UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | SUMMER 2016

PITTMED

INTO A WORLD OF LIGHT

SAHEL ON RESTORING SIGHT

SOCIALIZING

Follow the Medical Alumni Association (@PittMedAlum) on Instagram for fun facts like this one: You might have known that famed actor Jeff Goldblum is from Pittsburgh (West Homestead, to be precise), but did you know his father, Harold L. Goldblum, was a 1943 Pitt med alum? Head to the MAA's profile to see his yearbook pic, plus more flashbacks, photos, and even some med school fashion. And keep abreast of the stories behind and beyond our stories—join the conversation on Twitter: @PittMedMag

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Cara Masset, "Inside the World of OCD"

2016 Press Club of Western Pennsylvania
Golden Quill Award Finalist, Health/Science/Environment, Online
Cami Mesa and Elaine Vitone,
"Second Lives: A Pitt Medcast"

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

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CARVE 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 pumpkin 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

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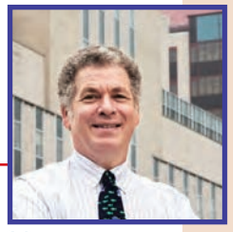

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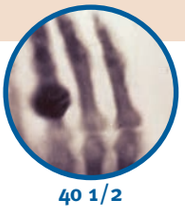
DEPARTMENTS



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FEATURES

CONTRIBUTORS

Editor in chief ERICA LLOYD has returned to home base, and the whole crew is excited that they are able to interact with more than a disembodied voice over the phone. Before materializing in front of our eyes this summer, she was living in Northern California for 16 years, running this show from afar. The epic journey back involved dodging bison as well as dodgy biker bars—but also awakening to the grandeur of the Tetons. In addition to bringing this magazine into form in 1999, Lloyd has contributed to *National Geographic News*, *Popular Science*, *Wired*, and *Radiolab*. Welcome back, chief!

ELENA GIALAMAS CERRI [typography for "Personalized Medicine, 101" and "Into a World of Light"] is the magazine's art director. For a decade following her graduation from Carnegie Mellon, she worked in Manhattan as a graphic designer for fashion-related publications such as *ELLE* and J. Crew catalog. Back then, she never would have thought that "fluorescence and microbiomes" would be part of her everyday "design vocabulary." Yet she loves the collaboration involved in editorial design. A typography enthusiast, Cerri is enamored with this issue's cover (her 68th cover for us), noting the font's attitude is "a little imbalanced, but that's what makes it interesting."

COVER

José-Alain Sahel, whose days are devoted to finding ways to restore sight, thinks a lot about light in our lives. (Cover: Elena Gialamas Cerri, Negative Space typeface by Kevin Richey for FontSpace, © 2016.)

PITTMED

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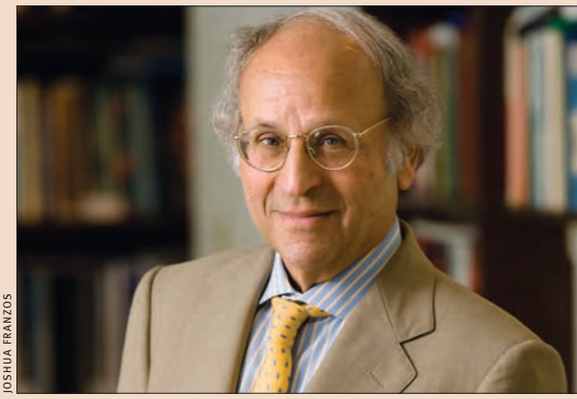
It has long been an axiom of mine that the little things are infinitely the most important.

—Sir Arthur Conan Doyle



JOSHUA FRANZOS

Well in advance of my getting to know Dr. José-Alain Sahel (our new chair of ophthalmology, see p. 12), I was already intrigued with the opportunities now afforded to extend what we are learning about the eye to the generality of biology. With this in mind, I'd invited Nathan Morehouse, an assistant professor of biological sciences, to lecture in my junior faculty seminar series. Among his research interests is the visual ecology of *Habronattus*, a genus of tiny jumping spiders known for their superior 360-degree vision.

Most jumping spiders are colorless and colorblind. But spiders in the *Habronattus* group are, as Nathan puts it, "little fireworks on the family tree of spiders," exhibiting explosions of color. Well, the males do anyway. The females, like their distant spider cousins, are quite drab; yet they have exquisite color vision—a key advantage of this trait is the ability to detect colorful but toxic prey. Males capitalize on the choosiness of females by presenting colors that their female counterparts—possible predators—are less likely to attack. (Eating a potential mate is a fairly definitive way of turning him down.) The species *H. pyrrithrix,* for instance, is named for the flame-red hair growing on the faces of males.

Nathan's work has shown that the females' sight has evolved with an amazing degree of sophistication and distinction; their complex photoreceptor filtering and trichromatic system may have arisen in response to changing coloration in males, and vice versa, over time. It's a fascinating example of coevolution. The males are evolving color, while the females are developing highly sensitive mechanisms to distinguish it.

