, **Aric Berning** studied biology and theatre, so becoming one of Pitt's standardized patients—i.e., actors trained to simulate clinical scenarios for med students—just made sense. "That was a blast," he says. "It's a way to give the medical students a chance to practice without actually hurting someone in the real world." Berning is also an adjunct professor at Pitt, teaching organic chemistry laboratory classes.

When **Sangki Oak** deployed to Afghanistan as a medic in 2009, he and another medic were tasked with opening a small clinic to treat patients in a remote town. Hundreds of people showed up, though the clinic had limited medical supplies. One of the patients was an ashen-gray 1-year-old carried in by her father. Oak couldn't figure out what was wrong with her, so he sent her to a larger center that could offer more comprehensive care. That was the turning point for him: He recalls thinking, *I can't be happy just being a medic . . . in a situation like this. I need to know more. Okay, I need to go to med school.* —Brady Langmann



CATHERINE LAZURE

Deep ZZZs

Maybe we can choose how long we sleep—but how deeply might depend on where our ancestors rested their heads at night.

A new study published in *SLEEP* showed that African ancestry is directly related to lower levels of slow-wave sleep (SWS)—the deep sleep during which the body restores essential physiological processes in organ systems. The study, led by Martica Hall, PhD professor of psychiatry, psychology, and clinical and translational science, and Indrani Halder, PhD assistant professor of medicine, examined sleep patterns of 70 African American and 101 European American adults.

"The greater your African ancestry, the less deep your sleep," says Hall. (The African American participants' genetic African roots ranged from 33 to 88 percent.)

Previous studies have shown that black populations tend to have shorter, more fragmented sleep compared to white ones; those results were linked, in part, with stress from perceived discrimination and lower socioeconomic status. But Hall and colleagues found that between 9 and 11 percent of the differences in SWS were linked to genetic ancestry, even after adjusting for these psychosocial variables.

"In the United States, we have remarkable, persistent race disparities in health—and that's including both mental and physical health," Hall says. "What these data tell us is that, maybe, the race differences in sleep that we see [contribute] to the race differences in health that plague our nation."

Hall is hopeful that this study could lead to clearer causal evidence in health disparities in African Americans, informing future therapies and public policy. —KB

RIP, BLACKLIGHT

A giant of genome sequencing retired last year after five years of service to the academic world. A fond adieu to the Pittsburgh Supercomputing Center's Blacklight—which, among other tasks, assembled complete genomic codes cheaper and years faster than machines preceding it. (We mean that literally: It fully sequenced genomes from base reads in a matter of weeks, as opposed to years.)

Blacklight is remembered by its coworkers as a team player, working nights and weekends to churn out data. It even extended its stay six months longer than expected. It's been replaced by a whippersnapper named Bridges, anticipated to have 12 times the memory capacity. Blacklight looks forward to mai tais on the beach or, more realistically, being broken up and sold for parts. —KB



COURTESY ROGER ST. FRANCIS

BEATS OF THE BRAIN

When Jacobo Mintzer, a neurodegeneration expert, saw a recital featuring cellist Norbert Lewandowski of the Pittsburgh New Music Ensemble and Charleston Symphony Orchestra, he wanted a closer look—at Lewandowski’s brain. When Lewandowski performs, he often closes his eyes, which made Mintzer curious about how the cellist perceives each composition.

With Lewandowski’s blessing, Mintzer, of the Clinical Biotechnology Research Institute in Charleston, S.C., contacted Pitt’s Alzheimer Disease Research Center’s Oscar Lopez, an MD, and James Becker, a PhD, to use UPMC’s magnetoencephalography (MEG) machine—which can map neural activity down to the millisecond. During MEG and MRI sessions, the scientists asked Lewandowski to listen to his own recording of Andy Akiho’s “Three Shades, Foreshadows” and imagine replaying the cello track. From this, they attempted to visualize how his mind works during a performance. When the piece slowed, the images of Lewandowski’s brain flashed red and yellow, anticipating the crescendo; but as the song built, it glowed blue and green, resting for the next buildup. His brain activated most during the softest measures.

“It’s extremely interesting,” Lopez says. He suggests that knowing how parts of the brain react to music could lead to better treatment and improved cognition for head-trauma victims, though neuroimaging studies on music’s role in cognitive rehabilitation are relatively new.

In September, Lewandowski played a solo show in Charleston—this time, for a roomful of doctors. He performed the Akiho composition as a screen behind him played the recorded images of his brain flashing (see above). —BL

Appointments

The brain care program at Children’s Hospital of Pittsburgh of UPMC has a new medical director—**Robert Clark** (Fel ’95), an MD, chief of the Division of Pediatric Critical Care Medicine at Children’s, and professor of critical care medicine and pediatrics. For the program, Clark plans to harness the wealth of electronic medical record data at Children’s to quantify current human and health care costs and ultimately use those data to bolster patient outcomes. Clark advocates moving further away from the traditional “pass-the-baton” approach between specialists to a more integrated, team-based concept of care.



Clark

Gastrointestinal immunologist **Timothy Hand**, a PhD, recently joined Children’s Hospital of Pittsburgh of UPMC and the School of Medicine as an assistant professor of pediatrics; he comes from the National Institute of Allergy and Infectious Diseases. Hand was named one of four scholars within the Richard King Mellon Foundation Institute for Pediatric Research; his work explores immunological modulation in the gut and its interaction with invading pathogens and the microbiome. This research could have implications for Crohn’s disease, enteric (intestinal) infections, and food allergies.



Hand

Chris Donnelly, a PhD and assistant professor of neurobiology, has joined the University’s Brain Institute to lead a major new basic science initiative to understand the molecular mechanisms of amyotrophic lateral sclerosis (ALS). Donnelly recently published findings in *Nature* suggesting that clearing a blocked passageway between the nucleus and the cytoplasm in motor neurons may be an approach to treatment. Donnelly’s research will be based in the new Live Like Lou Center for ALS Research.

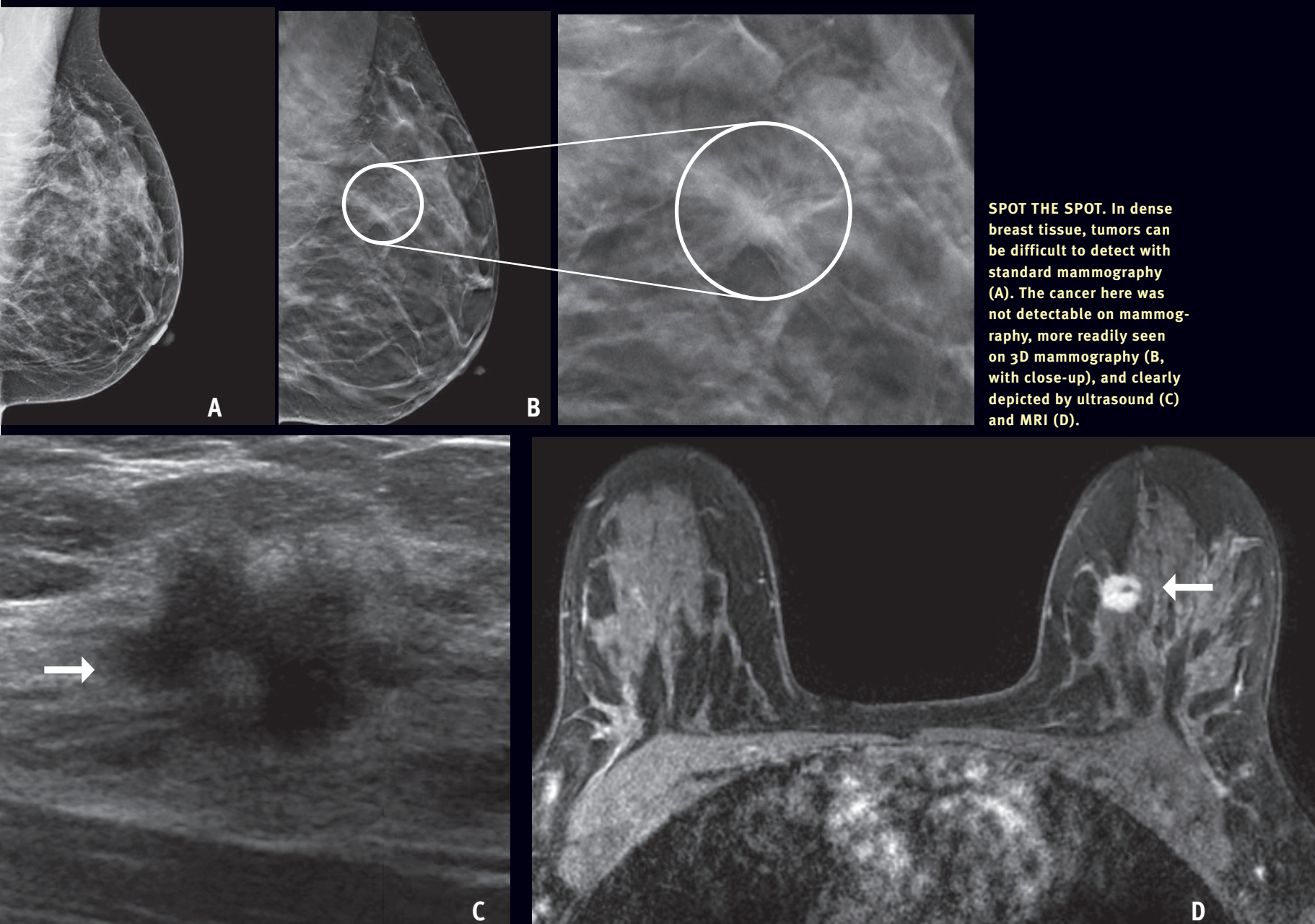


Donnelly



Thathiah

Also new to the Brain Institute—**Amantha Thathiah**, a PhD assistant professor of neurobiology. Thathiah joins Pitt from the University of Leuven and VIB Center for the Biology of Disease in Belgium, where she worked to understand the pathogenesis of Alzheimer’s disease. Most recently, she published findings in *Science Translational Medicine* showing that genetic deletion of the orphan G-protein-coupled receptor GPR3 alleviates memory deficits and reduces the amyloid plaque burden in Alzheimer’s disease mouse models. Her studies suggest that GPR3 could be a therapeutic target in drug treatment for Alzheimer’s. —KB



SPOT THE SPOT. In dense breast tissue, tumors can be difficult to detect with standard mammography (A). The cancer here was not detectable on mammography, more readily seen on 3D mammography (B, with close-up), and clearly depicted by ultrasound (C) and MRI (D).

GETTING SMART ABOUT BEING DENSE

It might not seem especially surprising that an esteemed professor of radiology, who literally wrote the book on breast imaging (a weighty 1,488 pages), diagnosed her own breast cancer.

"I've known since I was in high school that I had a family history," the University of Pittsburgh's Wendie Berg, an MD/PhD, says.

Berg was writing a chapter on risk models—methods that tally risk based on family history of breast and ovarian cancer, age, height, weight, and other factors. Berg's result came to a 19.7 percent lifetime risk—just under the 20 percent indicated for MRI imaging in addition to standard mammography.

Though her mammogram and tomosynthesis (3D mammogram) a year earlier had been clear, Berg, like about 40 percent of all women, has dense breasts that can make detecting cancer more difficult. Knowing this, and having led trials investigating supplemental ultrasound and MRI for that population, she opted for an MRI.

"I wasn't going to look at it," she says of the scan. Of course she did, and she saw a .9 centimeter tumor that the 2D and 3D mammograms had missed.

All ended well for Berg (who got the all-clear after a procedure and a month of radiation). But she was struck by how lacking physician advice seemed to be when it comes to dense breasts: "My own well-educated, well-intentioned doctor wasn't able to guide me. And, unfortunately, my experience is not unique," she says.

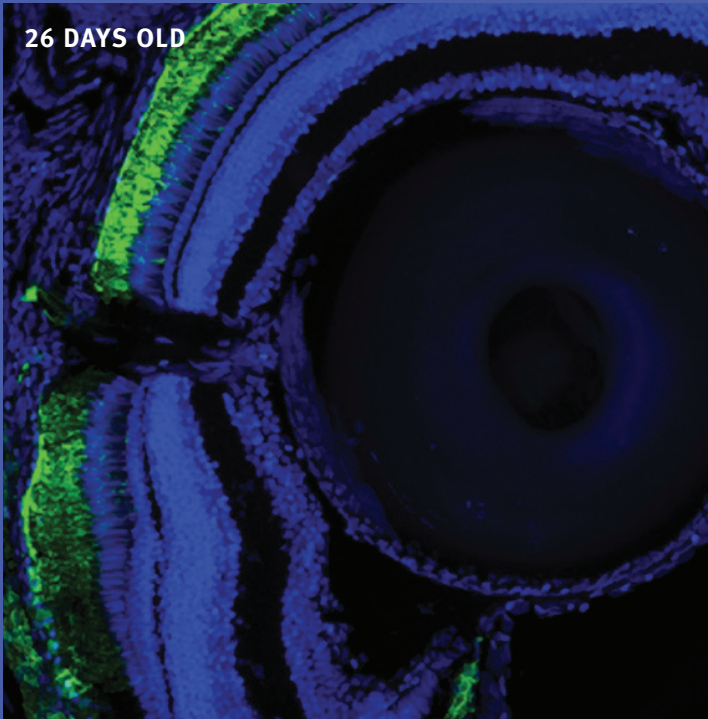
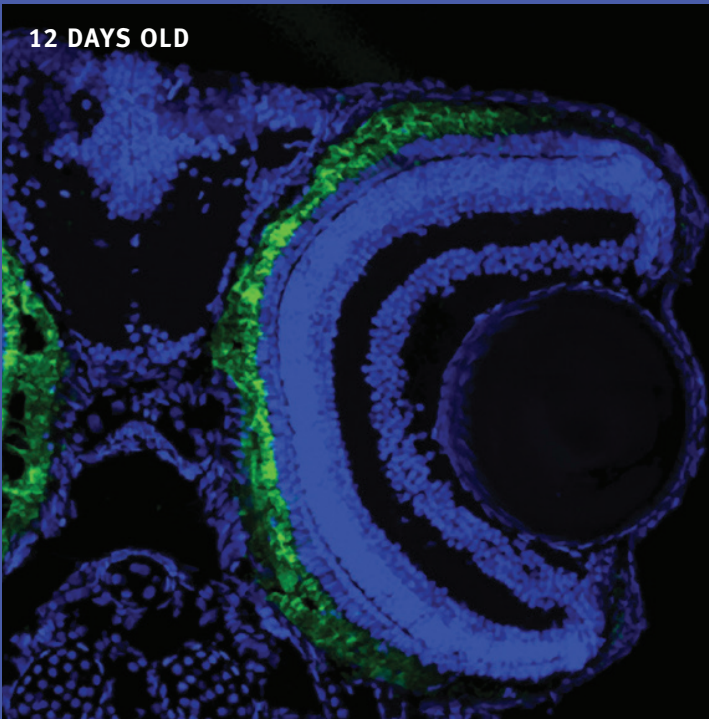
So, Berg joined with patient advocate JoAnn Pushkin and technologist Cindy Henke-Sarmento to launch DenseBreast-info.org, an online tool to educate patients and doctors about the implications of dense tissue: what it means for cancer risk, imaging decisions, and even insurance coverage.

"There's a huge gap in getting the message out about additional cancers which may be found by further screening and the potential for a false-positive which may result from supplemental screening," says Berg. "Women have to weigh the stress and harm of extra testing against possible delayed detection of cancer."

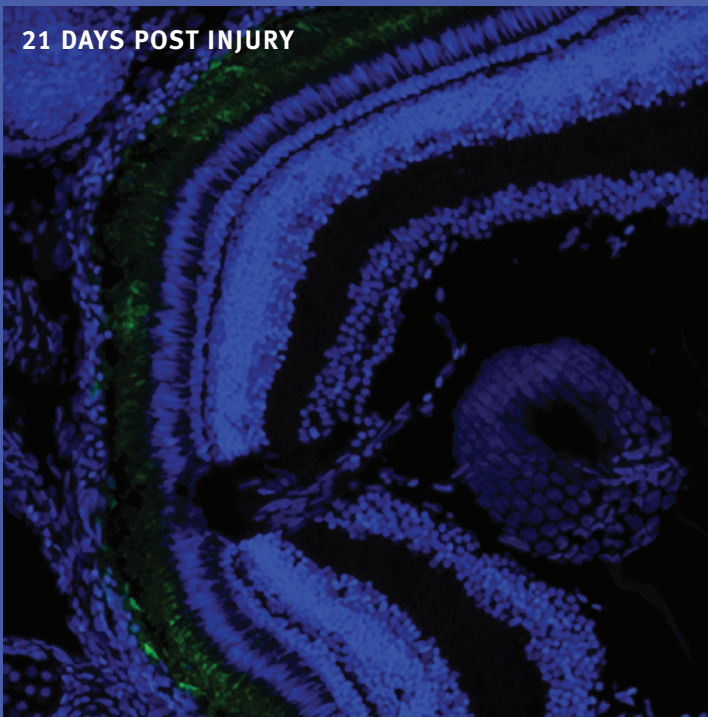
—Robyn K. Caggins

—Images courtesy Wendie Berg

NORMAL DEVELOPMENT



REGENERATION



Unlike mammals, zebra fish can regenerate cells in their retinas and retinal pigmented epithelia (RPE) after injury. **THIS PAGE:** The top row shows normal development of the RPE in zebra fish (green). The bottom row depicts RPE regeneration in age-matched sibling larvae seven and 21 days after injury, when green RPE cells begin to reappear. **OPPOSITE PAGE:** At 44 days post injury, zooming in further, the zebra fish has fully recovered its RPE (green) and photoreceptors (aqua).

SEEING ANEW

NAVIGATING RETINAL REGENERATION

BY KRISTIN BUNDY

“We FedExed all of our fish,” says Jeffrey Gross as he steps out of a brightly lit room full of 11,000 thin, green tanks of tiny, translucent zebra fish.

In August, the 12,000-some fish embryos

of ophthalmology and the E. Ronald Salvitti Professor of Ophthalmology Research.

Gross and his crew had been studying eye development and congenital eye diseases in Austin when Pitt enticed them with the opportunity to dive into the research they

progenitor cells, proliferate, and replace the injured cells.

In mammals, Müller cells recognize when an injury has occurred, but they get stuck in the process and don't de-differentiate or reinvent themselves before they proliferate. Instead, they build scar tissue.

Gross and his team plan on comparing mammalian Müller cells to those of zebra fish to see why they act differently. They are curious to learn whether gene expression influences the outcome.

“One idea is maybe the fish have evolved this amazing ability to [regenerate retinal cells], and there's a magic bullet that we don't have,” he says. Another possibility: Perhaps mammals once had this ability but then lost it at some point in their evolution. If it's the latter, Gross suspects they may be able to find a way to circumvent the genes that are turned on or off and help mammalian Müller cells regenerate just as swimmingly as those of the zebra fish.

Gross is also the director of the Louis J. Fox Center for Vision Restoration—perhaps the world's first regenerative ophthalmology center—which is now funding his research. A collaborative, multidisciplinary venture between the UPMC Eye Center and Pitt's McGowan Institute for Regenerative Medicine, the center brings clinical and basic science faculty together to advance ocular regenerative medicine. “This really is something unique to Pitt,” Gross notes.

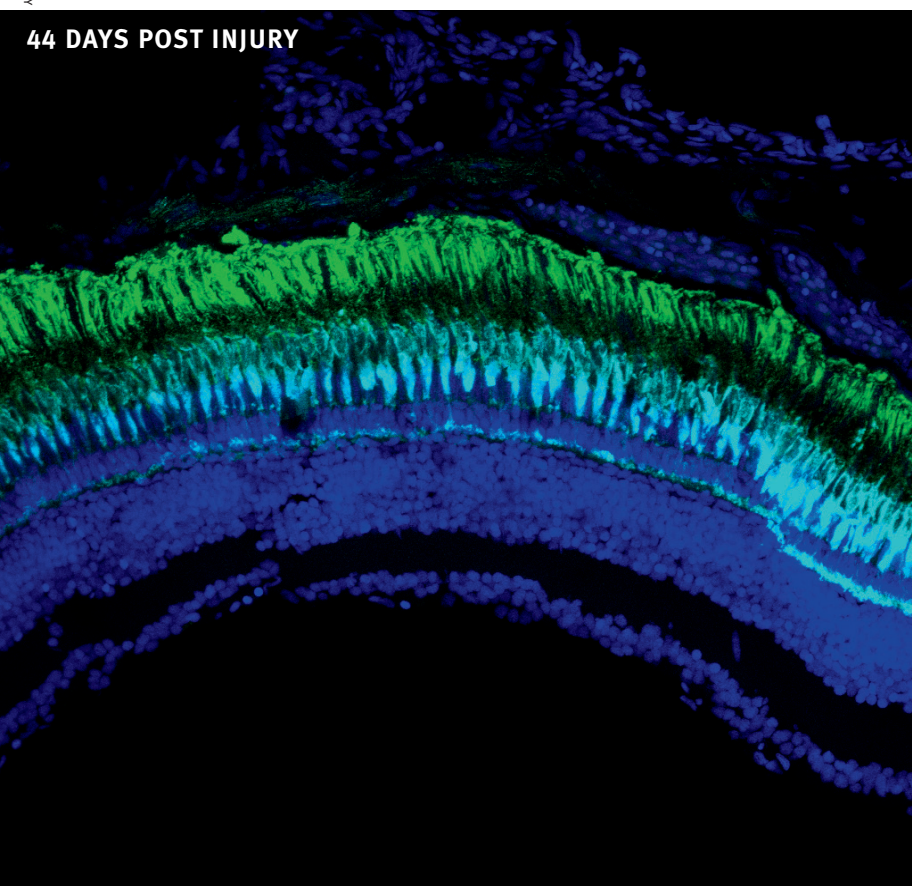
“We have so much expertise in ophthalmology, on the research side [and] on the clinical side. The McGowan [Institute] is terrific for regenerative medicine. We have all of these resources here at Pitt that are supporting the Fox Center. . . . It's really a gem,” says Gross. “Something that we can build off of to cure blindness.” ■

were most interested in—regenerative biology and its genetic and epigenetic mechanisms. For Gross, Pitt was an ideal setting: a medical school that's both a clinical and basic science powerhouse. (The fact that the new digs are home to one of the largest zebra fish facilities in the country gave Pitt a fin up, too; Gross's fish joined some 11,000 tanks full in Biomedical Science Tower 3.)

Why zebra fish? Because they have a remarkable ability to regenerate their retinas, explains Gross. “And these are the tissues that are affected in a lot of blinding disorders.”

In the zebra fish, Müller cells—the structural components of the retina that also play a role in homeostasis—regenerate in an elegant process. The cells recognize the injury, de-differentiate, determine which cell is needed, morph into

made the move from the University of Texas at Austin to their new home at the University of Pittsburgh School of Medicine, along with their handlers: four PhD students, two postdocs, and Gross, a PhD professor

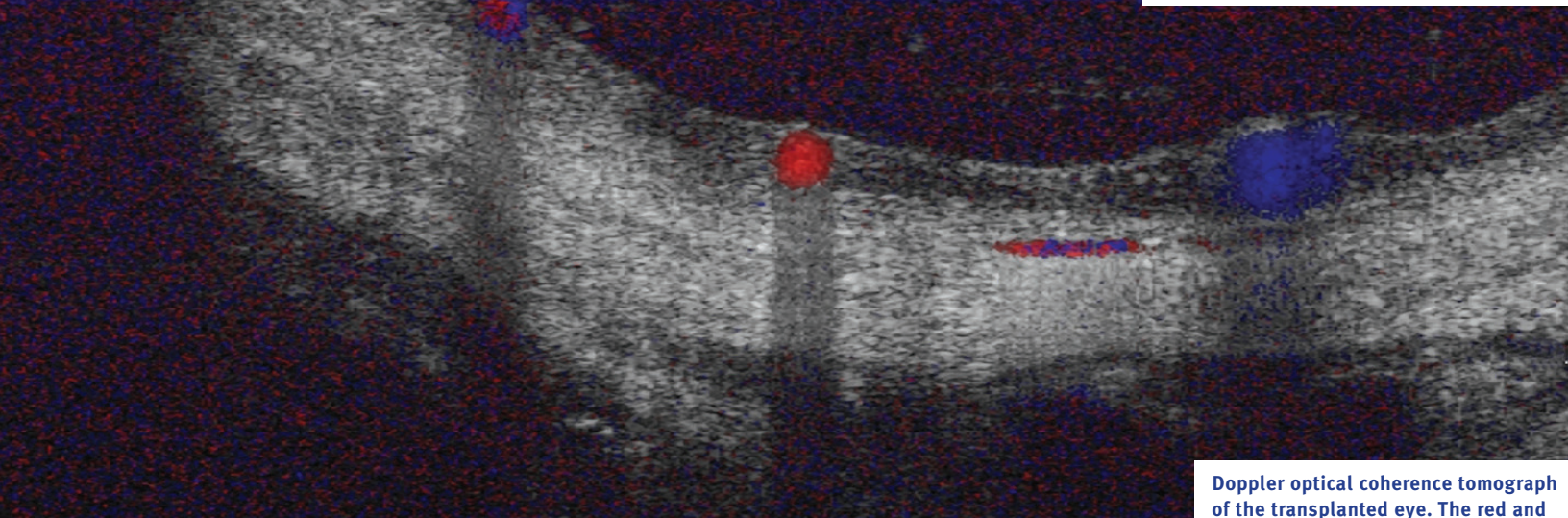


44 DAYS POST INJURY



HAND-EYE COORDINATION

FIRST VIABLE WHOLE-EYE TRANSPLANT, IN A RAT
BY KRISTIN BUNDY



Doppler optical coherence tomograph of the transplanted eye. The red and blue shown here depict blood flow in the vessels in real time.

COURTESY WASHINGTON LAB & THE OPHTHALMIC IMAGING RESEARCH LAB

“**T**hat’s the rat right there!” says Kia Washington (Fel ’08, Res ’11, Fel ’12), pointing to the scientific poster hanging in her office. “It inspires me. [And] I haven’t really had a chance to decorate.”

At first glance, it’s a bit startling because, well, not too many people have photographs of rats on their walls. But look closer, and it’s a marvel to behold—a white-furred, pink-eyed rodent that sees with an eye that was once not its own. This rat is the first viable orthotopic rodent eye transplantation model ever developed—a feat that was spotlighted at the Department of Defense’s annual Military Health System Research Symposium in August—and Washington, an assistant professor of plastic surgery and associate director of the hand transplantation program at Pitt and UPMC, led the group that pulled it off.

Yes, you read that right: hand transplantation. Washington acknowledges, “People always ask me, ‘Why is a hand surgeon doing research on eye transplantation?’ And I will say it’s kind of an evolution. You never know where things are going to take you.”

A plastic and reconstructive surgeon by training, Washington completed a fellowship at Pitt’s Thomas E. Starzl Transplantation Institute, where she built a functional face transplant model in the rat. This research, along with her clinical practice in microsurgery

and plastic surgery (she has surgical privileges at both UPMC Presbyterian and the VA Pittsburgh Healthcare System) prepared her for eye transplantation research, she says.

It all came together when Vijay Gorantla, an MD/PhD associate professor of plastic surgery at Pitt, approached Washington two-and-a-half years ago about joining a multidisciplinary, multi-institutional collaboration to study eye transplantation. The team needed an animal model. “That’s where my expertise of working on the face transplant model came in,” explains Washington. “I said, ‘Well, I can develop a model in the rat. We’ll just add an eye.’”

She quips, but this is no easy endeavor. Transplanting an entire eye involves many different tissue types (as do hand transplantations). In addition to the eye itself, the procedure includes the transplantation of the extraocular muscles, subcutaneous tissue around the eye, vessels, the optic nerve, and sometimes skin, like the eyelid. They call this vascularized composite allotransplantation, or VCA.

Whole-eye transplantation, although not a new concept (it was first attempted in the late 1800s), hadn’t been a viable option until just a few years ago, when Harvard’s Larry Benowitz and colleagues discovered a way to coax the axons of the optic nerve to regenerate—impressive, considering the central nervous system doesn’t typically regenerate easily.

Benowitz is a key member of the multi-institutional eye transplantation research group initiated by Gorantla. Joel Schuman, the former chair of ophthalmology at Pitt and former director of the Louis J. Fox Center for Vision Restoration, connected the Pitt team with Benowitz. Schuman also brought in Jeffrey Goldberg, chair of ophthalmology at Stanford, who is studying optic nerve neuroprotection and regeneration. Two PhD assistant professors of ophthalmology at Pitt—Kevin Chan and Michael Steketee—round out the group.

As Benowitz and Goldberg work on optic nerve regeneration, the Pitt people are optimizing and refining surgical procedures, transplanting the eye in Washington’s rat model and in human cadavers. They will also focus (so to speak) on issues surrounding rejection, tissue viability, immunomodulation, and plasticity of the visual cortex.

“It’s high-risk/high-reward research,” notes Washington. “It could go nowhere, but if it goes somewhere, it would be incredible to actually be able to restore sight for somebody through this type of surgical intervention.” She adds, “People are saying it’s a pipe dream, a moon shot, which it is. But I think it will happen in my lifetime. Do I think it’s going to happen five years from now? Probably not. Will it happen 20, 30 years from now? I think it’s a high possibility.” ■

A fluorescent zinc sensor tracks and measures synaptically released zinc in an auditory brainstem nucleus.

THINK ZINC

FOR BRAIN BALANCE

BY ALLA KATSNELSON

Our bodies are flooded with zinc—it is the most abundant mineral in the body after iron. It's thought to help power basic processes in the body, such as growth and immune function. Now, research from the University of Pittsburgh has found a specific and surprising role for the metal in regulating how neurons communicate; it probably figures heavily in neurodegeneration, learning, and memory.

Neurotransmitters—message-carrying chemicals—hang out at the branched endings of neurons in tiny sacs called synaptic vesicles. When it's time for a neuron to transmit a signal to the one next door, the vesicles dump their contents into the gap between the two cells. The neurotransmitters float across this synapse and dock at receptors on the other side.

Often, though, one key neurotransmitter doesn't make this crossing alone. For decades, scientists have observed that many vesicles containing glutamate—the main carrier of excitatory nerve signals in mammals—also contain free-floating zinc. Yet zinc's role in neurons was a long-standing mystery, because the tools available to track it weren't fast enough to follow its path. Researchers couldn't determine with certainty where it went or what its job was, says Thanos Tzounopoulos, a PhD associate professor of otolaryngology and neurobiology at Pitt, who also holds Pitt's Auditory Physiology Chair.

Tzounopoulos's group recently used new tools to reveal some answers: namely, that zinc is a neurotransmitter in its own right, and it holds a mighty vocation in a previously unknown pathway that the brain uses to fine-tune neural signaling. These findings were published in two *Proceedings of the National Academy of Sciences* articles last year.

Tzounopoulos, who studies the auditory system, had been curious about zinc's job

description since reading some 15 years ago that brain areas involved in hearing have abundant amounts of the mineral. But he didn't get around to looking into zinc until arriving at Pitt in 2008. At a dinner following his job talk, he happened to sit next to Elias Aizenman, a PhD and Pitt professor of neurobiology who studies zinc's role in nerve-cell death. Conversation led to collaboration, which yielded a 2013 article showing that the mineral interferes with glutamate's excitatory signal. But technological limitations still hamstrung the prospect of determining its role more precisely.

Not long after he and Aizenman completed their study, Massachusetts Institute of Technology chemist Stephen Lippard heard Tzounopoulos give a talk about it. Intrigued, Lippard offered to develop a fluorescent sensor that could track zinc in a quantifiable way, as well as a chelator—a compound designed to intercept and capture zinc the instant it's released from the vesicles.

Tzounopoulos's group deployed these tools to look at a class of auditory neurons that receive signals from cells with zinc-rich synapses. They tracked zinc's effects on a particular type of glutamate receptor called the extrasynaptic NMDA receptor, positioned just outside the synapse. Tzounopoulos was particularly interested in what would happen at these receptors because neuroscientists are starting to believe that stimulating them can trigger cell death.

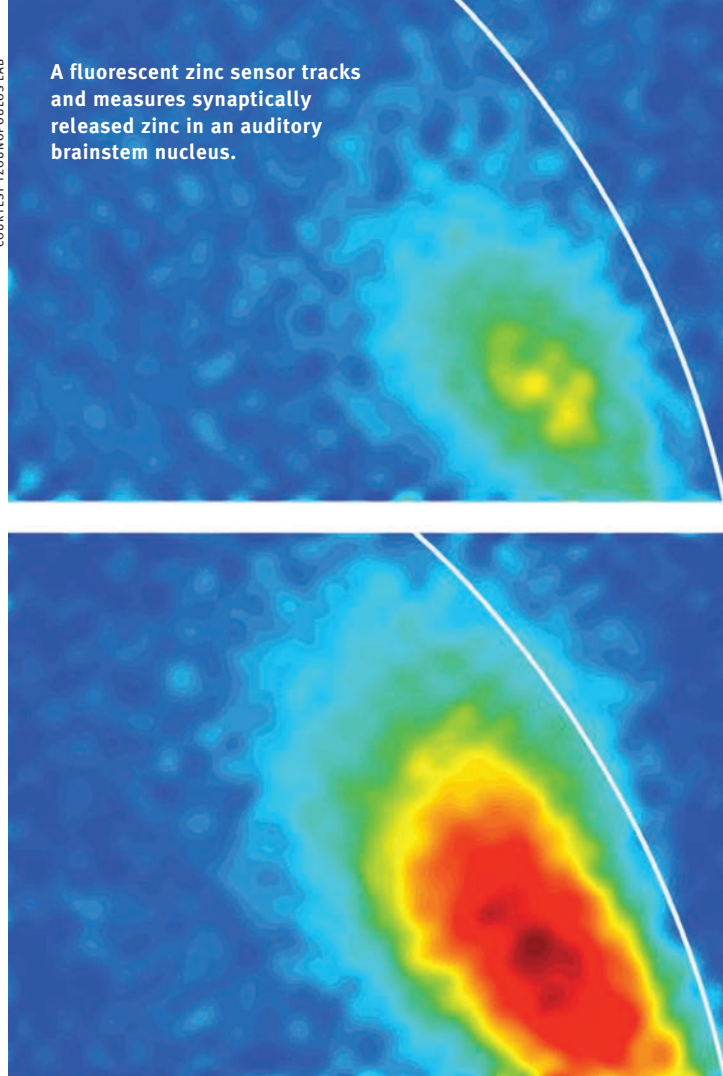
In their May 2015 study, the researchers showed that zinc diffuses into the synapse and surrounding region as a neurotransmitter and that it interferes with the extrasynaptic NMDA receptors. "This means that, in the same vesicle, you have an activator of the receptor—glutamate—and the brake for its

activation—zinc," he explains.

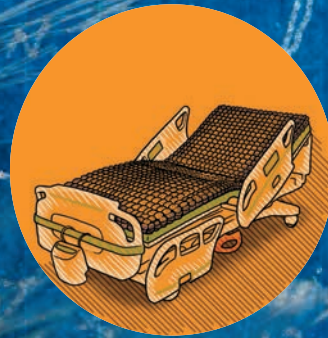
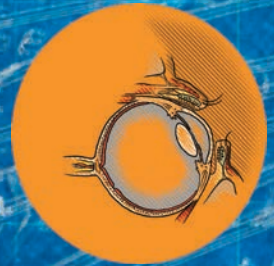
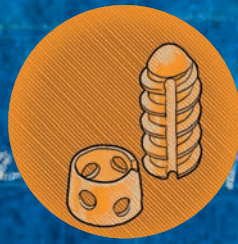
By dampening such stimulation, Tzounopoulos adds, zinc could be having a neuroprotective effect. "These extrasynaptic receptors are extremely important [in] neurodegenerative diseases—when the balancing and fine-tuning of the receptors is out of whack, it can lead to neurodegeneration," he says. "They have to be kept in check."

The group's more recently published work demonstrates for the first time a wider role for zinc: The mineral serves as the gas and the brakes for another major type of glutamate receptor, called the AMPA receptor, involved in proper brain functioning. They found that zinc is coreleased with glutamate in some areas of the neocortex (the most recently evolved part of the brain, which is often impaired in neurodegenerative diseases). This tag-teaming affects AMPA receptor response, which suggests that zinc has a fundamental role in modulating how strongly neurons connect to each other at any given time.

Further, it seems that zinc probably acts on other types of receptors besides glutamate receptors. "Now that we have the right tools," says Tzounopoulos, "we can explore what other partners of the synapse may be modulated by zinc." ■



LESSONS



To get new ideas to the clinic, professors become students once again.

COULTER PROGRAM TEACHES ACADEMICS
TO THINK LIKE ENTREPRENEURS
BY JENNY BLAIR

FOR THE PROF

A couple of years ago, a group of Pitt researchers decided the humble eyedrop was due for an upgrade. Eyedrops are messy and sometimes prone to interact with other medications—“a terrible way to get drugs into your body,” Morgan Fedorchak, a PhD assistant professor of ophthalmology, says.

So the group got creative and invented an alternative: SoliDrop, a slow-release eye gel.

THEN THEY GOT STUCK.

Coming up with a neat medical technology in the academic setting is one thing. Commercializing it is quite another. You need a striking study, a snazzy prototype, an airtight business plan—all of which require money most grants don't cover and skills most professors haven't learned. This stage between innovation and commercialization is often referred to as the valley of death.

But the SoliDrop researchers are optimistic. That multidisciplinary team includes Fedorchak, who helped develop the gel alongside Steven Little, a PhD and Pitt's chemical engineering chair (among other titles), Ian Conner, an MD/PhD and assistant professor of ophthalmology, and Joel Schuman, an MD and former chair of ophthalmology. In hopes of seeing the gel in patients someday, Fedorchak and Conner are taking a crash course in how to commercialize the gel, and they've gotten sufficient funds to put the invention in front of external investors—thanks to the Coulter Translational Research Partners II Program at the University of Pittsburgh—or Coulter@Pitt.

The program helps researchers with new medical technology ideas attract investment. Each year, five \$100,000 Coulter grants go to Pitt clinician-engineer teams that have identified an unmet clinical need and come up with a feasible, patentable solution.

ILLUSTRATIONS | MICHELLE LEVEILLE/ARTIFACT GRAPHICS

But “last-mile money,” in the words of Coulter project manager Suneera Bhatia, is not enough. The teams also have to learn how to get an idea ready for licensure or a new company. In the jargon of commerce, this process is called de-risking, and Coulter@Pitt teaches researchers how to do it. When it’s time to present to potential investors, the researchers are boardroom ready.

Previous awardees, Fedorchak recalls, told her to be prepared—“that [Coulter was] going to take us outside of our comfort zone as scientists, as purely academicians. I thought I was ready for that, but it definitely was a challenge,” she says. “I learned so much through the process.”

If the name Coulter sounds familiar, you may have heard of the inventor Wallace Coulter. He patented an automated blood-cell-counting device in 1953, later founding the company that became Beckman Coulter.

Coulter@Pitt funds come mostly from a five-year, \$667,000-per-year grant made by the Wallace H. Coulter Foundation to the Swanson School of Engineering’s bioengineering department in 2011. Only 16 U.S. universities have received these grants.