I left Nathan's lecture thinking how easy it is to take for granted what is literally underfoot. These spiders—each about the size of a fingernail—have larger lessons for us. In this single instance of a coevolutionary conga between visual systems and visual signals, we see basic processes that ultimately lead to the biodiversity of our world.

Nathan is one of several evolutionary biologists who collaborate with faculty in the medical school. These partnerships are important because we see coevolution in many processes relevant to human health. The arms race between humans and bacteria, for example, has given rise to drug-resistant strains. And Amish children who live in homes in close proximity to horses and cows and the microbes they harbor are protected from asthma to a greater extent than children in Hutterite families who practice more industrialized farming and inhabit more "sterile" homes further removed from livestock. (Iowa's Peter Thorne, who did his postdoctoral work here at Pitt, was among the authors of this recent breakthrough *New England Journal of Medicine* paper.)

Our intellects and ideas also coevolve. It strikes me that the dawn of abstract art and atonal music may have influenced the fathers of molecular biology (and vice versa). At about the same point in time, art, music, and science all brought into focus the roots of what we see, hear, and inherit. It's not as much of a leap, so to speak, from tiny jumping spiders to much larger questions as one might think.

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

NOT-SO-SECRET AGENTS

Certain infectious agents, such as herpes simplex viruses (HSV) 1 and 2, cytomegalovirus (CMV), and the protozoan *Toxoplasma gondii*, can infiltrate nerve cells, and these infiltrators have long been accused of speeding cognitive decline.

A paper in December's *Alzheimer Disease & Associated Disorders* clarified this connection. Vishwajit Nimgaonkar, an MD/PhD professor of psychiatry and human genetics; Mary Ganguli, an MD/MPH professor of psychiatry, epidemiology, and neurology; Chung-Chou Chang, a PhD professor of medicine, biostatistics, and clinical and translational sciences; and colleagues assessed the mental acuity of more than 1,000 seniors throughout five years. They found that although HSV-1 doesn't seem to be implicated in attention, language, and memory issues in older adults, HSV-2, CMV, and *T. gondii* are associated.

"[This result] points us in a new direction," says Ganguli, "and could open up possibilities for both prevention and treatment. Clinical trials could test the effectiveness of antiviral medication to ward off decline, and public health experts could develop strategies for preventing exposure in the first place."

—Jennifer Larson

FOOTNOTE

Pitt's School of Medicine and Graduate School of Public Health faculty amassed more than $414 million from the National Institutes of Health last year, ranking fifth in the nation overall. That cash is a hefty chunk of the University's total NIH funding—at $475 million, up $19 million from 2014. Pitt's total places us above the University of Michigan, UCLA, University of Washington, and Stanford University, to name a few notable peers.

Goldstein

MARY BRADY

Presidential Praise for Pitt

This February, Tina Goldstein, a PhD associate professor of psychiatry and director of psychotherapy for pediatric mood disorders at the University of Pittsburgh, received the U.S. government's highest honor for young scientists—the Presidential Early Career Award for Scientists and Engineers (PECASE). She and the other winners celebrated the honor with President Barack Obama at the White House this May.

Goldstein's studies of treatment for adolescents with bipolar disorder and suicide prevention in that population are supported by nearly $2.5 million in grants from the National Institute of Mental Health.

Pitt's Ervin Sejdic, assistant professor of electrical and computer engineering and of bioengineering, and Elizabeth Skidmore, an associate professor and chair of occupational therapy, both PhDs, also received PECASE awards. The School of Medicine's first winner, in 2000, was Karl Kandler, a PhD, UPMC Professor of Auditory Development and Plasticity, professor of otolaryngology and neurobiology, and director of the auditory research group. Overall, seven Pitt faculty members have been PECASE awardees. *—Robyn K. Coggins*

CAMI MESA

Overheard: Fluid Dynamics

In 2003, Michael Moritz (shown above), an MD, and his fellowship mentor, Juan Carlos Ayus, rocked the parenteral nutrition boat with a paper in *Pediatrics*. They presented evidence against the use of hypotonic IV solution (fluid with less sodium than a patient's plasma)—a practice that had been entrenched in pediatric hospital care for 50 years. They argued that the solution could cause hyponatremia, or low sodium levels, and eventually neurological problems and death. Today, Moritz says, "over 20 prospective studies in over 2,000 children" have proven him right—that isotonic fluid, with sodium concentration matching patient plasma, is appropriate for most patients.

Moritz, now clinical director of pediatric nephrology at Children's Hospital of Pittsburgh of UPMC and professor of pediatrics, published an October review article in the *New England Journal of Medicine* about the physiological principles of IV fluid selection. "Changing fluid practice is a simple and safe measure which can be taken to improve patient safety and will save lives," he says.

What made you realize that a change in IV solution administration was needed?

Dr. Ayus and I observed that almost all hospitalized patients were at risk for hyponatremia from elevated hormone levels that prohibit the kidneys from releasing water. With that, I wanted to know why hypotonic IV solution became standard of care. There was really no data to support the practice—it was based on the sodium concentration of breast milk and cow's milk.

What tactics did you take to manage the controversy?

Physicians were fearful that isotonic fluids would cause fluid overload and hypernatremia [high sodium levels]. We thought, if we repeat our message and explain it in very clear terms, eventually it would catch on. We wrote letters to the editor, commentaries, and reviews correcting misconceptions. Fortunately, this sparked a renewed interest in the topic, and investigators around the world began conducting studies and verifying our concept. Now, societies are developing consensus guidelines on fluid therapy in children and adults, when before there were none.

—Interview by Kristin Bundy

Faculty Snapshots

The University of Pittsburgh School of Medicine boasts two recipients of the National Cancer Institute's Outstanding Investigator Award this year, which provides funding throughout seven years. (Pitt's Thomas Kensler, a PhD, received the award last year.)

Olivera Finn will use her $6.2 million in Outstanding Investigator funding to support the development of new cancer vaccines. A Distinguished Professor of Immunology and Surgery, Finn investigates the ways our bodies identify and fight cancer. Finn, a PhD, was the founding chair of Pitt's Department of Immunology. She also received the American Association of Immunologists Lifetime Achievement Award this year.

Finn

Patrick Moore will use his $6.4 million of funding to support his investigations into how viruses turn normal cells into cancer, among other areas of cancer virology. Moore, an MD/MPH who is the American Cancer Society Distinguished Professor of Microbiology and Molecular Genetics, leads the University of Pittsburgh Cancer Institute's Cancer Virology Program and holds the Pittsburgh Foundation Chair in Innovative Cancer Research.

Moore

The Association for Psychological Science has named Rebecca Price a "Rising Star." Codirector of the Pittsburgh Neuroimaging and Treatment Outcome Lab, Price works at the intersection of clinical and neurocognitive research. She develops novel ways to treat anxiety, depression, and suicidality using computer-based interventions and pharmacological approaches. Price is a PhD assistant professor of psychiatry.

Price

Snyderman

Carl Snyderman presented the Semon Lecture to the Royal Society of Medicine in London. The November 2015 lecture was titled "Paradigm Shifts in Skull Base Surgery and the Creative Process." Snyderman, an MD professor of otolaryngology and neurological surgery, is codirector of the Center for Cranial Base Surgery at UPMC. He is internationally recognized for helping to develop a technique to remove brain tumors through the nose with an endoscope, which limits trauma to the brain, eliminates scars from facial incisions, and shortens recovery times.

—Elizabeth Hoover

Flashback

Happy birthday, Scaife Hall! Construction of the building began in 1954 with the help of $15 million in grants from the Sarah Mellon Scaife Foundation, the A.W. Mellon Educational and Charitable Trust, and the Richard King Mellon Foundation. In 1956, the building, designed by the architectural firm Schmidt, Garden, and Erikson, opened to students and faculty. Scaife Hall may be 60, but it's nowhere near retirement: School officials are raising funds for a brightly lit west wing addition with student lounges, classrooms, and labs.

HISTORICAL SOCIETY OF WESTERN PENNSYLVANIA

Pride in the Curriculum

Jason Rosenstock, MD associate professor of psychiatry and director of that department's medical student education program, knows that patients identifying as lesbian, gay, bisexual, transgender, or queer (LGBTQ) can experience implicit or overt bias when seeking care. Lack of provider awareness about recommended treatments and screenings, such as Pap smears to detect cervical cancer in transgender men, or limited insurance coverage for LGBTQ-specific needs, can be roadblocks to appropriate care. Even an intake form that only offers MALE or FEMALE for gender options can make some patients reluctant to visit the doctor.

Rosenstock, Dena Hofkosh, an MD and associate dean for faculty affairs, Christopher David, a third-year medical student, and others have been working with Pitt med course directors to integrate more LGBTQ-related content into the curriculum to ensure responsible and competent care for LGBTQ patients. During the Behavioral Medicine course, for instance, med students now discuss the case of an 18-year-old transgender woman dealing with depression. And as part of the Medical Interviewing course, students now encounter cases involving well-functioning and healthy same-sex couples to present normative examples of LGBTQ lives. Kristen Eckstrand, an MD/PhD and second-year resident in psychiatry who coedited a clinical guide to LGBTQ health care, believes that more opportunities for students to rotate at centers with higher proportions of LGBTQ patients is an important component of students' training.

Hofkosh, Eckstrand, David, and Rosenstock are members of Pitt's PRIDE Health, a collection of more than 200 students, faculty, and staff focused on patient care and other issues faced by the LGBTQ community in medicine. (They also advocate for individuals born with differences of sex development.) PRIDE's efforts, Rosenstock says, will "improve the climate to make more individual physicians and medical practices welcoming and culturally proficient in the care of LGBTQ patients and their families." *—Rachel Mennies and Robyn K. Coggins*

Top Physician-Scientists

Six Pitt physician-scientists were recently inducted into two vaunted organizations—the Association of American Physicians (AAP) and the American Society for Clinical Investigation (ASCI).