At Pitt, additional institutional contributions—from the Swanson School of Engineering, Schools of the Health Sciences, Office of the Vice Provost for Research, and Innovation Institute—bring Coulter@Pitt’s annual budget to \$1.2 million. Each year, five innovator teams chosen by the Center for Medical Innovation are awarded \$200,000 to seed their projects.

“Whatever that last barrier is, or last set of barriers, [Coulter] will fund that,” says David Brienza, a PhD and professor of rehabilitation science and technology and of bioengineering, who is another Coulter grant awardee. Potential barriers might include clinical studies or marketing research.

Figuring out those needs is a high priority—and happens before any project is funded. Each spring, after passing an early selection round, seven to 10 candidate clinician-engineer teams enroll in a semester-long course called From Benchtop to Bedside. Nicknamed B2B, the course is taught by serial entrepreneur Babs Carryer, director of education and outreach at Pitt’s Innovation Institute, along with noted guest speakers from industry.

In B2B, doctors learn to do market research. Engineers learn when to call a clunky prototype good enough. And everyone learns the language of business. The teams meet with students from Pitt’s law and business schools to put together business plans. They study regulatory requirements, intellectual property rights, and market-research techniques. They think deeply about who their customers are. In the process, they add rigor and clarity to their proposals and ultimately develop a polished pitch for investors.

After completing B2B, five teams are chosen to receive grant money. They’re each assigned to a project manager who helps them set and navigate milestones. Each team is co-led by a clinician and a scientist/engineer.

Teams get plenty of advice and mentoring, beginning with an oversight committee, a kind of “board of directors” who come from clinical practice, industry, academia, venture capital, regulatory affairs, and health care economics. Additionally, some 80 advisors serve as Coulter@Pitt mentors, including Sanjeev

Shroff, a PhD who is principal investigator of the program, as well as chair of the Department of Bioengineering; co-PI Stephen Badylak, a DVM, MD/PhD, and deputy director of the McGowan Institute for Regenerative Medicine; and co-PI Marc Malandro, a PhD and the Innovation Institute’s founding director. Other advisors include angel investors, medtech business leaders, and people who know how to navigate regulatory hurdles at the Food and Drug Administration and its equivalents abroad.

Coulter@Pitt collaborates with the med school’s Clinical and Translational Science Institute, which works with researchers at an earlier stage in the innovation process. At a later stage,

BIZ DEVELOPMENT 101

A LOOK AT A FEW COULTER-SPONSORED INVENTIONS, AND WHAT ACADEMICIANS ARE LEARNING ABOUT THE BUSINESS WORLD

the Innovation Institute serves as “our pipeline to the market,” as Coulter@Pitt director Max Fedor puts it, helping license Coulter-packaged technologies to an existing company or start a new one.

Coulter defines a success as at least \$500,000 in professional investment. By that measure, Pitt’s program has had several.

Two new companies have formed around Coulter@Pitt innovations. One, NanoVision Diagnostics, offers an early cancer-detection technology developed by Yang Liu, a PhD associate professor in the departments of medicine and bioengineering. Leading the clinical side of the project are co-PIs Randall E. Brand, an MD professor of medicine, and Rohit Bhargava, an MD associate professor of pathology.

The other company, Formabone, is commercializing a resorbable bone putty developed by bioengineering professor Prashant Kumta, a PhD (who has several other engineering and dental school appointments), and periodontics chair Charles Sfeir, a DDS and PhD who is also director of the Center for Craniofacial Regeneration. Sfeir is also working on another Coulter project.

Two Coulter software products—InterACTION, which assists physical therapists during joint rehabilitation, and PIVOT, which helps diagnose ligament tears in the knee—have been optioned by Impellia, a company founded by retired Pittsburgh Steelers quarterback Charlie Batch. Several other projects, according to Fedor, are “ripe” and ready to move into licenses or startups soon.

The whole process can be humbling, with the professor becoming a student once again. But Fedorchak says it’s rewarding: “This is what every scientist hopes for, right? Not to be hunched over a bench their entire career and never have anything get outside the laboratory,” she says. “I see it as a very welcome kind of problem and work to do.”

MAKE EYEDROPS GEL

Glaucoma patients are critically dependent on eyedrops to help control the sight-threatening rise of pressure within the eye. But eyedrops may be so poorly absorbed that they have to be applied several times a day in high doses—a regimen that can be almost impossible to adhere to and can cause unwanted side effects.

“Eyedrops are very inefficient,” says assistant professor of ophthalmology Morgan Fedorchak (PhD ’11). “There are all these permeability barriers designed by nature to keep things out of your eye.”

SoliDrop, whose inventor team includes Fedorchak and assistant professor of ophthalmology Ian Conner, is administered like an eyedrop, but then at body temperature turns into a gel. It settles in the pocket under the lower eyelid and slowly releases the drug over the course of a month. In animals, Fedorchak says, the gel stays put and has great therapeutic effect. (Fedorchak is also an assistant professor of chemical and petroleum engineering; Conner, who holds a secondary appointment as assistant professor of bioengineering, directs the UPMC Eye Center in Bethel Park.)

Coulter money has allowed the SoliDrop team to start gathering safety data to bring to the FDA for an Investigational New Drug (IND) application. At the same time, the team is looking into licensing strategies and partnerships to fund an IND clinical trial.

Fedorchak says she learned so much in the B2B course that being chosen to receive funding was “icing on the cake.” And Coulter’s flexibility regarding how funds are spent, she says, has given them great freedom, allowing her and Conner to hire business consultants, look into manufacturing methods, and do toxicity testing.

Lesson learned: Be nimble. When Fedorchak and Conner realized they needed to change their original milestones—a change that would affect tens of thousands of dollars’ worth of their Coulter funds—Fedorchak gingerly approached the team’s project manager, Shubhangi Lal, with a revised plan of action.

“She didn’t even blink. She was like, ‘Okay, let’s do it,’” Fedorchak recalls. “The buzzword is ‘pivot.’ We’ve pivoted rather dramatically. It’s great.”

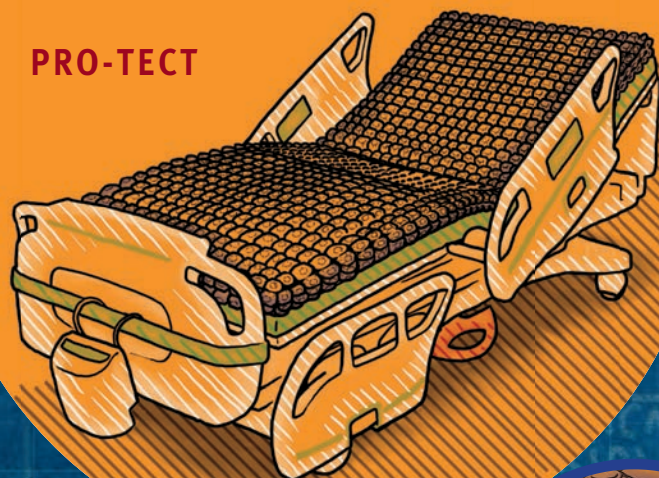


SoliDrop

CBI SEI 3.0KV X500 10µm WD 8

An alternative to the humble eyedrop.

PRO-TECT



KEEP IT COOL

Lying flat in bed for days or weeks can lead to pressure ulcers in critically ill and injured patients. As the skin over the sacrum—the large bone at the bottom of the spine—suffers unremitting pressure and friction, it can break down, causing wounds that sometimes require surgical removal of large areas of skin and muscle. These ulcers can be difficult to prevent and harder to reverse. In the United States, their burden is estimated as high as \$11.6 billion annually.

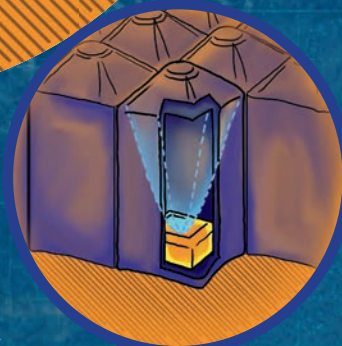
Enter **PRO-TECT**, an air mattress with a cooling gel inside. As the body exerts downward pressure at the sacrum, the cooling elements conduct heat away from that area of the body. This allows the tissue to withstand the pressure and shear force, without causing or worsening an ulcer—or lowering the patient’s overall body temperature.

PRO-TECT is the brainchild of David Brienza, a PhD and a professor of rehabilitation science and technology and of bioengineering, and trauma surgeon Alan Murdock, an MD; it grew from Brienza’s research on wheelchair cushions. The team is now engaged in a clinical trial.

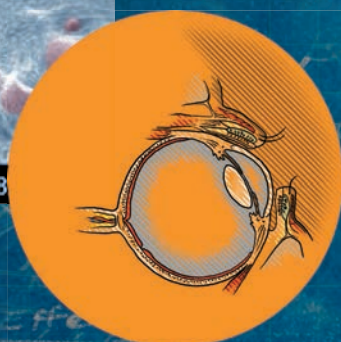
Lesson learned: Ugly can be beautiful. An engineer’s perfectionism can be the enemy of good business development—at least at first.

True to form, Brienza began intent on a polished product. But potential licensees told the team it might need to redevelop the product anyway. The Pitt group learned to focus on providing evidence that the mattress could be effective, developing a functioning prototype for testing purposes instead.

“We wanted to perfect the product,” says Brienza. “Then that all went out the window. We said, ‘Let’s just make something that works, even if it’s ugly.’”



Embedded in the bed is a cooling gel.



SOLEFUL STIMULATION

Neuromodulation is a mysterious but effective therapy for a number of disorders. Somehow, if you electrically stimulate a peripheral nerve, that stimulation can send signals along the spinal cord and cause changes in brain neurotransmitters; and those neurotransmitters can affect a seemingly unrelated part of the body, including the muscles controlling the bladder. One FDA-approved overactive bladder (OAB) neuromodulation device on the market requires weekly in-office neuromodulation sessions delivered via a needle inserted behind the ankle.

The **FootStim** team takes a different approach. Instead of needles, FootStim uses stickers on the sole of the foot to deliver the electrical pulses to branches of the tibial nerve. This noninvasive device could be used by patients at home. It would also be a cheaper alternative.

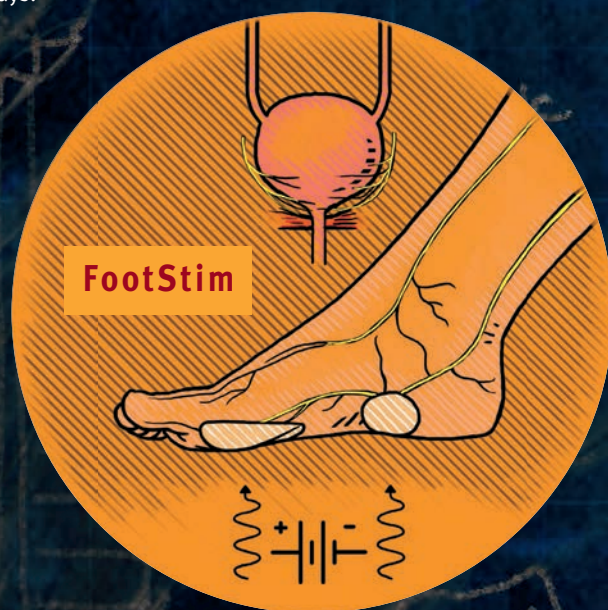
In a study of eight healthy human volunteers, a single 90-minute stimulation session with FootStim led to a temporary 200 cubic centimeter increase in bladder capacity, with no side effects. A second study of 19 women with a form of urinary incontinence found that 16 responded to a nightly three-hour session with FootStim, with statistically significant reductions in symptoms.

More studies need to be done, says assistant professor of urology Christopher Chermansky, an MD. But if the technology is effective, it could hit the market within three to five years. Already, FootStim has caught the eye of a company in California, and the team hopes to license their product next year.

Chermansky's co-PI, associate professor of urology Changfeng Tai, a PhD, says Coulter money is very different from a National Institutes of Health grant. "Less than half is about the science," he says. "More than half is about development, business, venture investment, all those things. They asked us to develop a business plan. I never [had to write] that before," he adds, laughing.

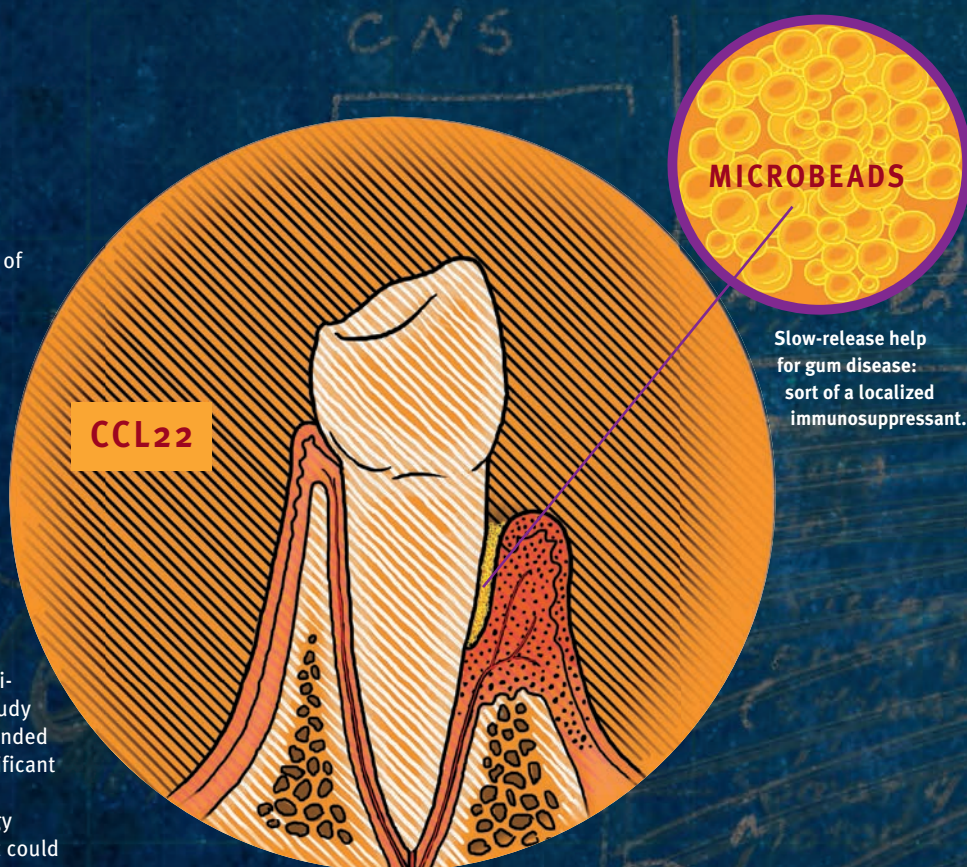
Lesson learned: Business is, in large part, who you know.

The biggest advantage to the Coulter experience, Tai says, was the links it provided to business people. You can't move forward without the right alliances. "Without Coulter, we [would] never meet those people," he says.



FootStim

Electrical stimulation of the foot can help bladder control.



CCL22

MICROBEADS

Slow-release help for gum disease: sort of a localized immunosuppressant.

IMMUNE TO GUM DISEASE

Getting your teeth professionally cleaned to reduce their bacterial load around the gumline has long been a mainstay in preventing and treating periodontitis (gum disease). But periodontics professor and chair Charles Sfeir, a DDS and PhD, and Steven Little, a PhD, the William Kepler Whiteford Professor and Chair of Chemical Engineering, and professor of immunology, think there's a better way.

In periodontitis, the immune system is actually part of the problem. Though bacteria trigger the disease, it's when immune cells overreact to those bacteria that the accompanying bone destruction takes place. By contrast, when it comes to tumors, the danger is when the immune system fails to act. That's the clue Sfeir and Little were looking for.

Tumors ought to be highly inflammatory, alerting immune cells to destroy them. Yet they can survive, in part, by deceiving the immune system. Tumors exude a chemical signal called **CCL22**. That signal binds to receptors on regulatory immune cells, and those regulatory cells then alter the surrounding population of immune cells in favor of nondestructiveness. In effect, the tumors broadcast an "all is well" message.

Sfeir and Little devised a way to package CCL22 into degradable polymers that are deposited in powdered form beneath the gumline, where they stick in place and allow for sustained release of CCL22. As it does with tumors, the chemical signal promotes an anti-inflammatory environment in the immediate surroundings.

They've gotten a similar approach to work in animal models of dry eye disease—an inflammatory breakdown of the tear ducts—and even in limb transplants.

"We have rats that are walking around for over 200 days with another rat's leg, and they're on no systemic immunosuppression with these treatments," Little says.

The team is now looking for further funds with which to produce a patient-grade version of CCL22 and begin a safety study. "Coulter money is kind of keeping us alive," Little says.

Lesson learned: Grants aren't just for science anymore.

The Coulter@Pitt's lessons weren't entirely new to Little and Sfeir, who say they already had a good grasp of the commercialization process. But Sfeir has observed that Coulter changes the way researchers think about a grant—"You're not just doing it to publish papers," he says. Instead, Coulter mentors advise researchers to allocate funds for, say, consultants who can prepare pitches and do market research. "There's a bit more oversight than you would see in a regular grant, and that's very intentional on Coulter's part," Sfeir says.

WALK UP LEARNING

Joseph Samosky, a PhD assistant professor of bioengineering and director of Pitt's Simulation and Medical Technology Research and Development Center, is passionate about building a better medical simulator. His connection to the subject is personal: Both his parents suffered from medical errors, and better training might have prevented those mistakes. Plenty of evidence shows that simulator training translates to better performance among providers, he says.

That said, modern-day simulators can be cumbersome. They're bulky and nonversatile, and they require dedicated infrastructure and costly technician time. Moreover, they don't teach students anything on their own.

So Samosky and Pitt's John O'Donnell, a DrPH professor and chair of nurse anesthesia, are developing **BodyExplorer**, an expandable, customizable training system that will offer multiple plug-and-play training options—such as breathing-tube placement or IV medication administration techniques—much the way a smartphone runs apps. BodyExplorer is intended to be so user-friendly that a student could walk up, turn it on, and start learning any of a wide array of tasks, complete with plenty of feedback on her performance.

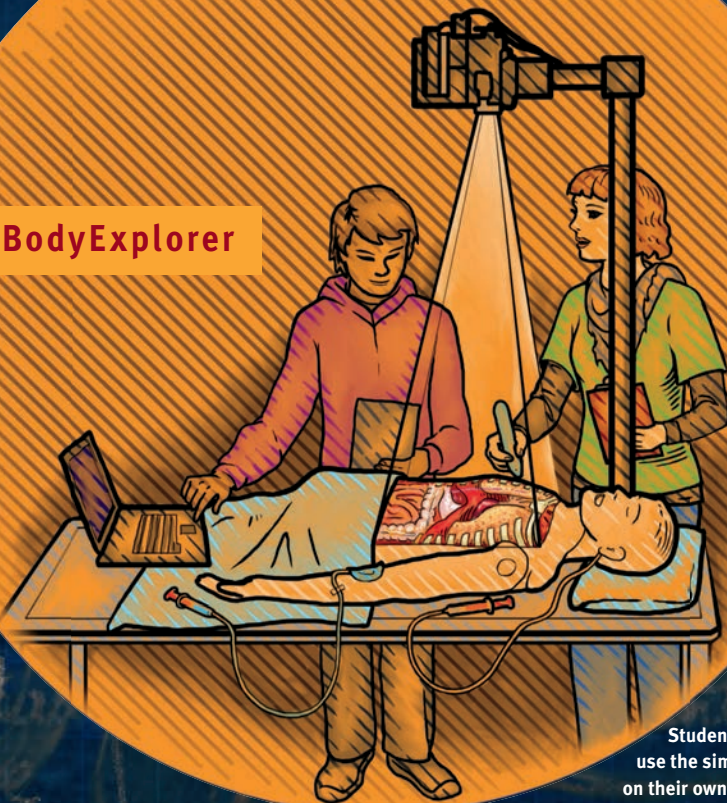
Investors have noticed. Samosky's team is in discussions with a party regarding licensing the product, and a new company could be developed as early as next year.