William Osler and six other physicians established AAP in 1885; it recognizes standout clinical and basic science researchers who are contributing to the pursuit of medical knowledge and its clinical application. Pitt inductees include David Brent, an MD, professor of psychiatry, pediatrics, and epidemiology, and Professor of Suicide Studies; Brian Zuckerbraun, an MD and the Henry T. Bahnson Professor of Surgery; and Anne Newman, an MD/MPH, epidemiology department chair, director of the Center for Aging and Population Health, and the Katherine M. Detre Professor of Population Health Sciences.

ASCI is a physician-scientist honor society created in 1908 for investigators under the age of 50 who successfully convert laboratory results into innovative clinical practice. This year its new members include Pitt's Caterina Rosano, an MD/MPH and professor of epidemiology; Bernhard Kühn, an MD/PhD, associate professor of pediatrics, and director of research for pediatric cardiology; and Stephen Chan, an MD/PhD, associate professor of medicine, and director of the Center for Pulmonary Vascular Biology and Medicine. *—Ali Greenholt*

CAMI MESA

SEW THOUGHTFUL

Once a month at St. Louise de Marillac Parish in Upper St. Clair, about 25 women gather to measure, cut, and sew with purpose. Their product: robes for women undergoing treatment for breast cancer. The garments are made from scrubs patterns, with slits on the front and sides held together by Velcro.

"The Velcro opening allows the patient to expose only the part of the breast that has to have radiation treatment. This helps keep them covered instead of lying there totally exposed like hospital gowns would do," says Karen Radu (pictured above), founder of the group at St. Louise de Marillac.

The seamstresses got their start in 2009, after Radu heard about Arlene Segar of Monroeville making these comfy robes. She shared her patterns, and since then the St. Louise ladies have fashioned 5,000 robes for hospitals in the Pittsburgh area, including UPMC Shadyside, UPMC Jameson, and others. Radu and her crew work solely from donations and grants; one of their biggest donors is Magee-Womens Hospital of UPMC.

The volunteers slip a well-wishing card into each robe pocket; that often spurs a call or a thank-you card from the women undergoing treatment.

"I always share the notes and letters with the group when we meet," says Radu. "It brings all of us to tears most of the time; [the volunteers] know how much they are appreciated." *—Kristin Bundy*

Next Generation

The Howard Hughes Medical Institute (HHMI) annually funds students to conduct a yearlong stint of "basic, translational, or applied biomedical research" as they pursue an MD degree. This year, 79 research fellows were chosen, five of whom are Pitt Physician Scientist Training Program students expected to earn their MDs in 2019.

Pooja Karukonda, with mentor Christopher Bakkenist, a PhD, hopes to "change the paradigm of [cancer] therapy" by shifting the focus to the body's own defense mechanism, the immune system. Because certain immune-system cells are vital to cancer-destroying effects after radiation, Karukonda is investigating whether radiation can actually activate the immune system to jump-start the natural healing process.

Thiagarajan (Thiagu) Meyyappan studies type 1 diabetes, in which the immune system destroys its own insulin-producing cells. Meyyappan, mentored by Jon Piganelli, a PhD, and Steven Little, a PhD, uses regulatory T cells to try to combat this irregular immune system function while also maintaining normal immune responses to viruses and bacteria.

Wai Lok Tsang and mentor Thanos Tzounopoulos, a PhD, are chasing phantoms—phantom sounds, that is. Tinnitus, affecting nearly 15 percent of the population, causes people to perceive sounds, such as ringing, buzzing, or static, that aren't actually there. Though tinnitus currently has no cure, Tzounopoulos and Tsang hypothesize that zinc can suppress the neurotransmitters that cause hyperactivity in an auditory region of the brain stem, perhaps eradicating the irritating noises.

Mondira Ray, motivated by experiences with cancer patients, wants to "help bridge the gap between cause and cure." As part of the Big Data for Better Health project, Ray, with mentors Ziv Bar-Joseph of Carnegie Mellon University and Pitt's Rebecca Jacobson, an MD, is integrating genomic cancer data into revamped computational models to produce better strategies for preventing, diagnosing, and treating breast and lung cancer. Using algorithms that analyze electronic health records, machine-learning programs can use those data to predict clinical outcomes, resulting in better patient care.

Tolani Olonisakin, with mentor Janet S. Lee, an MD, is one of 13 HHMI fellows nationally returning for a second year. Olonisakin is studying how a protein produced predominantly by platelets interacts with neutrophils, the first responders of the immune system. Olonisakin says understanding this interaction is critical to developing a drug that effectively targets these molecules, which she hopes could help fight the "urgent threat" of antibiotic resistance. *—Ali Greenholt*

HIT 'N' KNIT

If you're looking for Maggie Wright outside of the laboratory, you might need to call her by her derby name, "Poppin' Fresh."

Wright—a neuroscience PhD and postdoctoral researcher in the lab of H. Richard Koerber, PhD professor of neurobiology—is also a competitor with the Steel City Roller Derby, captaining the Allegheny Avengers and skating on the league's A-team, Steel Hurtin'. (She's shown above in the yellow jersey, calmly checking an opponent from the Indianapolis Naptown Roller Girls.)

"Derby," says Wright, "has been a great outlet for me as a physical activity—as well as an opportunity to meet some amazing people."

Wright has been competing since 2012; she got her start in Cleveland while attending Case Western Reserve University.

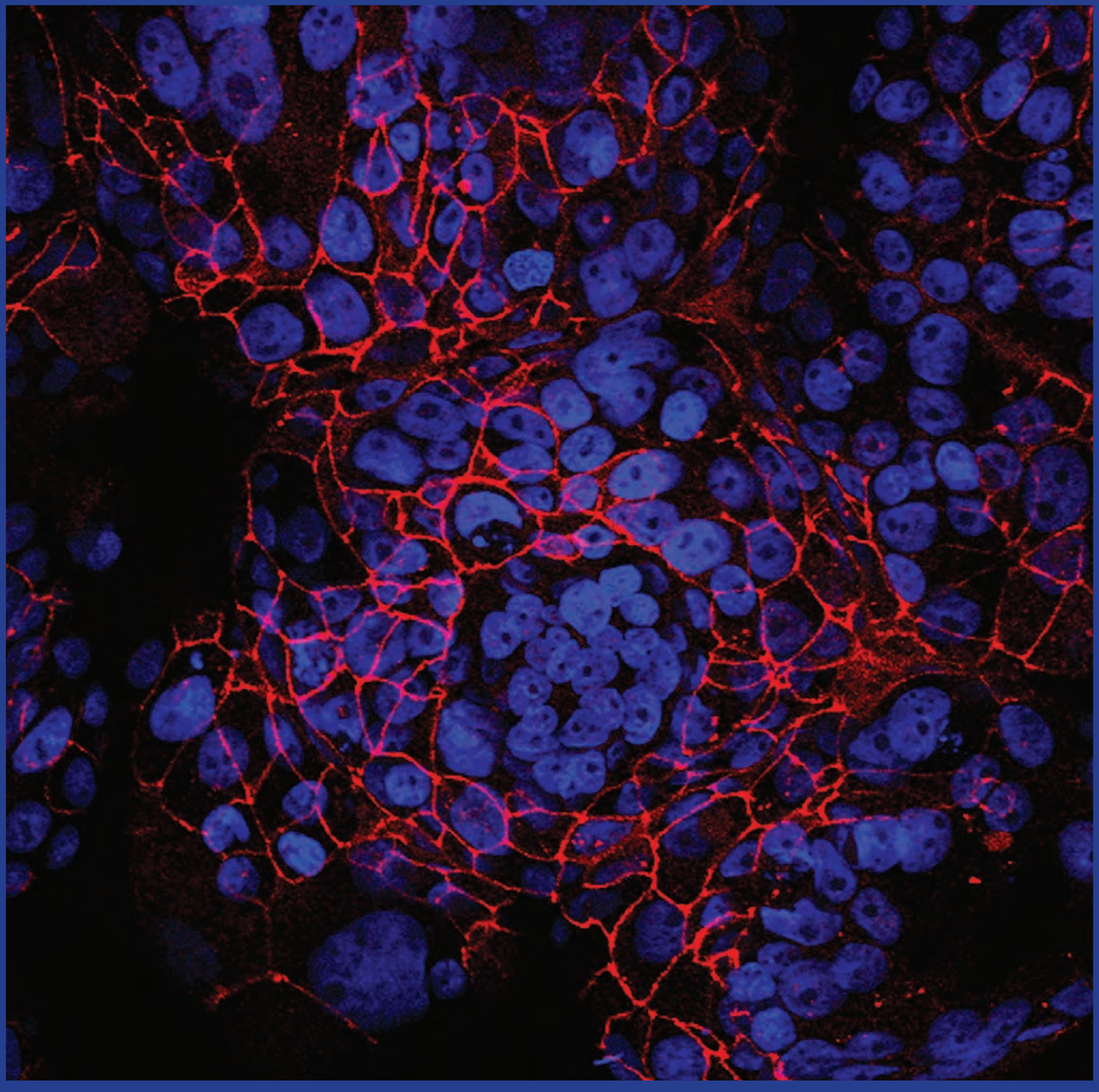
Wright's dissertation, defended in February, focused on the development and maintenance of Merkel cells—skin cells that help us sense touch. She currently studies how such somatosensory receptors regain function after injury.

Neuroscience and roller derby may seem to have little in common; but Wright says the two complement each other, as each requires serious patience and mental fortitude.

Wright's off-rink avocation has a fringe element, as well—that's yarn-bombing, a street art wherein bombers create cozies for bike racks, cars, trees, bridges, whatever strikes their fancy. Wright also happily engages in more traditional knitting projects: "I've done a lot of hats, socks, baby blankets, gloves, and an ear cover that fits around my bike helmet for the winter months."

—Rachel Mennies

—Photo by Karl Zemlin



Placental cells are notoriously tough to culture—they need to move. Here, the cells (nuclei in blue) thrive in a churning microgravity bioreactor. Certain cell types fuse into conglomerates called syncytiotrophoblasts (red), which defend a fetus against infection.

OPPOSITE PAGE: In traditional, 2-D culture (left column), microbes (green) have free rein. But in Coyne's 3-D culture (right column), spherical-shaped syncytiotrophoblasts form and fend them off.