Lesson learned: Consider all the stakeholders.

As an engineer, Samosky figured at first, naturally enough, that the person he needed to bear in mind as he designed BodyExplorer would be the health science student who'd be training on it.

"But here's the thing: The student is not the person buying the system," Samosky says. It's essential to consider the perspective of a med school or hospital administrator who's wondering if she needs to build a simulation center or can cut costs by using a turnkey, on-demand learning system like BodyExplorer. Coulter's training helped him refine that vision.

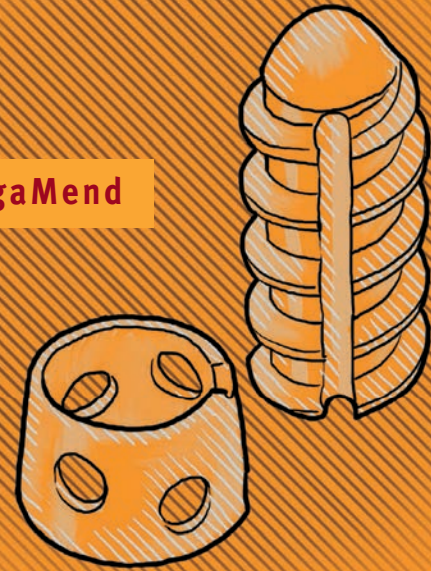
BodyExplorer



Students can use the simulator on their own.

Healing versus replacing ACLs.

LigaMend



NO LONGER TORN

Tears in the anterior cruciate ligament (ACL) are among the most common knee injuries—200,000 such injuries befall Americans each year. The ACL typically heals so poorly that surgical reconstruction—replacing the injured ligament with a graft—has been a go-to treatment for decades.

Yet reconstruction is less than ideal, says bioengineering professor Savio L-Y. Woo, a PhD, DSc, and DEng who is also on the core faculty at the McGowan Institute for Regenerative Medicine. Postoperative complications like osteoarthritis are common, and papers on surgical techniques for ACL reconstruction are being published all the time.

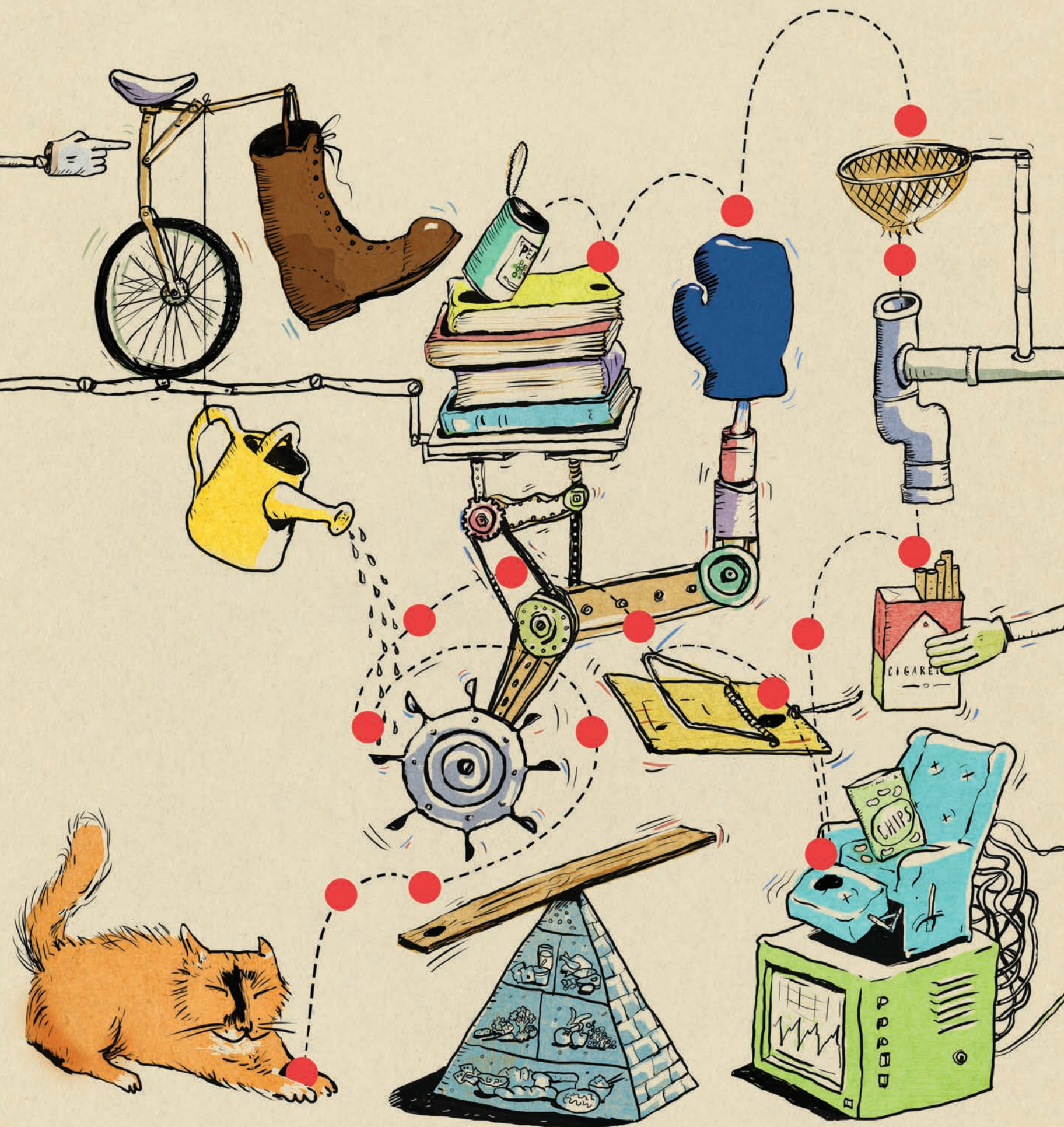
"When you have a procedure that has that many techniques," Woo says, "obviously something is not working right."

Woo, scientific PI, and his partnering clinical PI, associate professor of bioengineering Patrick McMahon, an MD, invented an alternative device, one that could heal the ACL and eliminate the need to replace it with a graft. Called **LigaMend**, it consists of FDA-approved extracellular matrix bioscaffolds and a collarlike resorbable magnesium ring. The ring loads the ligament where it attaches to the femur, preventing that attachment from weakening from lack of use during the long healing period. The bioscaffolding accelerates healing after surgical reconnection of the injured ligament. Studies in animals have shown promising results at 12 weeks, and the team is looking to carry that through to 26 weeks.

"If the attachment site is maintained and [does] not deteriorate," Woo says, "then we've really got ourselves a brand-new approach."

Lesson learned: Time it. "As academics, we don't work on a timeline," Woo says. "One question leads to another question, because we're not product-oriented, at least me. [But] the world is changing, and I need to adapt."

For more info on Coulter@Pitt, which accepts applications each fall, contact Max Fedor at maf210@pitt.edu.



ANOTHER WAY OF DOING SCIENCE
BY SHARON TREGASKIS

CAUSE AND EFFECT

In 1979, multiple scientific teams working independently in London, New York, Paris, and Princeton began zeroing in on a mysterious protein that seemed to speed cancer growth. They later named their quarry p53, a nod to its apparent 53-kilodalton weight.

Early studies suggested that the code responsible for the protein—the gene *TP53*, since found on the short arm of human chromosome 17 and in the DNA of most mammals whose genomes have been sequenced—was an oncogene, the cancer biology equivalent of your car’s accelerator.

Scientists would only discover years later that those first experimental cell lines had featured rogue forms of p53. As it turns out, unmutated p53 is actually more akin to a brake. It regulates the activity of other genes, monitoring the fidelity of the cell-division process, stopping erratic cell replication, and spurring repairs.

In cases of irreparable mutations, p53—dubbed “molecule of the year” by *Science* in 1993 and now widely known among cancer biologists as the “guardian of the genome”—induces senescence and even programmed cell death to stop precancerous cells in their tracks, before things get ugly.

Data can deceive and confuse. Getting it to reveal meaningful relationships is the charge of a new team of big thinkers from Pitt, Carnegie Mellon, and the Pittsburgh Supercomputing Center.

ILLUSTRATIONS | STACY INNERST

But like Longfellow's little girl with a curl, when *TP53* goes bad, it goes horrid—hence that early mistaken oncogene hypothesis. We now know that more than 50 percent of cancers feature mutated *TP53*; it's the most commonly mutated gene found in human malignancies. It's also among the more potent; tumors in which biopsies reveal *TP53* mutations behave more aggressively and are associated with worse patient outcomes.

"The excitement generated by [p53] and its fellow tumor suppressors is reaching a crescendo," wrote *Science's* then editor-in-chief Daniel Koshland Jr. 23 years ago when the journal made its molecule of the year announcement, "with exhilarating possibilities for prevention and cure of cancer."

The possibilities of p53 remain tantalizing, yet the quest to realize them in the past quarter

turn to computers to help them discover connections within data. But the CCD team is actually asking computers to, effectively, play a collaborative role in the process of scientific inquiry. This group—and the few others like it elsewhere—is overhauling how modern science is done.

"You want to know what experiments are worth doing out of the millions that could be done," says Clark Glymour, a PhD and founding chair of Carnegie Mellon's Department of Philosophy. (That's right, philosophy. Glymour's realm is the study of knowledge, a.k.a. epistemology, how we know what we know.) Glymour is the CMU lead for the CCD, a partnership of Pitt, CMU, and the Pittsburgh Supercomputing Center.

Glymour (pronounced *glee-more*) says he and his colleagues can put together "search procedures that suggest what experiments are most worth doing because the computer

a grant to collect a large volume of data saying, *I don't know what I'll find, but I'll first collect data and find out later*, the grant would be doomed to fail," says Xinghua Lu, an MD/PhD who codirects Pitt's Center for Translational Bioinformatics and heads the CCD's cancer team. "The reviewers would certainly criticize the application as a fishing expedition with no hypothesis. Nowadays, biology is becoming more of a data science, and data-driven hypothesis generation is more accepted."

With this approach, you might hit the jackpot. But it's also not particularly difficult to find patterns and associations that mean nothing.

Consider what some jokesters revealed using data compiled by the U.S. Department of Agriculture, the Centers for Disease Control and Prevention, and the like: The per capita consumption of cheese has a 95 percent cor-

It's not surprising that researchers would turn to computers to help them discover connections within data. But this team is actually asking computers to, effectively, play a collaborative role in the process of scientific inquiry.

century has turned into a long, hard slog. Part of the issue is the mind-boggling volume of biomedical data now available to investigators. Advances in biotechnology have fueled the exponential growth of biomedical datasets.

The prospect of coaxing gold from the dross has become epic. "The good news is that we have so much data. But the bad news is that we have so much data," says Jeremy Berg, University of Pittsburgh PhD professor of computational and systems biology and Pittsburgh Foundation Professor.

The challenge? Even more than having the means to churn it all is the problem of finding real meaning. Or, for Berg and his colleagues: "meaningful relationships that lead us to new insights in health and disease."

Complicating it all, notes Pitt's Gregory Cooper, MD/PhD director of the new Center for Causal Discovery (CCD), a group trying to figure all this out, is not just the many data points, but the enormous number of variables—"even more than the number of data points at times"—that can arise in the medical world.

It's not surprising that researchers would

returns the most likely results."

"The possibility space is vast," says philosopher of science Richard Scheines, a PhD and former graduate student of Glymour's who is now dean of CMU's Dietrich College of Humanities & Social Sciences. "If you can't sift through all those possibilities intelligibly, it's impossible to expect the community to run through the experiments. We're hoping we can give scientists a much narrower focus on what to confirm."

Meaning Amid the Morass

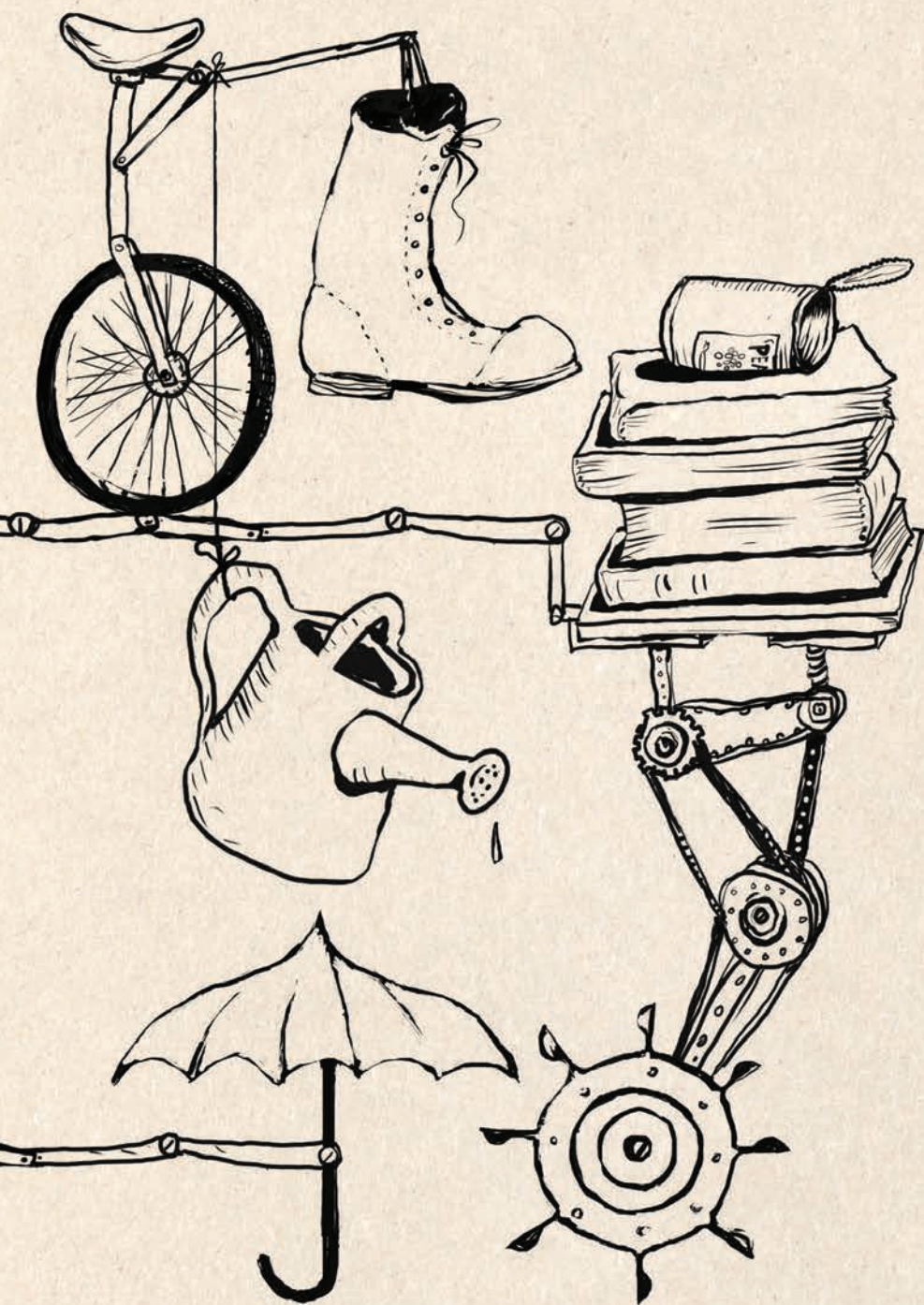
Before big data came along, scientific discovery was a granular process. Well-read investigators with a keen eye could (and still do, of course) integrate the latest published articles with their own observations and experimental manipulations to spark new hypotheses.

Naturally, as more opportunities for collecting and distilling data have become available throughout the past few decades, many scientists have looked in those corners for answers. Yet, "20 years ago, if you wrote

relation with the number of people who died by becoming tangled in their bedding. The divorce rate in Maine has a staggering 99 percent correlation with per capita consumption of margarine. Such spurious associations aren't fabrications. (See an array of head-scratching graphs compiled using publicly available datasets on tylervigen.com.)

The trouble, as anyone who's taken an introductory statistics class knows, is that correlation does not equal causation.

To find meaning amid the morass, the CCD team is building computational tools to reveal networks of causal relationships from big biological data. As with any process of innovation, they'll have to jump their share of hurdles, from protecting the privacy of patients whose cases appear in datasets to developing new techniques for optimizing computation speed and efficiency. They're also working out theories to guide the crafting of algorithms that can sift through more data points and variables than mere mortals can keep in mind. What's really unique about their enterprise is how they are deploying



What's disrupting that pathway? The huge number of variables in health can make the work of finding meaningful relationships in biomedical data astonishingly complex.

artificial intelligence and machine learning techniques to generate likely hypotheses for scientists to test.

We can imagine that science will always rely on clever, well-read researchers with keen instincts, yet with millions of data points accumulating and overall funding for basic research plummeting, investigators have little time to waste. “We could be a lot more efficient in terms of how we store and share data and how we analyze it,” says Cooper, a Pitt professor of biomedical informatics and intelligent systems.

“This is a very focused effort on trying to make that whole effort of going from datasets to insight and knowledge much more efficient.”

Founded with an \$11 million, four-year grant, the CCD is one of 11 centers nationwide established as part of the National Institutes of Health’s Big Data to Knowledge (BD2K) initiative. Each enterprise has a unique agenda. Pitt and CMU are committed to causality, Stanford to data annotation and retrieval efforts, Harvard to patient-centered data collation, and so on.

When Cooper decided to apply for BD2K funds in 2013, he had a deep well of talent from which to draw. Cooper arrived at Pitt in 1990, when he joined an early group of biomedical informatics researchers. He came, in part, for the chance to work with Glymour, a scholar of probability, machine learning, and causal discovery (who then had an adjunct appointment in Pitt’s Department of History and Philosophy of Science). Pitt’s Ivet Bahar, a PhD Distinguished Professor, who holds the JK Vries Chair of Computational and

Systems Biology, and Berg are principal investigators for the center.

In the realm of cause and effect in biomedicine, the CCD cast is a dream team.

Bahar founded what's now called Pitt's Department of Computational and Systems Biology in 2004. She's among the leaders of a new field that's starting to make sense of dynamic, complex interactions within the human body—events obscured when investigators focus on a single variable. Berg is founding director of UPMC's Institute for Personalized Medicine and the University's associate vice chancellor for science strategy and planning for the health sciences. (He is also a former director of the National Institute of General Medical Sciences at the NIH.)

For his part, Glymour has devoted more than three decades to pondering theories of knowledge—including what constitutes compelling evidence (both Freudian psychology and Einstein's theory of general relativity have captured his gaze). In the '80s, he and CMU colleagues Peter Spirtes and Scheines developed TETRAD, a software program that can generate causal inferences (now in its fifth iteration).

So how do these big thinkers think science should work?

Exhibit A: Cancer

Let's go back to p53 and use it as a case study. PubMed lists more than 79,000 papers in the scientific literature that mention the protein. Libraries of biological samples, genomic sequences, and tumor imaging are widely available. Electronic medical records document the clinical trajectory of individual patients with and without mutated forms of p53. Wet-lab analyses reveal ever greater detail about the protein's (dys)function. "In the old days, the data just wasn't available," says Adrian Lee, a Pitt PhD professor of pharmacology and chemical biology. "Now people have to share the data. There are thousands and thousands of [experimental results available]. It's like a gold mine for computational biologists."