THE GREATEST BARRIER REEF

TEACHING PLACENTAL CELLS TO LIVE IN A DISH | BY ALLA KATSNELSON

As an expectant mother's body pipes blood into the placenta, the blood swirls over a seabed of villi that look a bit like the polyps of a coral reef. Coating these structures is a layer of what are called syncytiotrophoblasts, cells that prevent viruses and other microbes from getting to the developing fetus. Researchers know little about these cells (or the human placenta in general, for that matter). But when syncytiotrophoblasts fail, the outcome can be disastrous.

"If you're thinking about how an infectious agent associated with congenital disease—*Toxoplasma gondii*, cytomegalovirus, rubella virus, and now Zika—crosses the placental barrier, it's these cells you should be studying," says the University of Pittsburgh's Carolyn Coyne, PhD associate professor of microbiology and molecular genetics. She studies how viruses bypass a host's cellular barriers.

One problem is that placental cells are tough to work with. Though post-delivery placental tissue is accessible enough, placental cells are difficult to isolate, difficult to grow, and don't stay around for long. With some cell types, cultured cell lines can model what happens in the body, but with placentas, not so much; syncytiotrophoblasts form when more basic cells called trophoblasts fuse, but that fusion is difficult to coax in the dish.

Recently, however, with the help of a technology developed by NASA, Coyne and her colleagues have created the first reliable cell-based system for culturing placental cells. They describe the approach in a report published in *Science Advances* in March.

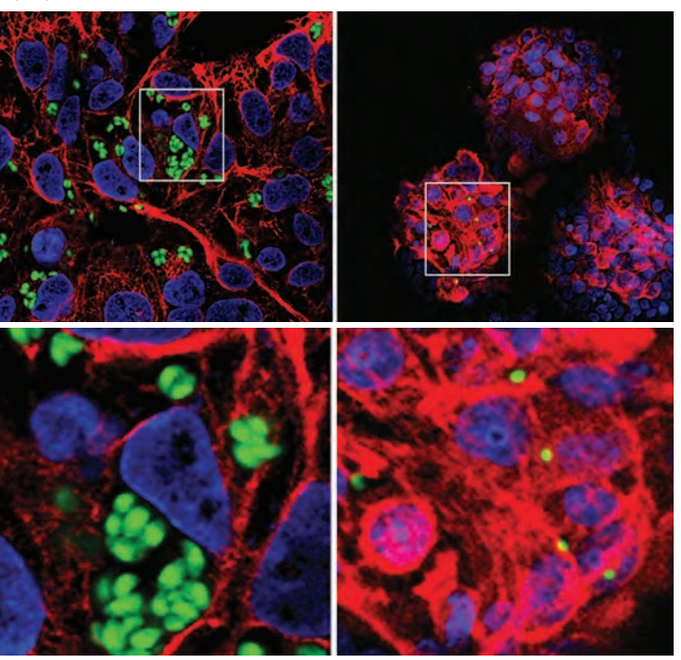
Eight years ago, when Coyne was pregnant, she couldn't help wondering whether the viruses she worked with could harm her baby (she was studying gut cells at the time). The published literature didn't provide an answer. So she turned to Pitt's Yoel Sadovsky, MD, scientific director of the Magee-Womens Research Institute, and the Elsie Hilliard Hillman Professor of Women's and Infants' Health Research, for some placental cells as well as advice on how to work with them (a discussion that led to a collaboration that's still going strong). She learned that primary placental cells are highly resistant to viral infection, but cultured placental cells are the opposite—very permissive. To probe placentas' antiviral powers, then, the team would need a better model.

Her first thought was of the movement of maternal blood and the sheer force it generates. Could a 3-D system awash in fluids be the missing ingredient? For its work on the gut and the blood-brain barrier, her lab had recently bought a NASA-developed microgravity bioreactor that keeps the culture medium circulating constantly. (The device looks like a slushie machine.) The bioreactor not only produces sheer force, but also mimics the membrane curvature of a placental coral reef by seeding cells on a matrix of tiny, porous beads.

The researchers tried several existing trophoblast lines that failed to grow in the system. Then the team realized that in trophoblasts' natural environment, they tango with lots of other cells. So after putting several combinations through the bioreactor, the team hit upon a cell line that formed syncytiotrophoblasts in the presence of certain endothelial cells. "Morphologically, it was very clear," Coyne says. The fused cells they had cultured also secreted pregnancy-associated hormones and upregulated the set of genes that they would typically in a pregnant woman's body.

Coyne's team is still perfecting the system. To make it easier to use, they've found a way to remove the syncytiotrophoblasts from the beads and plate them in a plastic dish. With the new technique, researchers can begin to explore the mechanics of how disease-causing agents do or don't cross the placental barrier.

In April the group published a paper in *Cell Host & Microbe* showing that cells taken directly from the placenta following delivery resist Zika virus infection. "These cells exist to keep pathogens out," Coyne says. By manipulating the genetics of the cell line, they hope to understand how resistance is mounted and explore several possible explanations for how a virus might break down or bypass it. (Maybe placental cells from early stages in gestation are not as resistant, Coyne says. Or maybe the virus gets in via some other trophoblast type. Or maybe it's not infecting placental cells at all, but hitching a ride on an antibody or some other "Trojan horse" instead.) Once the mechanism becomes clear, she says the 3-D system could be fertile ground for a new pursuit: screening for therapeutic compounds that could restrict infection. ■



PERSONALIZED MEDICINE, 101

A CLINICIAN'S CRASH COURSE ON THE FUTURE OF MEDICINE | BY ROBYN K. COGGINS

TYPOGRAPHY: ELENA GIALAMAS CERRI

This May, CVS Pharmacy announced a partnership with 23andMe, a genetic testing company, to sell test kits directly to consumers for about $30. Spit into a test tube, mail it off, and six to eight weeks and a $169 lab fee later, you'll have data on your genome, no prescription necessary. Inevitably, says Philip Empey, a PhD and PharmD assistant professor of pharmacy and therapeutics at the University of Pittsburgh, patients will bring results like these—and the questions they raise—to pharmacists and physicians: *What does it mean if I have a mutation associated with such-and-such disease?*

In a lecture room in Friendship this March, a group of 60-some health care professionals pondered these and other uncertainties over beer. …Well, not literally. Empey handed each of them a PTC taster strip, which tests for a trait associated with a specific gene variant. About three-quarters of Americans have the trait, which means they should find the strip's taste overly bitter—India pale ale–averse types, by heredity. On the penultimate night of this unique course, the clinicians found out whether their genetics accurately predicted their palates.

Throughout eight weeks, "Big Data and Healthcare Analytics—A Path to Personalized Medicine" covered topics ranging from patient communication to compatibility of electronic health record systems at breakneck speed, for four dense hours per session. Pitt's Institute for Personalized Medicine (IPM), the Big Data to Knowledge Center of Excellence, and the Schools of the Health Sciences organized the course with funding from the Jewish Healthcare Foundation.

To some of these docs, nurses, and pharmacists, the taste-test (i.e., gene variant) results were a surprise. Those who crinkled their noses at the bitterness of the strip on the first class night didn't necessarily have the gene variant. "Why wouldn't it be a perfect match?" Empey posed to the class. A number of possible reasons emerged: medical conditions, other interfering genes, an error in the genotyping, or even a pre-class taco dinner. There are pitfalls in relying too heavily on genetic data in the clinic.

The students used a Pitt School of Pharmacy–developed software called Test2Learn, an educational tool allowing users to upload their 23andMe profiles to explore variants in more detail. (The software, which Empey's team developed, also gives the option to use anonymous volunteer patient datasets instead; no one in the room could tell whether classmates were analyzing their own data.) Select a variant—rs713598, in the taste-testers' case—then click Test2Learn's "Interpret Gene" button. The software spits out keg-loads of genomic detail.

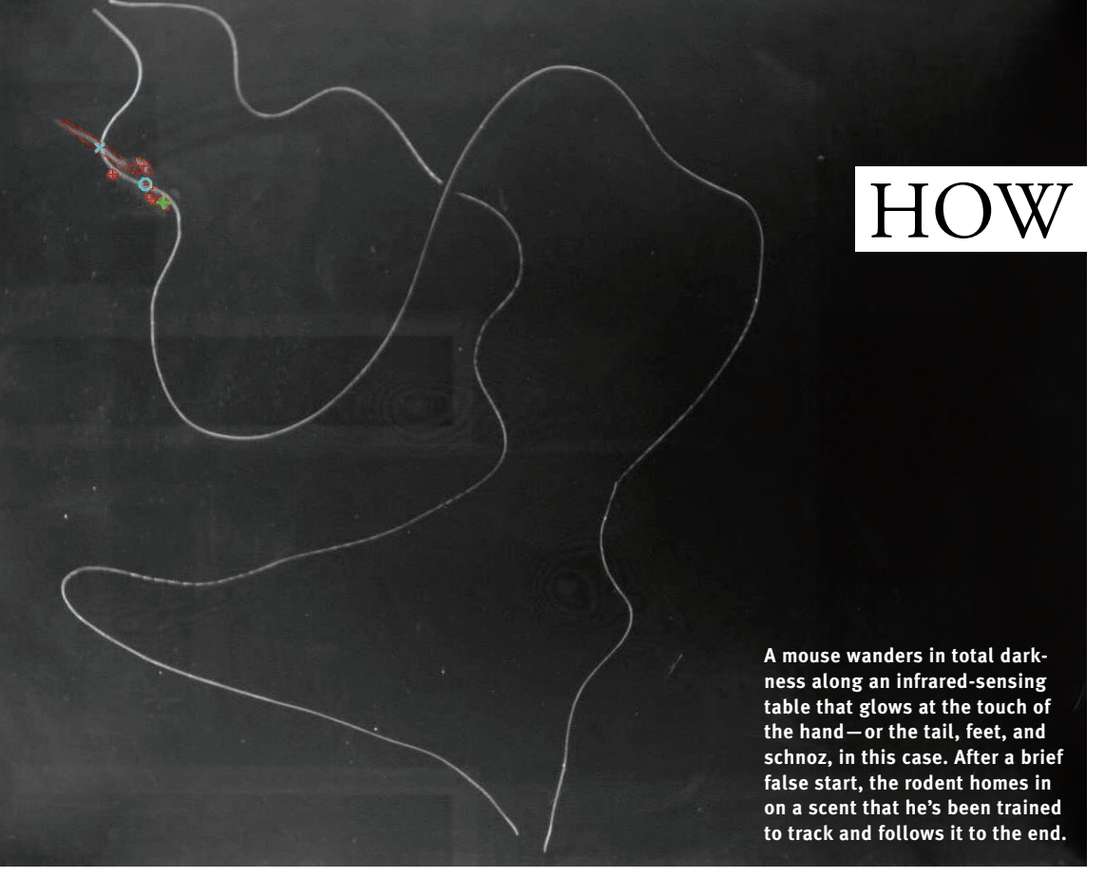
Empey also covered weightier scenarios in the course. Consider warfarin, the widely prescribed anticoagulant used to treat and prevent blood clots and heart attacks. The medication requires delicate dosing, as the risk of fatal bleeding is real. In addition to clinical factors, he explained, there are two genes (*CYP2C9* and *VKORC1*) that are relevant to its prescription. (Again, personalized medicine is never just about genetics—complex variables are the norm rather than the exception.) Usually, doctors administer warfarin in a trial dose of 2 to 5 milligrams, then adjust levels, milligram by milligram, throughout several weeks to find a therapeutic equilibrium. With genetic testing, that guesswork—and the risks, costs, and time involved—dissipates.