But despite decades of efforts, notes Lu, molecular therapy directly targeting mutant p53 has remained elusive.

And that's just one gene. Any given tumor

might have as many as 10,000 glitches scattered throughout hundreds of genes within its genome.

The majority of those coding errors are irrelevant—passengers, if you will—whereas a few key mutations drive a tumor's growth.

"There is an urgent need," says Lu, to develop methods to find cancer drivers.

Yet investigators tend to simplify their experimental models by considering each mutation in isolation. That's like focusing on a single vehicle for insights into what's happening during a Los Angeles rush hour. The reality is vastly more complicated on the roadways and in the human body. Rogue genes frequently exhibit a diabolical synergy, amplifying one another's effects and silencing healthy genes that might lessen the damage. Compound the layers of variability embodied within a single patient by the millions of people with cancer, and the problem of identifying relevant targets and developing tailored treatments fast becomes a conceptual and computational quagmire.

When cancer biologist Lee arrived in Pittsburgh in 2010 to direct the new Women's Cancer Research Center at the University of Pittsburgh Cancer Institute, he'd never heard of causal modeling. But for more than a decade, he'd been compiling huge datasets generated by the genomic sequencing of breast tumors; he knew there had to be a better way to make sense of the relationships between genetic codes and disease states in the quest for targeted therapies.

To find that method, he partnered with Lu. The work of rethinking science might seem pretty darn abstract, yet Lee and Lu share a decidedly practical bent. A native of Shanghai, Lu trained as an emergency physician and finished a master's degree in cardiology before traveling to the United States to pursue a PhD in pharmacology, advanced study in artificial intelligence and computer science, and a Pitt certificate in bioinformatics. Says Lu: "I have 10 years' experience seeing patients, and I really want whatever I work on to be as close to the clinical setting as possible."

Lu and Lee were determined to craft an algorithm to help them detect relevant trends. Their first step, says Lee, was bringing together collaborators with expertise in fields that have traditionally worked independently.

Algorithm development took months of fine-tuning before the team even thought of designing a wet-lab experiment to test any of the hypotheses emerging.

"We have these meetings, and Xinghua [Lu] says, *Hey, we did this*. We say, *Did you filter for this weird feature of this gene?*" says Lee. "And after they generate the algorithm, we test it; and it's right, or wrong, or half-right; and then they refine it." Once everyone agrees that the algorithm might be getting close, they apply it to additional datasets or design an experiment for the wet lab to test the suppositions. Says Lee: "It's an iterative process."

(He makes it all sound so polite. Glymour sees the approach of his separate research group like this: "We yell at each other, work out counterexamples, try simulations.")

Lu notes that the multidisciplinary environment of the CCD has allowed the team to reveal insights into p53 derived from a computer-generated hypothesis. By slicing and dicing details from two national datasets—one containing genomic information, the other with clinical details—they were able to identify perturbed signaling pathways that affect patient outcomes and zero in on a particular signaling complex triggered by the mutual activation of multiple mutated genes (including *TP53*).

After their algorithm generated its hypothesis about the signaling complex, the team designed a series of experiments in the wet lab to probe the computer's theory. By disrupting the signaling complex in the lab, they inhibited the cancer from growing.

It seems the computer was right—and because the same signaling complex becomes muddled in dozens of other types of cancer, including ovarian, lung, and esophageal, the team has a head start on identifying similar targets in a significant proportion of cancers afflicting other parts of the body.

Test Drives

This is the name of the new game—the computer as a collaborator.

And with this productive colleague, CCD investigators have identified a few biomedical challenges on which to test-drive their formulations. There's the cancer signaling pathways group, which generated the p53 study; headed by Lu, it's seeking targets for treatment. An

fMRI group, led by Glymour, is identifying causal influences among brain regions by digging into functional magnetic resonance imaging data. A lung group, led by Pitt's Takis Benos, a PhD professor of computational and systems biology with joint appointments in biomedical informatics and computer science, means to detect the cellular factors that lead to chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

"One of the things that we've found, perhaps not surprisingly," says Cooper, "is that when you start applying an algorithm to a particular domain—understanding cancer signaling pathways, for example—there are details that you need to attend to that are special to that area. The algorithms are modified to adapt to that area and the kind of data that's common in that area."

A fourth effort, led by Pitt's Jeremy Espino, an MD and director of information technology and open source software development for

vance plummets.

At a conference this fall, says Lee, a computer scientist presented a compelling technique for mining biomedical data, but a basic biological assumption he'd embedded within his algorithm was just plain wrong.

"The assumptions are often really, really naive," says Lee. "In that case, the first assumption was so utterly flawed, the outcome would have to be wrong. But without the assumption, you can't run the algorithm."

Without the input of biomedical colleagues, says Glymour, who's tackled the challenge of modeling everything from climate science to long-range prediction of forest fires, even mineral identification for a NASA robot, he's sure the algorithms he helps the fMRI group craft would fast collapse under their own weight. "My biological collaborators keep me from doing incredibly stupid things," he says, tongue only slightly in cheek.

The CCD's approach has investigators

are not so many drugs to target particular mutated genes. Even if you had those drugs, you could only help 1 or 2 percent of patients. Target a particular pathway, and you might help 20 percent of patients."

Says Lee: "Xinghua's network view is more of a systems approach, and it's a huge advance."

Sharing the Gospel

To speed discovery, the CCD is bringing more researchers into the fold. Last June, the center offered its first in-person training. The free, four-day course introduced 75 investigators from around the world to the concepts and software necessary to pursue causal discovery in their own research. Throughout the past year, the CCD has expanded its online offerings with recorded lectures, papers, and software tutorials.

"For this to be useful to a wider population of biomedical researchers," says Scheines, who leads the training effort, "we need to develop

"You want to know what experiments are worth doing out of the millions that could be done."

the Department of Biomedical Informatics, is slated to run for one year in partnership with scholars at Harvard. The team is establishing a cloud-based tool with which investigators anywhere in the world will be able to manipulate a massive autism dataset (on a server farm run by Amazon).

"This is a relatively new thing that's happening in research," says Espino. "Datasets are so large that it's difficult to even have enough computational resources to digest the information."

Like the other three projects, the Pitt-Harvard autism team will develop a proof of concept, then share their techniques so similarly complex datasets can be made more broadly accessible.

Good Old-Fashioned Good Assumptions

CCD investigators constantly balance their pursuit of clinically germane insights with the imperative to design computational processes elegant enough to crunch through relevant data in a timely fashion.

If the balance shifts too far in favor of computational elegance, biomedical rele-

cross-checking their assumptions throughout. "Xinghua knows the underlying statistical and mathematical models," says Lee, "and we can give input to make sure we don't generate spurious findings."

In their ongoing work, Lu, Cooper, and Lee are concentrating further on algorithms related to driver mutations.

"Say you have 100 genes, each in the same pathway, and in each of 100 patients, that pathway is differently mutated," says Lee. "But if they all affect the same output, you'd never notice."

Imagine, again, that LA traffic metaphor. There are many reasons why a midtown intersection may have recently started experiencing frequent pileups: nearby road construction or a recently opened office building, perhaps.

In effect, Lu's algorithm detects the vexed midtown intersection—the cellular signaling pathways where those mutations' effects converge. So instead of focusing on the many different causes of traffic jams that occur at the crossroads, engineers can modify the intersection to bring traffic flow back to normal.

"The majority of the mutated genes—you have no way to treat them," says Lu. "There

training materials for biomedical scientists who want to use data science approaches like ours and for data scientists who want to apply our techniques to biomedicine. We need to train both communities fairly broadly."

And, Scheines says, "We really want to get a community set up where people can work together."

Consequently, software developers throughout the CCD are making accessibility a top priority.

"Everyone has their own workflow, statistical packages, computational packages they use," says Scheines. "We need to make our materials easy to fold into their processes if they're going to be widely adopted."

"Causal discovery of biological networks from data—already nearly three decades in the making—has the capacity to advance science now," says Cooper. Glymour assumes a curmudgeonly tone. "I began this work in 1980," he says. "It's taken 35 years of just repeating this strategy, publishing results, for the NIH to pay attention. The turnover is not fast."

"It takes a while for people to absorb radical new methods, even with proof that they work." ■

NATHAN YATES GIVES SCIENTISTS
ANOTHER TAKE ON WHAT THEY'RE
STUDYING | BY NANCY AVERETT

A WIDER VIEW



Some patients with schizophrenia experience auditory hallucinations. Such illusions are among the most disturbing aspects of the disease. Patients often hear people talking to them or about them. The voice can be a running commentary on what the patient is doing at that moment, a conversation, an outright command, or even a warning. Pitt psychiatry faculty members Robert Sweet and Matthew MacDonald wanted to find out whether a protein-signaling problem in the brain might play a role in those hallucinations.

Based on previous research, the two hypothesized that such a signaling error would probably occur within the synapses in the auditory cortex of the brain. But, says Sweet, “the synapse has close to 2,000 proteins.” To look at each one would be time consuming and labor-intensive. Plus, he says, “when you just study a protein at a time, you’re not really getting a picture of the global function or dysfunction of the synapse in disease.”

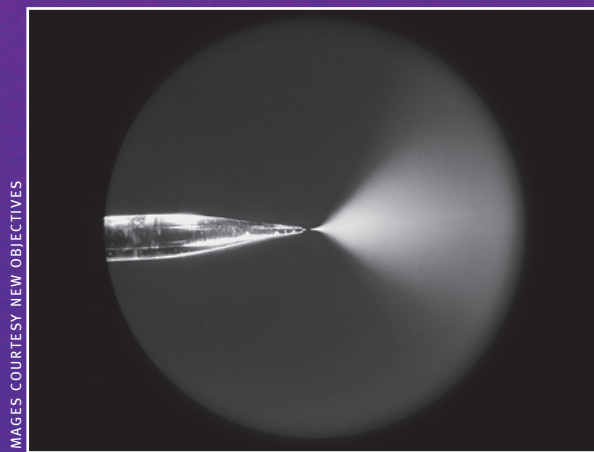
Here’s where Nathan Yates, associate professor of cell biology and scientific director of Pitt’s Biomedical Mass Spectrometry Center, enters the picture.

MacDonald, PhD assistant professor of psychiatry, and Sweet, MD professor of psychiatry, obtained auditory cortex tissue of deceased patients from Pitt’s brain bank,

both from people with no known history of mental illness and from people with schizophrenia. Then, with Yates's guidance, they used a mass spectrometer, which helps scientists identify relevant biological molecules in a sample by converting them to ions and sorting those by their mass-to-charge ratios. With this approach, they were able to quantify more than 150 synaptic proteins in that auditory cortex tissue, and they observed significant differences in the way 17 of those proteins were organized into a network in the tissue from people with schizophrenia.

"We found a group of proteins that hang out together in schizophrenic patients that don't really hang out in normal controls," MacDonald says, adding that they are pursuing more studies in this area.

Published in the June 2015 issue of *Biological Psychiatry*, this experiment is but one of several that Yates has been involved in since he joined the faculty in 2011. Yates, a 49-year-old chemist, is giving biomedical scientists all over the Pitt campus new perspectives on their work. As he puts it, his specialty areas of mass spectrometry and proteomics "provide a large amount of robust quantitative data that can help scientists observe and understand complex biological systems."



IMAGES COURTESY NEW OBJECTIVES

Nathan Yates has spent his career advancing technologies and building powerful software tools to help labs identify and quantify potentially important biological players. For instance, Yates coupled electrospray technology (close-ups shown on these pages) with ion traps for mass spectrometers. This offered researchers another way to observe big molecules, like proteins.

In a sense, Yates's expertise and the center's tools (which include powerful cloud computing platforms that Yates was instrumental in developing) enable investigators to pull back and identify important biological players that they may never have recognized otherwise.

Before Yates, a PhD, came to Pitt, he was at Merck and Co. When he was hired as a senior research chemist there in 1995, he was tasked with using his knowledge of mass spectrometry to screen large libraries of small molecules for drug discovery. The company was interested in evaluating thousands of molecules at once to identify those that bind proteins and alter given disease states (proteins involved in glucose regulation, for example, or perhaps those involved in regulating blood pressure). This required new software, which Yates created.

While doing that work, Yates began to think about how similar bioinformatics methods might be developed to analyze data

least as a starting point.

But Merck and Yates wanted to take a different path. They wanted to somehow measure and identify biologically relevant proteins without having to tell the machine what they were searching for. Such "unbiased" methods existed but weren't always reliable or scalable to large numbers of samples.

Yates set out to create a new bioinformatics method that could do this and do it quickly. He initiated a collaboration with mathematician colleague Matthew Wiener.

The men spent their lunch hours hunkered in front of their computers, eating peanut butter and jelly sandwiches as they tinkered with formulas. Months later, they had a powerful algorithm. Yates dubbed it "differential mass spectrometry."

"Let's say you take healthy and diseased cells, and you want to ask, 'What's different?'" Yates explains. "There have been lots of quantitative proteomics approaches for doing that, but what would typically come back is—instead of a short list of two or three or

in the hunt for protein biomarkers for a number of conditions. It allowed them to, for example, align and compare complex proteomic profiles obtained from the spinal fluid of patients with Alzheimer's disease and controls to reveal differences. Eventually, the approach was successful in identifying two robust candidate biomarkers that continue to show promise in independent studies for Alzheimer's disease. (Discovering and verifying such markers is a more involved and lengthy process than people probably realize, notes Yates. "Even with the financial muscle of large pharmaceutical companies," he points out, it can take decades.) Their work is outlined in the August 2015 issue of the journal *PLOS ONE*.

Merck knew what it was doing when it asked Yates to reimagine existing technology to find a biomarker. Yates had been an innovator and problem solver for every other lab he'd worked in, starting as a grad student.

"You know, Mother Nature is pretty funny; it tends to want to do what it wants, not what we think it does. So using this unbiased discovery method that Nathan created will help us find partnerships we had never considered."

on not just small molecules, but proteins, too. Then in 2002, Merck launched a major effort to discover protein biomarkers for a number of therapeutic areas, including neurology and oncology.

Such discoveries would make testing potential drugs more accurate and efficient; they might also help in the development of drugs that could halt progression of diseases before symptoms appeared.

Sometimes scientists use mass spectrometers in a targeted way, focusing the instrument on specific proteins or other biomolecules believed to be important to a disease or biological process. This approach offers "absolute molecular specificity that can't be achieved with traditional assays," says Yates. (Sweet, MacDonald, and Yates took a targeted approach in their schizophrenia study.)

With a targeted approach, you pretty much know what you are looking for—at

five proteins that you could follow up on—you could get a list that had a couple hundred proteins that were changing. That list might contain those five proteins that actually were changing, but it would also contain [dozens of] other proteins that were just changing due to random chance, so the experiments weren't very good at finding just the needle. They would find a lot of hay, too. You went from a big haystack with a needle in it to a not-so-big haystack with a needle in it.

"With differential mass spectrometry," he says, "it brings back the needle (or needles if two or three proteins change) itself, or nothing at all."

After creating the algorithm, Yates worked with software developer Andrey Bondarenko, who was employed by Rosetta Biosoftware, a subsidiary of Merck, to turn it into commercial software.

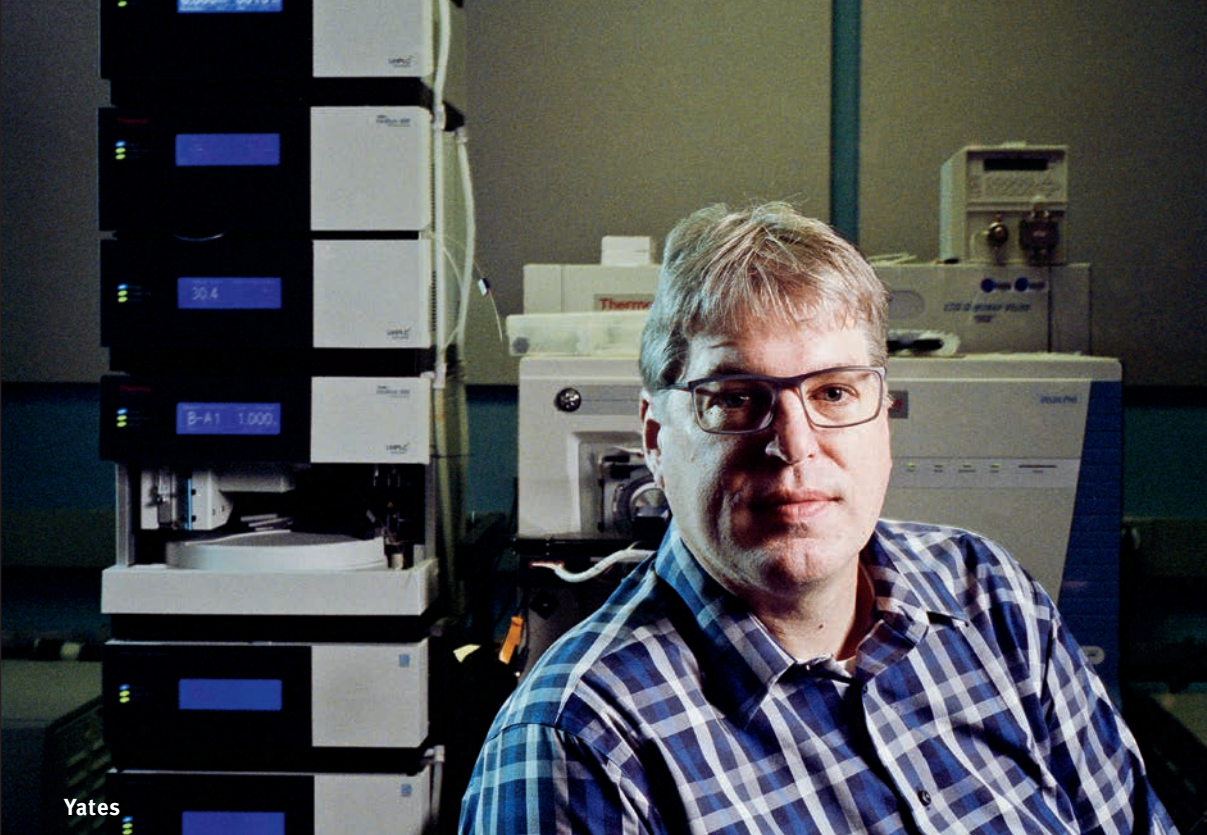
Merck, and Yates, used the new method

Yates was first introduced to mass spectrometry in the late 1980s when he attended the University of Florida for graduate school. His mentor there, Rick Yost, had made a huge contribution to the field. Fifteen years earlier, when Yost was a graduate student at Michigan State University, he had coined the first triple quadrupole mass spectrometer.

Mass spectrometers work by first converting molecules to charged particles (ions). Yost's triple quadrupole analyzed these ions in two steps—before and after they are broken apart—by colliding them into a gas.

"The [triple quadrupole] has revolutionized analytical science," Yates says. It's now the most widely used mass spectrometer in the world.

Yates adds, "It's really great for measuring trace-level analytes present in ultracomplex mixtures such as amino acids in a baby's



blood, or drug stimulants in blood sampled from racehorses, or harmful gases in the air on the space station.”

When Yates arrived in Florida, Yost’s lab was focused on a new type of mass spectrometer, a quadrupole ion trap, which was just coming on the market. It had the promise, but not yet proven capability, of performing very rapid ion analysis—which would make it less labor-intensive and costly to run.

Yates has always enjoyed finding out how things work. In fact, he likes to joke that he’s more mechanic than chemist. During their honeymoon, he and his wife, Jan, drove across the country in an old VW van with an engine that Yates rebuilt himself and tinkered with constantly to keep running. And when their historic Colonial home needed new air conditioning, rather than pay \$8,000 for a new system, Yates decided to get certified in air conditioning repair and install it himself.

With that kind of outlook, it was only natural that he would try to solve the practical problems of the quadrupole ion trap. So, with Yost’s blessing, he began trying different things to speed up the ion analysis. “He set up this very intense 24–7 use of the mass spectrometer,” Yost recalls with a hearty chuckle. “We figured afterward he’d done the equivalent of two years of mass spec in a week.”

Later, Yates briefly left graduate school to undertake a six-month co-op in research

and development at Finnigan (now part of Thermo Fisher), a Silicon-valley company that manufactures high-end mass spectrometers. While there, he helped to advance the capabilities of ion traps.

Today, the mass spectrometers that he uses for proteomics research at Pitt have ion traps inside them. Says Yates, “they’ve advanced into high-performance instruments that are a mainstay in proteomics and metabolomics research.”

After Florida, Yates took a postdoc at the University of Virginia in the lab of chemistry professor Donald Hunt. This was 1993; the field of proteomics was emerging, and Yates wanted to learn all he could about it.

Hunt was studying proteins in the immune system and was interested in finding out what an ion trap could do to improve his measurements. Yates went there to build an ion trap and then apply it to the analysis of proteins.

In the ’80s, a Yale chemist named John Fenn had invented a technique called electrospray ionization. (He won the Nobel Prize in Chemistry for this in 2002.) Fenn’s method allowed large biomolecules to be analyzed by mass spectrometers—a game changer for biomedical science.

Yates coupled electrospray ionization with the ion trap he was building. He also wrote software that modified how the ion trap operated and gave the software to the 20 to 30 labs around the world doing similar work.

From there, he took the Merck job oppor-

tunity, where he ended up developing differential mass spectrometry. Once Yates had developed this new tool, he was like a kid with a new computer game. He couldn’t wait to use it. He envisioned himself performing drug-target analyses to help Merck better understand the medications it was bringing to market. He knew there was value in it. Beyond the possibility of making drugs more effective, there was the issue of side effects. If drug firms don’t know to what proteins their drugs bind, they risk having to pull them off the market should toxic effects emerge. But company offi-

cials resisted Yates’s overtures.

“I was fascinated about the possibilities of using differential mass spectrometry for drug-target analysis,” he says. “And it was disappointing that I couldn’t communicate my excitement to the company.”

Yates began to look for a new job. He was close to moving to another position in industry when a contact at Pitt called and asked him to consider applying to the School of Medicine. Yates jumped at the chance, knowing the eventual move to academia would give him the freedom to pursue his drug-target research, as well as other interests.

Again he knocked on the door of “cracker-jack” software designer Bondarenko, who was using cloud computing to develop advanced software tools for scientific analysis. The two teamed up with Amazon and created a cloud-based platform, CHORUS (chorusproject.org), that allowed mass spectrometry labs around the world to work together by sharing computational tools and data.

“Instead of paying large upfront costs to purchase software, install computers, and hire experts to analyze mass spectrometry data, any researcher with a connection to the Internet can now log on to CHORUS and begin analyzing data in minutes,” Yates says.

CHORUS, which is operated under a not-for-profit public-private partnership, went live in 2013; already 1,200 scientists and 220 labs around the world are using it.

These days, Yates and Bondarenko (now

heading Seattle-based InfoClinika) are working on a version of differential mass spec to make available on the site. With the software, says Yates, "It's practical to measure and analyze millions of data points in a few minutes, a task that was not possible with older manual methods."

Yates is all about getting datasets out of individual labs and into collaborative environments. At a recent conference in São Paulo—after a friendly soccer match among the attendees and some beer drinking—Yates befriended a Brazilian researcher doing proteomics work on the Amazon rain forest and convinced him to put his data up on CHORUS. Yates advocates for such data sharing because he believes it will help propel the field of proteomics forward at a much

research he so badly wanted to do while at Merck as he collaborates with Lans Taylor, a PhD and director of the University of Pittsburgh Drug Discovery Institute and Pitt's Allegheny Foundation Professor of Computational and Systems Biology. (Interestingly, Merck is now intrigued by the idea and is collaborating with Pitt and Yates.) Among other projects, Yates is looking at the widely used diabetes drug metformin, a medication whose molecular mode of action is not completely understood. He wants to use differential mass spectrometry to uncover what it binds to.

"It's the most widely prescribed treatment for type 2 diabetes," he says. (He notes that he's "swinging for the fences" on the metformin effort but remains optimistic.)

"Finding the molecular target of met-

formin for a bite. Yet being able to monitor one's proteomic or metabolic profile would be akin to "draining the pool so you can see all the fish."

Both Yates and Lee believe sports teams will be early adopters of this sort of personal health-monitoring technology. They imagine teams would be able to keep an eye on their players' protein levels and determine whether anyone is showing signs of physical stress before a full-fledged injury occurs.

Explains Lee: "The coach might say to the pitcher, 'Son, you look tired,' and the pitcher will say, 'I'm not tired!' Now, what if before each inning, the pitcher spit into a cup, and Nathan was monitoring that, and he saw markers for stress? He could say to the coach, 'Uh-oh, this guy's about to blow out an elbow.'"

Imagine, he says, if people could monitor their own proteomes on a daily or weekly basis. That would offer doctors and patients new information that could reveal, say, evidence of muscle damage or perhaps even cancer before a tumor forms.

faster pace and eventually bring about better health therapeutics.

His approach is revving up proteomics research at Pitt and elsewhere. In addition to his work with MacDonald and Sweet, Yates has worked with Robert Sobol, formerly a member of the University of Pittsburgh Cancer Institute, now molecular and metabolic oncology program director at the University of South Alabama Mitchell Cancer Institute. The two studied protein pathways involved in DNA repair. They hope to uncover previously unknown protein partnerships.

"When you do this on the entire proteome, you're able to identify novel things, things you would not have thought about," Sobol says.

"You know, Mother Nature is pretty funny; it tends to want to do what it wants, not what we think it does. So using this unbiased discovery method that Nathan created will help us find partnerships we had never considered."

Yates is now performing the drug-target

formin could lead to the development of new and improved treatments for patients," he says.

In Yates's vision of the future, his efforts (and those of others who are advancing the use of mass spectrometry) will help people take charge of their own health. Imagine, he says, if people could monitor their own proteomes on a daily or weekly basis. That would offer doctors and patients new information that could reveal, say, evidence of muscle damage or perhaps even cancer before a tumor forms.

Yates's mentor in this area is Mike Lee, who also trained as an analytical chemist under Rick Yost and was with Bristol-Myers Squibb before leaving to become a consultant. Lee specializes in bringing together people in academia and industry to work on difficult problems in health care. He likens today's health measurements—heart rate, height, weight, and the like—to dropping a fishing line into a murky pond and hoping

Lee notes that even if individual health tracking can't stop a condition from developing, it is likely to offer advantages in terms of choosing a treatment. For instance, two people might get the same kind of cancer but need different combinations of medications to fight the disease as it evolves.

"In addition, most drug dosages are set for an 'average human'—40-year-old white men," Lee says half-jokingly. But with personalized proteomics, doctors could better tailor drug regimens to a petite woman or an Asian man.

How close is a future of personal proteome monitoring? Hard to say. The human proteome is a highly complex system; tens of thousands of proteins in our bodies interact with each other in myriad ways. Unraveling those mysteries won't be easy. And giving clinicians and laypeople information they can act on is another issue.

But, Yates says, "It's an exciting time to be working on some of these questions." ■

A LONG WAY TO GO

ON DISPARITIES PAST, PRESENT, AND FUTURE



Former Secretary of Health and Human Services Louis Sullivan has clear ideas about how to improve the health of the nation as a whole.

Photos by Tom Altany/CIDDE

In 1958, when Louis W. Sullivan began his residency at Cornell, he was the only black intern in New York Hospital. Summoned to the office of E. Hugh Luckey, physician in chief, he went with trepidation. Luckey, a Tennessee native with a heavy Southern accent, surprised the young doctor.

“Luckey ... wanted to let me know he was interested in my succeeding, and that he would support me,” Sullivan said. “This gave me the assurance that there was someone there who really cared about what I was trying to do. In two years [at the hospital] I had only one negative experience. A patient objected to my examining him, and he was immediately discharged. That’s the kind of thing we need to see more of now.”

Sullivan, who served as Secretary of the U.S. Department of Health and Human Services from 1989 to 1993, recalled this incident in a lecture titled “The Long Journey to Health Equity in America,” delivered on Oct. 2, 2015, to an audience of Pitt medical students, physicians, and other health care professionals. While there are still far too few minorities in the health professions, he said, we must support the ones who are there now.

In a talk rich in historical perspective and dense with data, the 82-year-old hematologist and founding dean of the Morehouse School of Medicine traced the evolution of disparities in both health and the health professions throughout the past century, citing milestones from the 1910 *Flexner Report* to the 2010 signing into law of the Patient Protection and Affordable Care Act (ACA), also known as Obamacare.

Looking forward, Sullivan offered a clear set of recommendations for improving the health of the nation as a whole: increase access to health services; instill better health behaviors; streamline what is a very “bureaucratic” health care system; develop guidelines to address ethical challenges brought

by technological and scientific advances; and preserve humanism in the therapeutic relationship.

In the end, Sullivan exhorted listeners to be role models in their communities. “The greatest reward in my life has been seeing young people develop as professionals and go off and do great things. Medical students represent the vitality and future of our society,” he noted.

Sullivan’s talk was the culminating event in the daylong Health Disparities Conference 2015, hosted by the Physician Inclusion Council of UPMC/Pitt. His comments were followed by a panel conversation that included Esa Davis, an MD/MPH and assistant professor of medicine; Larry Davis, a PhD, dean of the School of Social Work, and director of the Center on Race and Social Problems; and Patricia Documét, an MD/DrPH, associate professor of behavioral and community health sciences and clinical and translational science, and scientific director of Pitt’s Center for Health Equity. Jeannette South-Paul, an MD and the Andrew W. Mathieson UPMC Professor and chair of the Department of Family Medicine, moderated the discussion.

Recently, *Pitt Med* had the opportunity to ask Sullivan a few follow-up questions.

How effective can the Affordable Care Act be in reducing health disparities if 20 states have decided not to expand Medicaid?

I think states not expanding Medicaid will have a definite adverse impact on the health of low-income citizens, which includes a large number of minorities. Those states that have expanded Medicaid have seen significant reductions in the percentage of their populations who are uninsured, and hospitals have seen reductions in the amount of uncompensated care they have to provide. We have under way a significant effort to improve the health behaviors of our citizens to prevent what can be prevented. But if you have a financial barrier to seeking care, which is the case for a lot of people who are poor or low income, you won’t be able to change your health behaviors. I think the failure to expand Medicaid is very short sighted on the part of those governors. It is walking away from what I see as a community responsibility to provide access to health care for our citizens, and one that will pay not

only in humanitarian terms but in economic terms, as well: a healthier population that’s working, with reduced illness and injury and therefore less need for social support services.

What can academic health centers (AHCs) do to recruit and support a diverse clinical workforce?

I see this as a long-term effort. To expand the pipeline, AHCs need to form relationships with colleges so that students get career counseling, strong academic training, and, most important, financial planning. The cost of getting a health professional’s education is so expensive. We have a system that only upper-income students can navigate financially.

Increasing diversity in the workforce requires a commitment of leadership—from

“If you have a financial barrier to seeking care . . . you won’t be able to change your health behaviors.”

the CEO on down. It should be an institution-wide priority, not simply a slogan that no one gives serious attention to.

What can AHCs do to reduce health disparities in their surrounding communities?

Too often in our country we have a great AHC sitting in an urban area with serious health problems and very little interaction between them. It would be good to have the leadership of the AHCs discuss health issues with community leaders—elected officials, city council members, ministers, teachers, presidents of associations. They are the ones who have the credibility and the trust of the people who live there. Next, there needs to be a discussion about the status of the health of the people in the community. What are the problems? What are the barriers? And then, AHCs must work with community leaders to set up the programs. A program may be good from a medical point of view, but if it’s not embraced by the community it won’t be as effective. Organizations in the community could host such programs—whether it’s a community health center or the YMCA or a church. In other words, have the programs out in the community where people live, rather than waiting for the community to

come into the AHC.

Do you think the topic of health disparities is part of the larger conversation taking place in this country about race?

Yes, I do. This is my perspective. When I was in medical school and postgraduate training, the civil rights movement was very active. And the aggregate of these activities—the bus rides into Mississippi; the counter sit-ins in Greensboro, N.C.; the march in Selma—raised the consciousness of the nation to these issues. The net impact was to focus people’s attention on this and to say, “This is wrong, and we’re going to do something about this.” Now we’ve gotten away from that, and people have settled back into their zones of comfort or retreat. We need to reach out and have more positive out-

comes, rather than these confrontations we’ve seen throughout the past few years.

One recent example is the University of Missouri. It seems the failing there was that the president had not responded to communications from the black students about the indignities to which they were subjected. These were not addressed, it reached a boiling point, and then [there was] the explosion. In my view, that could have been avoided if there had been some response to show that the president was working to resolve the problems. We need to have more active leadership about this.

The U.S. Census Bureau predicts that by 2044, non-Hispanic whites will be a minority. Can we increase the number of minority health professionals fast enough to keep up with that shift?

By 2044 I hope we have a lot more diversity than we have now, but I would not be surprised if we still fall short in terms of how representative the nation’s health professionals are of its population, racially and ethnically. This kind of change takes time. Becoming a health professional is a lifelong goal. So we need to reach out to youngsters who are in fourth or fifth grade; it will be 15 or 20 years before they come into the system.

We can, and should, make some other changes, too. For example, I'm working on a project right now involving dental therapists. It's a two-year program started by the Alaska Native Tribal Health Consortium in 2004 to train high school graduates in primary dental care and simple extractions and fillings. This is a new model, and this is similar in some broad respects to the physician assistant and nurse practitioner programs in medicine in the early '60s and '70s. At that time, there was a lot of resistance from physicians. But now they're working alongside physicians, and this helps increase access to health care. I see the health system changing dynamically so that 10 to 20 years from now, we'll see different kinds of professionals working alongside the dentists and the doctors.

If you were Secretary today, what would you address most urgently?

I would mount a much more vigorous educational campaign about the ACA. I think one of the mistakes that [President Obama] and [Secretary Kathleen Sebelius] and others made when this legislation was passed was that they did not make an effort to inform the public about what was in the statute and what its intentions were and why it would be important to everyone. They left it to those members of Congress who were ideologically opposed to paint a very negative picture of it for the American public. This allowed suspicion and mistrust to build up. The administration has been playing catch-up ever since.

Second, when the insurance exchanges were about to become operational, back in 2013, the administration did not prepare the public. The impression given was that on October 1, they'd flip a switch, and everything would be ready. But a lot of the exchanges didn't work. And that again gave ammunition to opponents to say, "Look, it's not working." The wise thing would have been to say, "[October] 1 is coming, and there may be technological glitches, and, we'll address them." At this juncture, what needs to happen is a strong educational effort about the features of the ACA—why it's good, where it's working, what to expect. ■

—Adapted from a conversation with Sarah C. Baldwin. Robyn K. Coggins contributed to this report.

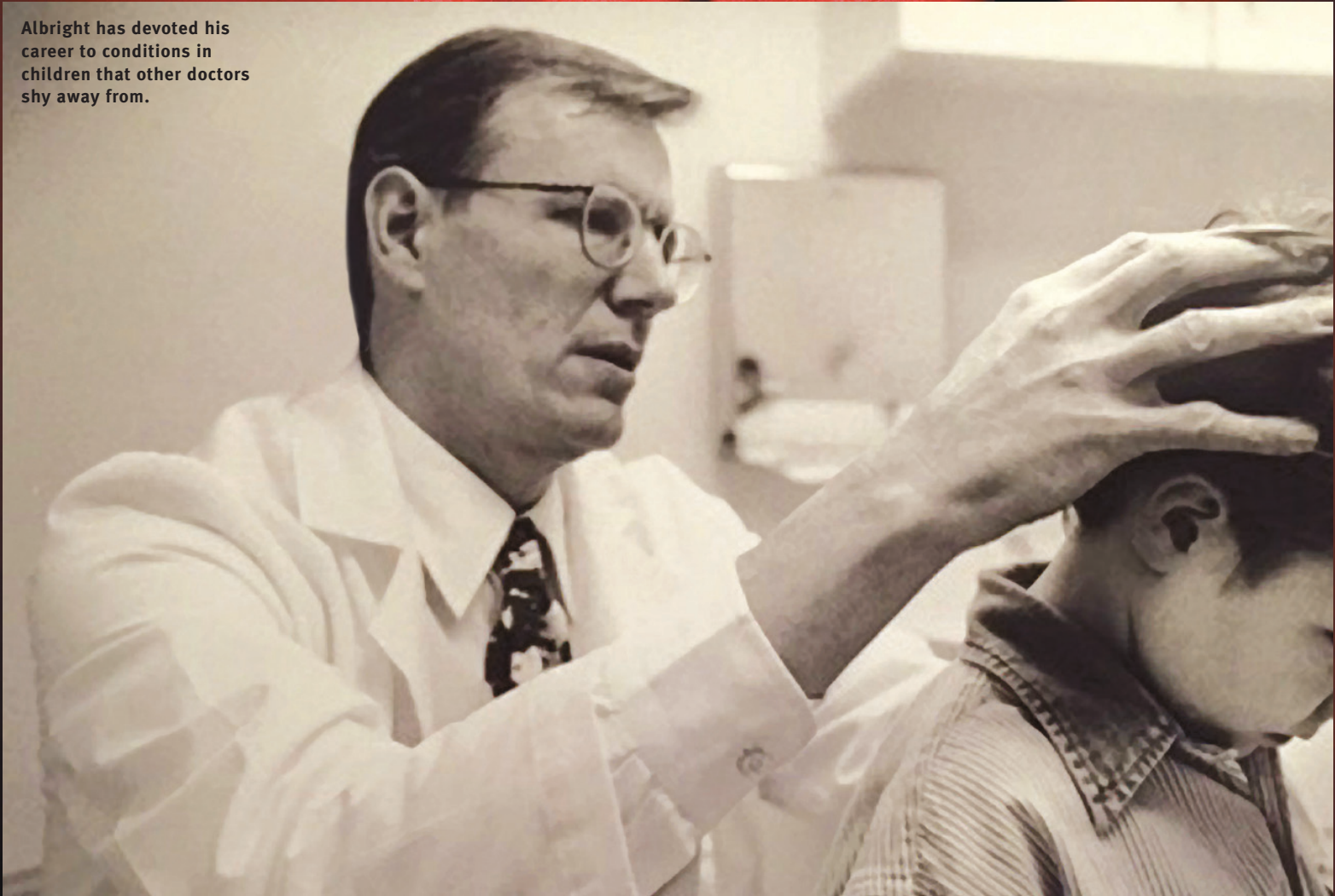


FROM TOP: Jeannette South-Paul moderated a panel discussion following Sullivan's talk. As part of the discussion, Esa Davis (red checkered dress) highlighted the need to get black boys interested in medicine in elementary school if we hope to get them into the physician training pipeline at all. Patricia Documét spoke on addressing isolation and health care access for Latino men. Larry Davis (bottom right) discussed what's happening in the states that did not expand Medicaid under the Affordable Care Act.



WHERE OTHERS DON'T GO

Albright has devoted his career to conditions in children that other doctors shy away from.



**NEUROSURGEON ESCHEWS
FAMILIAR TO BRING
COMFORT TO CHILDREN
BY KRISTIN BUNDY**

The damage resulted from an anesthetic disaster. About 30 years earlier, during a tonsillectomy, her brain suffered a lack of oxygen that eventually changed the shape of her body. Involuntary muscle contractions—known as dystonia—distorted her into abnormal postures, causing lifelong pain.

At 35 years old, she entrusted her future to another surgical team—oddly, led by a pediatric neurosurgeon. He had treated her for years but decided to try something new, after she said a small dose of baclofen injected in her spinal fluid helped. Giving up on oral baclofen, the common but often ineffective treatment for dystonia, he implanted a pump that infuses baclofen right into the spinal fluid.

A. Leland Albright (Fel '76, Res '78), the pediatric neurosurgeon, didn't know what the outcome would be, but he was known to carefully bank on educated guesses. In serious conditions for which no good solution was available, he'd adopted the approach of "try and see" (his preferred phrase over "trial and error").

Two days after the woman's procedure, nearly all of her symptoms were gone. "It was like she had a miracle!" Albright recalls.

Encouraged by these promising results, Albright obtained appropriate permissions from the Human Rights Committee of Children's Hospital of Pittsburgh of UPMC and the National Institutes of Health and was soon at the forefront of bringing this new treatment to the clinic. The use of the baclofen pump in children suffering from dystonia and spasticity (stiff, inflexible muscles)—common disorders associated with cerebral palsy (CP)—has since benefited hundreds of children around the world.

(Albright recalls how, before this procedure, many parents of his patients with severe generalized spasticity and severe generalized dystonia would take turns waking up every couple of hours to reposition their children in the night to help them find rest. And they would do this for years.)

Albright built a career treating severe disorders that few other neurosurgeons would devote themselves to. His life is one of venturing where others don't.

Albright's mentor Peter Jannetta was one of the preeminent neurosurgeons of the late 20th century. Jannetta led the newly formed Department of Neurological Surgery at Pitt in the 1970s. Albright was one of his first residents. Although Albright admits he had never heard of the pediatric subspecialty when he began his residency at Children's in 1974, he would become one of the first pediatric neurosurgeons at Pitt, following Donald Reigel and John Vries. Jannetta eventually named Albright chief, and the division soon gained esteem. (By the mid-'90s, Albright and pediatric neurosurgeon colleagues Ian Pollack and P. David Adelson became the senior editors of the book *Principles and Practice of Pediatric Neurosurgery*. The latest edition came out in 2014.)

Albright treated and operated on children with spina bifida, brain tumors, and head injuries, but he's also devoted to children with disabilities for which there's no cure. Albright

explains that few physicians specialize in caring for children with movement disorders arising from brain and spinal cord abnormalities, despite the many who are disabled by these conditions.

Albright formed what's thought to be the nation's first multidisciplinary team to treat spasticity and movement disorders in kids. Often, children and their families would have to visit many specialists over multiple appointments at various locations. At Children's, Albright convened all of the specialists—pediatric neurosurgeons, fellows, residents, psychiatrists, occupational and physical therapists, and nurse practitioners. They offered every known treatment for these disorders, and children came from around the country to be evaluated and treated.

"The incredibly gratifying aspect of taking care of those kids, particularly those with CP and other movement disorders," Albright says, "is that we can make changes in their quality of life that are dramatic."

Albright adds, "A lot of people don't want to go into [pediatric neurosurgery] because there is so much grief. But I found it a wonderful way to express the love of God for the children and their families."

Albright completed medical missions in several countries, including South Korea, Venezuela, and Nigeria, in his decades-long career. The culmination of those efforts came in 2010, when he and his wife, Susan Ferson, a pediatric nurse practitioner, decided to sell their house and move to Kijabe, Kenya (about an hour and a half drive from Nairobi). They'd planned to devote six years of their lives to treating children, teaching pediatric neurosurgery, and establishing a self-sustaining pediatric neurosurgery department at the Kijabe Hospital—what would become one of the first such departments in Africa.

The team came up against many barriers in Kijabe. In addition to operating with old equipment and unreliable electricity, Albright was also in the precarious position of deciding whom to treat. Thousands of families sought out the team's care. And for most, Albright had to consider more than the disease. Would the parents be able to return the child for follow-up? Would the child die because, although the surgery might be successful, the child might not be able to receive postoperative irradiation? Could the parents afford more potent, but more costly, antibiotics? Often he and his team had to weigh the likelihood of

impoverishing a whole village against providing treatment to a child.

Despite these limitations, Albright cared for more children in Kijabe per year than he was able to in the United States. Along with a Ugandan pediatric neurosurgery fellow whom Albright trained, Humphrey Okechi, Albright performed more than 5,000 operations at Kijabe Hospital in four years. The most operations he had done in a year in the States was 330.

The hours were long and the work was challenging, but, as Albright and Ferson write of their time in Kenya in a paper published in the *Journal of Child Neurology*, "... we have an inner sense of peace that we are where we should be, doing what we should be doing, and we give thanks for that. We cannot always say we enjoy it, but we love it."

Albright had to cut his time short in Kenya after being diagnosed with chronic fatigue syndrome (thought to be caused by a virus, not overworking). In early 2015, Albright and Ferson moved to La Grange Park, Ill., where he is now taking seminary classes to become an ordained minister through the Lutheran School of Theology at Chicago.

Late last year, Albright was presented with a lifetime achievement award—the Franc D. Ingraham Award for Distinguished Service and Achievement—by the American Association of Neurological Surgeons. Pollack—mentee and friend of Albright's (who's now the A. Leland Albright Professor of Neurosurgery and division chief at Pitt)—introduced Albright during the award ceremony.

When Albright took the podium, he didn't give a presentation on any of his clinical advances. Instead, he directly addressed the younger neurosurgeons, urging them to recognize the children who need their care, encouraging them to seek new answers and get comfortable with the uncertainty of it all.

"There are three disorders that you need to consider devoting more of your career to because nobody's interested," he told them. "And that's children with serious head injuries, the 1 percent of children who have epilepsy, and the 1 out of 320 children in the U.S. that have spasticity or movement disorders." He went on: "There are tens of thousands of children that we need to devote ourselves to."

When he finished, several physicians approached him, ignited by his commitment to these children, seeking an exchange of ideas on how they could continue what he'd started. ■

*People and programs
that keep the school
healthy and vibrant*



SCAIFE UNDER THE KNIFE

RENOVATIONS ON WISH LIST

BY KRISTIN BUNDY

She may have undergone some face-lifts in the past, but none compares to the renovations and expansion administrators have proposed for Scaife Hall. Existing areas of the medical school—the lobby, student lounge, and offices in particular—are being assessed for possible reconstructive surgery to give the building a fresher, more modern look. The biggest enhancements would come with the addition of a seven-story west wing and updated anatomy lab fit for 150 learners.

If the full wish list comes to fruition, future med students will have more access to interactive learning while getting to see the literal light of day during

A new medical education addition—the proposed west wing—would provide a bright learning environment.





ABOVE: A classroom built for team-based learning on the fifth floor would offer an interactive, round-table setup, with flat screens at each table.



A new anatomy lab on the top floor is designed with enhanced, interactive learning in mind.

their studies. Floor-to-ceiling windows are planned throughout most of the new spaces.

A University of Pittsburgh planning committee reviewed teaching facilities at peer institutions, including Stanford University, Duke University, the University of Virginia, and Johns Hopkins University, to see how the proposed Pitt construction would measure up. They've pulled in architects from the Boston firm Payette to balance upgrades while maintaining the architectural integrity and history of Scaife Hall, which was opened in 1955 (the same year Jonas Salk announced Pitt's polio vaccine was deemed safe and effective).

The master plan includes a multiphased approach, with proposed construction starting this year and finishing around 2021. In total, more than 200,000 square feet are under review for renovation. Of course, these augmentations come at a cost. The bill for the project is estimated at \$100 million. If you are interested in defraying a portion of the surgical costs, the school welcomes your support. ■

For more information on naming and giving opportunities, contact Jennifer Gabler: 412-647-3792 or jag188@pitt.edu.

LASTING IMPRESSIONS

LEVYS AND LEADING MINDS

BY LORI FERGUSON

"Marshall was a genius," says **Stanley Levy** (MD '49) of his brother, **Marshall** (MD '53). "He was first in his class in medical school and the first person to get a first-year residency at Mount Sinai Hospital in internal medicine without having interned there or done a residency anywhere else. And while there, he was awarded a National Research Council Fellowship, which is not normally given in medicine."

A renowned nephrologist and rheumatologist, Marshall Levy would become known for describing the pathology of the kidney in sickle cell disease, among other contributions.

Marshall earned his BS from Pitt in 1948 before continuing to the School of Medicine. He practiced and taught at Pitt-affiliated hospitals for 43 years, serving for a time as president of the staff at UPMC St. Margaret and at Montefiore. Stanley notes that he and his brother came of age as admission caps on Jews were ending at the medical school and that Marshall worked to increase understanding among

people of different faiths. In addition to leading both Jewish and Catholic hospitals in his professional career, while an undergrad, Marshall served as president of the local YMCA, where he swam regularly.

When Marshall died in 1999, Stanley joined his brother's widow, Lois, in establishing the Marshall S. Levy, MD, Memorial Lecture at the medical school. The endowment has grown in the intervening years through donations from family, friends, and alumni.

The fund supports an annual lecture by a leading clinician or researcher in rheumatology, selected by a committee headed by Larry Moreland, an MD, the Margaret Jane Miller Professor of Arthritis Research, Department of Medicine, and chief of the Division of Rheumatology and Clinical Immunology. The 2015 lecturer was Betty Diamond, an MD and head of the Center for Autoimmune and Musculoskeletal Diseases at the Hofstra Northwell School of Medicine.

As rheumatologists home in on the immune system as central to many diseases under their care, the field's scope has expanded. Says Moreland, "The Levy lectureship not only allows us to honor Marshall Levy's legacy as both a clinician and educator but also to ensure that future generations of rheumatologists have the opportunity to learn from the leading minds in the field."

Stanley, an internist, is effusive in praise of his brother, yet he too has had a commendable career, including a 20-year stint as the doctor of Jack Kevorkian. That's not the only notable person who's crossed his path. At one point during his naval officer training, Stanley shared a Passover seder with Albert Einstein; an autographed English translation of his theory of general relativity manuscript now rests in his library. (Stanley's collection includes many other original writings by Einstein, as well as a first edition of Charles Darwin's *On the Origin of Species*.)

At 89, Stanley still sees patients twice a week and travels from his home in Bloomfield Hills, Mich., to a low-income senior apartment complex in Detroit to deliver care. ■

To learn more about supporting the Levy Lecture, contact Gary Dubin: 412-647-9113 or dgary@pmhsf.org.



Stanley (left) and Marshall Levy



CLASS NOTES



STEVE LEIMBERG/UNSEENIMAGES.COM

Marasco

'50s

Joe Marasco (MD '57) served 13 years as director of medical education at Pittsburgh's St. Francis Medical Center, as well as eight years as director of continuing education. "Training residents was one of the really fun parts of practice—it kept me on my toes." Marasco was also president of the American College of Radiology and the International Society of Radiology. Today, the retired physician and longtime violinist is engaged in a different type of education—sharing the joys of classical music with others as a life director of the Pittsburgh Opera and as executive director of the Amelia Island Chamber Music Festival. Marasco's latest coup: helping to arrange a January 2016 performance by cellist Yo-Yo Ma.

'70s

In a busy restaurant, people with normal hearing are able to take advantage of dips in background noise to follow conversations. Those

wearing hearing aids, however, may struggle to hear because their devices aren't programmed to catch the quieter moments. **Charlotte Reed** (PhD '73), principal investigator in the Research Laboratory of Electronics at MIT, is examining ways to improve processing technologies in hearing aids. The results of a study her team published in the *Journal of the Acoustical Society of America* in July suggest that the way the brain's speech processing interacts with a noise interruption can have a large effect on the intelligibility of speech in fluctuating noise backgrounds. "The consequences of hearing loss extend to all aspects of life," she says. "We're trying to devise hearing aids that will work better and make people want to use them and improve their quality of life."

'90s

Six months before Pope Francis celebrated mass in Philadelphia last fall, **Richard Scarfone** (Pediatrics Resident '90, Pediatric Emergency Medicine Fellow '92) began preparing for crisis situations that might arise during the papal visit. As medical director of emergency preparedness and an attending physician in the Department of Emergency Medicine at Children's Hospital of Philadelphia, Scarfone is part of a hospital-wide leadership committee that organizes frequent disaster drills, develops responses like family reunification plans, and strategizes ways to effectively handle crises from school shootings to disease outbreaks to snowstorms. Fortunately, the main challenge during the pope's visit was a shutdown of highways and bridges that meant 1,000 hospital staff had to be housed in the hospital for three nights. Scarfone's team is preparing an article about the papal preparations to give guidance to other hospitals.

Head and neck surgeon **Craig Buchman** (Otolaryngology Resident '96) is renowned for his clinical work and research on acoustic tumors, cochlear implants, and hearing preservation in disease

management. In the last decade, he has focused on using electrocochleography (which measures the ear's electrical response to sound) as an objective measure of inner-ear function in patients undergoing cochlear implant surgery. Buchman was recently named the Lindburg Professor and head of the Department of Otolaryngology at Washington University School of Medicine in St. Louis.

Jonathan Pletcher (MD '94) is director of medical services for Princeton University Health Services, which supports everyone from athletes to employees. Previously, he served as clinical director of the Division of Adolescent and Young Adult Medicine at Children's Hospital of Pittsburgh of UPMC and assistant professor of pediatrics at Pitt. As part of Pitt's Leadership Education in Neurodevelopmental Disabilities and Related Disorders program, Pletcher taught leadership skills to graduate and postgraduate students, practicing professionals, and families of children with disabilities.

'00s

Stanford assistant professor of pathology **Edward Plowey** (Anatomic Pathology Resident '06, Clinical Neuropathology Fellow '11) is committed to increasing understanding of Alzheimer's disease. Plowey and his team are studying mechanisms of protein degradation in brain cells, which are impaired in aging and age-related neurodegenerative diseases. "The resulting loss of protein homeostasis results in cell stress that leads to impairment and loss of brain synapses—the connections through which brain cells communicate and regulate complex behaviors," he explains. Plowey was recently awarded the Young Physician-Scientist Award from the American Society for Clinical Investigation. He did his undergrad, residency and fellowship training, and a pathology post-doc at Pitt.

'10s

Erica Nakajima (MD '15) (who, by the way, was a Howard Hughes Medical Institute Fellow at Pitt) spoke at a TEDx event at the George School in Newtown, Pa., her alma mater, in June. Nakajima told the audience about a carpentry project that she took on more than 10 years ago at the small Quaker school outside Philadelphia—and the mentors who helped her finish it. "I was really surprised at what I was capable of." Finishing a behemoth bookcase, Nakajima says, helped her tackle future research projects and taught her the importance of mentorship. Nakajima hopes to continue her research in cancer metabolism and patient care at Vanderbilt University, where she is now a resident in internal medicine.

—Lori Ferguson and
Brady Langmann



Nakajima

DR. YUM

FERNANDO ON KIDS AND EATING

The 6-year-old boy's BMI was in the 98th percentile. He was an active kid, but he loved processed food and was at risk for constipation, chronic abdominal pain, and attention issues.

His parents looked for help. They went to Yum Pediatrics in Spotsylvania, Va.—the office of Nimali Fernando (MPH '98, MD '99). Yum Pediatrics has an in-office test kitchen, where Fernando and health coaches offer cooking classes. The couple signed up for the Parenting for Wellness Seminar, an eight-meeting series that teaches parents how to raise healthy, adventurous eaters. "After a couple of months, I saw his body mass index plummet into the normal curve," Fernando says of the boy. "He had a calmness about him, and it was probably because he was actually eating real food."

Fernando—known as Dr. Yum around her community—also helps families learn about nutrition through her nonprofit organization, the Doctor Yum Project, which she started with her husband, Daryle Darden (MD '99). At Fernando's office, patients can learn how to cook a bean burger from the waiting room's TV or grab fresh vegetables from the garden outside. "What I found in my career is that so much of the symptomatology that we see can have a direct correlation to food," Fernando says.

In October, Fernando's guide, *Raising a Healthy, Happy Eater*, was published. Coauthored with feeding specialist Melanie Potock, the book features recipes and parenting tips; it also showcases what kids around the world eat, from crepes to kimchi. Fernando's own children have "food passports" where they keep track of their culinary adventures—with souvenirs like a message in Amharic from an Ethiopian restaurant.

"Be joyful about mealtimes and eating," Fernando says of the book's core message. "We want parents really to be able to not focus on food going into the mouth, but the experience of being at the table as a family." —BL



Fernando (left) and Potock

COURTESY DARYLE DARDEN



FUNNY BONES

Henry Mankin (MD '53, seated) demonstrates an unusual treatment on Kurt Weiss (in scrubs, Res '08) to the amusement of Pitt med students who are members of the Orthopaedic Surgery Interest Group. Mankin spoke to the group last fall, recalling tales of his student days. Mankin and Weiss have known each other for some time. Mankin was among the docs who treated the adolescent Weiss (now Pitt assistant professor of orthopaedic surgery) for osteosarcoma. Mankin is the Edith M. Ashley Professor Emeritus at Harvard, senior research consultant for the Orthopedic Oncology Service at Massachusetts General Hospital, and a member of Pitt med's Board of Visitors.

COURTESY CHRIS MURAWSKI

OBITUARIES

DAVID J. GNARRA

DEC. 3, 1943–JAN. 8, 2015

At a hospital in Nebraska, a boy needed a spinal tap and was afraid. So his doctor, David J. Gnarra (MD '68), jumped on the table, gave him surgical gloves, and let the boy pretend to give him the procedure first.

"He knew how to provide comfort," says Anisa Hoie, an oncology nurse who worked with Gnarra for more than 30 years.

Gnarra, an associate professor of pediatrics-hematology/oncology for the University of Nebraska Medical Center and Children's Hospital and Medical Center, Omaha, died in January 2015.



Gnarra

Before joining Omaha Children's, Gnarra spent two years in the Philippines as a pediatrician for the air force, then worked as an assistant professor of pediatrics for Creighton University in 1975. Gnarra brought state-of-the-art pediatric oncology practices to Omaha Children's through membership in the Children's Oncology Group.

In 1985, Gnarra helped start Camp CoHoLo—short for courage, hope, and love—in Nebraska for children with cancer. Active with the camp for 14 years as medical director, Gnarra helped build the program, which now hosts up to 190 kids for eight days each summer. He shimmied with them at dances, let them climb on him in the pool, and tip-toed on the high wires when they dared him. Today, in a garden at Camp CoHoLo, there's a cement bench in Gnarra's memory. "He would just go out there and do it all with [the kids]," Hoie says. "This last year we have missed him immensely." —BL

JOHN S. GOULD

MAY 10, 1939–SEPT. 29, 2015

After joining the University of Alabama at Birmingham's Division of Orthopaedic Surgery in 1975, John S. Gould (Res '71) realized he was the only formally trained hand surgeon in Alabama—and likely one of a handful in the entire Southeast. Shortly afterward, he started a fellowship program at the university.

"It was kind of a new field," says his wife,



Gould

Sheryl Hartford Gould. “He trained so many hand surgeons at UAB, and they went all over the Southeast.”

Gould later expanded his scope. He served for a decade as chief of orthopaedic surgery at the Medical College of Wisconsin, where he established a fellowship for foot and ankle surgery. He eventually returned to UAB and helped design total joint replacements for arthritic ankles.

Gould, named a professor emeritus at UAB in 2015, also wrote several books on orthopaedics and even penned a novel inspired by his grandfather’s experiences escaping the Russian army. *Kovno Gaberna* was published in November 2015.

When Gould’s former students approached Sheryl after his death, they told her what the down-to-earth surgeon had taught them. “What they learned from him, and what they pass on to their students, was not only the surgery, but also how to treat patients and how to conduct your own life,” she says. —BL

SEYMOUR KRAUSE

JULY 16, 1918–NOV. 3, 2015

Seymour Krause (MD ’43, Res ’49) opened the first cardiac rehabilitation center in the Pittsburgh region. During his 70 years of medical practice, Krause served thousands. When patients moved out of state, many would return to Pittsburgh solely for appointments with him.

“Seymour was such a gentleman,” says Lawrence Adler (MD ’57, Res ’60), Krause’s professional partner of 50 years and cofounder of the rehabilitation center. “He cared so much about his patients and about doing the right thing.”

Krause died Nov. 3 at his home in Oakland. He was 97.

Born to Hungarian Jewish immigrants, Krause grew up in Braddock, Pa., and received his BA and MD from Pitt. After pausing his residency at Montefiore Hospital to serve as an air force physician in World War II, Krause returned to Pittsburgh to finish his training and start his practice. He went on to serve as head of cardiology at Homestead Hospital and Braddock General Hospital, president of the American Heart Association of Western Pennsylvania, and clinical assistant professor at his alma mater.

Krause encouraged his patients to practice healthy living habits like not smok-

ing—advice that few doctors gave at the time. Rita Coultas, a nurse and Krause’s coworker of 38 years, says the cardiologist treated the whole person, heart and all.

—Susan Wiedel

KATE D. RYMAN

JULY 21, 1969–NOV. 18, 2015

Kate Ryman did dangerous work to make the world a safer place.

Last fall, she and coprincipal investigator Amy Hartman, assistant professor of infectious diseases and microbiology in Pitt’s Graduate School of Public Health, received a \$7.6 million grant from the U.S. Department of Defense to develop therapies against viruses that can be used as bioweapons.

Ryman, associate professor in the medical school’s Department of Microbiology and Molecular Genetics, was an expert in the viral pathogenesis and host response in alphaviruses, including those that cause Venezuelan, western, and eastern equine encephalitis (EEE). These diseases, especially EEE, have high mortality rates in humans and no existing antivirals. They occur naturally—but they are also potential agents of bioterrorism.

Ryman began her career at the University of Surrey in the United Kingdom, where she earned her BS and PhD in microbiology. When her mentor Alan D. Barrett, an authority on the yellow fever 17D vaccine, relocated his lab to the University of Texas Medical Branch in the early ’90s, Ryman followed. From there she went to the University

of North Carolina at Chapel Hill to work as a postdoctoral fellow with Robert Johnston, with whom she gained expertise in mosquito-borne virus pathogenesis and disease.

UNC is also where she met her husband, William Klimstra, then a graduate student. By 2001 the two were at Louisiana State University Health Sciences Center, sharing lab space and working with Biosafety Level 3 pathogens. In 2010, they joined Pitt’s Center for Vaccine Research (CVR).

Two months later, Ryman was diagnosed with metastatic leiomyosarcoma, a rare and aggressive cancer. Throughout her treatment, Klimstra says, and “all the successes she had, she was battling this constantly and was not cancer free at any time.”

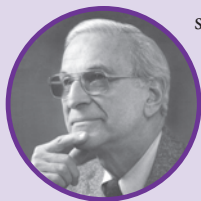
Klimstra, Pitt associate professor of microbiology and molecular genetics, is a coinvestigator on the DOD grant. He calls Ryman a pioneer in the study of artifacts of laboratory growth in viruses, and says her work with EEE virus—such as identifying its failure to grow in certain tissues—was “fundamental.”

According to Ryman’s postdoctoral mentor, Johnston, now executive director of Global Vaccines, “Kate was quick to laugh and slow to anger. She was an excellent scientist, a caring teacher, an exceptional colleague, and a wonderful friend.”

Hartman, her co-PI, says, “Kate has left a significant imprint as an accomplished virologist... It is my hope that I and her other colleagues in the CVR can carry on her legacy.” —Sarah C. Baldwin



Ryman



Krause

IN MEMORIAM

'40s

ALBERT IANCU
MD '42
SEPT. 20, 2015

IRVIN Q. SOBEL
MD '43
DEC. 18, 2015

CARMELLO A. RANII
MD '46
SEPT. 8, 2015

MARTIN D. REITER
RES '46
SEPT. 30, 2015

LEE M. HERSHENSON
MD '49
NOV. 19, 2015

'50s

JOSEPH L. MAZZA
MD '51
DEC. 22, 2015

JOHN E. WEIGEL JR.
MD '54, RES '55, RES '58
SEPT. 8, 2015

JOHN N. WALL
MD '55
DEC. 10, 2015

RICHARD HARDY MALEY SR.
MD '56
OCT. 23, 2015

'60s

RICHARD S. RICHARDS
MD '60
SEPT. 14, 2015

VOLKER BREITFELD
MD '67, RES '68
SEPT. 27, 2015

'70s

JAMES R. KASKIN
MD '70
NOV. 10, 2015

DAVID B. STARK
MD '76
SEPT. 28, 2015

'00s

AARON T. DAGGY
RES '05
DEC. 07, 2015

FACULTY

VINCENT C. ALBO
MD '55, RES '58
NOV. 3, 2015

JEANNE A. COOPER
RES '54, RES '56
NOV. 14, 2015

RONALD T. STANKO
MD '73, FEL '76, RES '79
NOV. 2, 2015

DAVID SHULKIN UNUSUAL RESIDENCY, PRESIDENTIAL APPOINTMENT

BY NICK KEPPLER

General medicine residents spend their days seeing patients, mastering clinical skills, absorbing a ton of information, and developing a bedside manner. When David Shulkin (Res '89, Fel '90) trained at Pitt, he also spent a lot of time going through stacks of file folders.

Shulkin, who had followed his wife-to-be, Merle Bari (Res '90), to Pitt, where she pursued her dermatology residency, asked his advisors to allow him to study care costs at insurer Blue Cross of Western Pennsylvania. It was the first time a resident had made such a request, Shulkin recalls. "They were amazingly open to allowing me to explore my interests and my desire to understand how [the business of] health care works."

Shulkin would go on to manage huge health care systems, including one of the nation's largest: the U.S. Department of Veterans Affairs.

That early Pittsburgh study on health care costs was so fascinating and promising, Shulkin stayed on an extra year as a general medicine fellow to complete the project.

His findings, published in the *Annals of Internal Medicine* and covered on the front page of the *Pittsburgh Post-Gazette*, showed that doctors largely had no knowledge of the cost of the care they provided. This was leading to the rise of a managed care industry to keep costs in check—yet the increase in administrative costs was also raising the price of health care. "We were at the beginning of a trend showing health care costs were set to explode," he recalls, "and as we now know, that's become a fundamental issue in health care design."

Shulkin would later spend four years as

president and CEO of New York's Beth Israel Medical Center and serve as the president of the New Jersey-based Morristown Medical Center. He also founded DoctorQuality, an early informational Web site for health care consumers.

In 2015, Shulkin became the VA's under secretary for health. (President Obama nominated him in March, and the Senate confirmed him in June.) The VA is a behemoth of a health care system: Its annual budget is \$59 billion; the system employs 300,000 people; and it stretches across more than 1,500 facilities. As if that isn't enough of a challenge, Shulkin is taking the helm at one of the most difficult times in the department's history. In June 2014, 35 veterans died waiting for care from the VA system of Phoenix. Subsequent investigations by several government agencies showed the system was buckling under increased demand for care. Nationwide, about 57,000 patients were waiting for appointments, and VA facilities had kept secret waiting lists and falsified data. The scandal led to the resignation of Secretary of Veterans Affairs Eric Shinseki and the early retirement of Shulkin's predecessor, Robert Petzel.

As part of the VA's new leadership, Shulkin says he is walking a balance between implementing

reforms and helping VA employees keep their chins up in light of a difficult job and public scrutiny. "The morale at the VA today is not where it needs to be," he says. "It's demoralizing to work as hard as I know our employees work and not be recognized for that work."

He says his other key goals are ensuring that every veteran who needs immediate care gets it and that others are seen within 30 days or are given the option to see a private-sector provider. (The latter is an option provided by the Veterans Access, Choice and Accountability Act of 2014.)

Shulkin still credits that unusual residency rotation at Pitt and the advisors who signed off on it with his position in the VA.

"If it wasn't for the experience they allowed me to have, to be different from the typical resident, I'm not sure I would be where I am today." ■



CIDDE/MIKE DRAZDZINSKI

The VA's Under Secretary for Health David Shulkin (center) and VA Secretary Robert McDonald (flanking him on the right) visited Pitt in November 2015.

A FRIEND INDEED

Do you know an alum who's doing something great? We're all ears at medmag@pitt.edu.

STRETCH-TASTIC

In this episode, blue-costumed Elastigirl spots an evil Purple People Eater lurking in the distance. Mustering her stretchy superpower, Elastigirl reaches farther and farther until —*gotcha!*— she snags the purple villain and injects poison. Minutes later, the Purple People Eater explodes. *Elastigirl Saves the World from Cancer!* At least until next time.

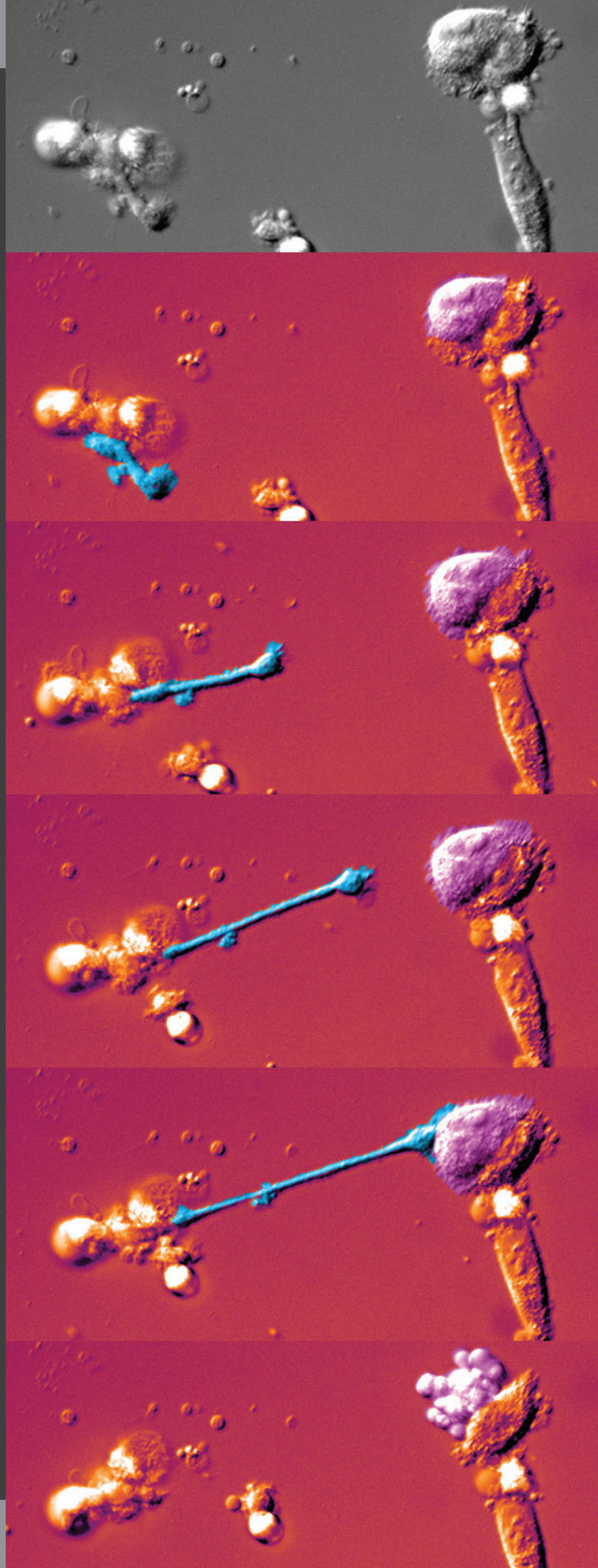
This series of images shows, in reality, a human natural killer cell (blue) attacking an A375 human melanoma tumor cell (purple) in a petri dish. Captured by Pitt's Per Basse, it's one of the first series of images to uncover this aggressive behavior of natural killer (NK) cells live in action. Basse is an MD/PhD/DMSci, associate professor of immunology, and assistant director of the University of Pittsburgh Cancer Institute's Cell and Tissue Imaging Facility. He's interested in ways of better engaging immune systems contending with cancers and says he almost fell out of his chair when he witnessed the NK cell's elasticity. Neither he nor any of his fellow NK researchers knew of this hidden superpower.

"It's encouraging," he says, noting that NK cells in the body don't have much space to move among tumor cells, which are packed like grapes. "If they can stretch out like this, they could stretch out in all sorts of directions, like amoeba crawling between other cells."

Basse's photo series was one of 20 winners of UPCI's 2015 "Images of Fighting Cancer" contest. The winners were showcased at the Science as Art exhibition at Pitt's Science 2015 event in October; they are now on permanent display in the research wing of the Hillman Cancer Center, home to UPCI—which, by the way, was founded 30 years ago by Ronald Herberman, whose lab discovered NK cells.

Meanwhile, research into the mysterious superpowers of NK cells continues. "I like to say they'll *stretch* far to help us get rid of cancer," Basse quips.

—Cara Masset
—Images Courtesy Per Basse



CALENDAR

FOR ALUMNI & FRIENDS

MEDICAL ALUMNI ASSOCIATION EXECUTIVE COMMITTEE BOARD MEETING FEBRUARY 24

6 p.m.

University Club, Conference Room B

For information:

Ashley Knoch at 412-648-9059

akk57@pitt.edu

HEALTH SCIENCES ALUMNI RECEPTION APRIL 14

7 p.m.

UPMC Lemieux Sports Complex

For information:

Rachel Edman at 412-864-1957

rge6@pitt.edu

PITT ALUMNI RECEPTION

Cosponsored by Alumni Relations, Health Sciences, and the Pitt Alumni Association

APRIL 21

6 p.m.

Sheraton Erie Bayfront Hotel

Erie, Pa.

For information:

Rachel Edman at 412-864-1957

rge6@pitt.edu

CLASS OF 2016 LUNCHEON MAY 20

11 a.m.

Alumni Hall, J.W. Connolly Ballroom

For information:

Ashley Knoch at 412-648-9059

akk57@pitt.edu

MEDICAL ALUMNI WEEKEND SEPTEMBER 23–25

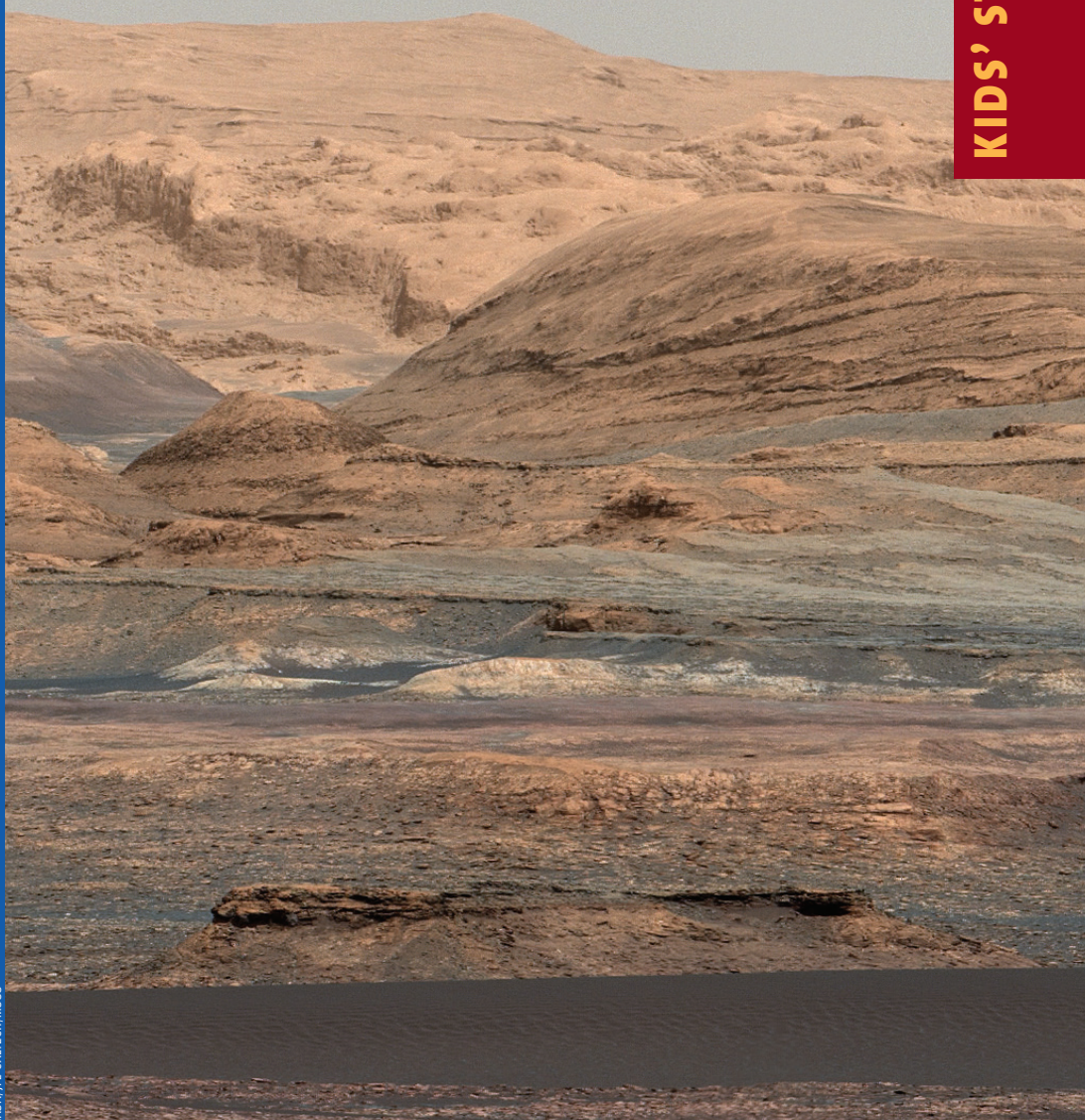
For information:

Ashley Knoch at 412-648-9059

akk57@pitt.edu

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

Could this be your front lawn someday?



NASA/JPL-CALTECH/MSS



FOR REAL! TWEEN SCIENCE

Ever wonder what it would be like to live on Mars? There are big challenges to life on the “red planet,” aside from its lack of food, breathable air, and liquid water.

For one, Mars’s surface is really cold, sometimes dipping hundreds of degrees below freezing.

And Mars’s atmosphere is thin—too thin for us. We humans are used to the Earth’s protective ozone layer and magnetic field. Without a comparable block, Martian citizens would be exposed to a lot of cosmic radiation, which causes sickness—imagine the worst sunburn ever, but through your entire body (and leading to brain damage, as well as cancer). These rays would be an issue on the yearlong journey to the planet, too.

Furthermore, Mars’s gravitational pull—what keeps your feet on the ground—is weaker than what we’re accustomed to. Low gravity might be great for dunking a basketball, but it would be tough on a human body. Without strong gravity holding you down, your muscles and bones would grow weak from lack of resistance. Even the spine starts to straighten out—way beyond good posture.

So could the planet ever be colonized by the likes of us? Maybe. Living underground, bundling up, and lots of weight lifting could help, notes Pitt astronomy professor Arthur Kosowsky. And apparently, Martian colonists could stay abreast of what’s new on Earth. Thanks to modern technology, “People could stream Netflix on Mars and read the [newspaper] each day,” says Kosowsky. —Robyn K. Coggins

For more science for kids, visit howscienceworks.pitt.edu.

HEY, BUD.

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