There are about 2,400 known associations between drugs and genetic variants; Empey said 33 medications have guidelines with evidence for clinical use.

"This is our future," he told the class. "We've got work ahead of us, training clinicians to use this information."

Throughout the course, IPM ethicist Lisa Parker, another course codirector and PhD professor of human genetics in the Graduate School of Public Health, extensively lectured on the ethical and psychosocial concerns of sequencing. Other course directors included Yvette Conley, a PhD professor and vice chair for research in the School of Nursing; Empey, who's associate director of pharmacogenomics for IPM; and Rebecca Jacobson, an MD/MSIS professor of biomedical informatics and pathology. Jacobson is also chief information officer for IPM. All told, nearly 20 instructors from across biomedical disciplines lectured.

Plans are brewing for a second round of the course. ■



A mouse wanders in total darkness along an infrared-sensing table that glows at the touch of the hand—or the tail, feet, and schnoz, in this case. After a brief false start, the rodent homes in on a scent that he's been trained to track and follows it to the end.

COURTESY NATHAN URBAN LAB

HOW THE NOSE KNOWS

SNIFFING OUT OLFACTION

BY ELAINE VITONE

A tracking hound can scout out a fugitive who had a 24-hour head start. A trained pig can snout out truffles buried 3 feet underfoot. Even your average human, whose sniffer is far inferior by comparison, will eventually find whatever foulness is stinking up the kitchen. But scientists still have little idea how any of us are doing this.

Most studies of olfaction have focused on discrimination—how the nose knows whether it's caught wind of banana or cherry, for instance. Neurobiologically speaking, "that's a pretty simple task for a mouse," says Nathan Urban. But recently, Urban, whose lab has studied the brain networks involved in mouse olfaction for 13 years, has been hot on the trail of a much more complex olfaction task of localizing odors, a marvel of nature that no manmade technology can replicate.

Last fall, Urban, PhD professor of neurobiology, and Bard Ermentrout, PhD professor of computational and systems biology, both of Pitt, became part of a National Science Foundation–funded multi-institutional team, to the tune of $6.4 million. The olfaction faction also includes Justus Verhagen, a rodent neurophysiologist from Yale; John Crimaldi, a fluid mechanics expert from the University of Colorado; Lucia Jacobs, an evolutionary psychologist from Berkeley who's focusing on studies of dogs for the project; Jonathan Victor, a computational neuroscientist from Cornell; and Katherine Nagel, a fruit-fly olfaction investigator from New York University. Their collaboration was born at the NSF Olfactory Ideas Lab workshop in June 2015.

The team is mapping the smelling brain and its minute mechanisms, and building computational models and other experiments to understand how scents move through the air. They hope to sketch out common principles across several species—which might one day inform new technologies (explosives-sniffing robots, mosquito-olfaction muddlers). Such principles might also provide insight into a number of neurological disorders in humans—including Alzheimer's, autism, and Parkinson's—in which sensory processing suffers.

Among the Urban lab's ongoing studies are those of mice amid blind scent-tracing tests (see image above). One year into this three-year award, his team is yielding intriguing findings.

For one, individual mouse neurons are "lousy devices," he says. Stimulate one 10 times in a row, and it will fire maybe five times. "If the S key on your keyboard only worked half the time, you'd throw it away," Urban notes. And yet somehow, collectively, the neurons in these networks are not just good, but great at what they do in many animals, rodents included. (Giant rats have been trained in landmine detection in several countries. The pint-sized patrols have already secured millions of miles.)

"How you get useful, robust, reliable function from unreliable components has been one interesting area for us to explore," Urban says. He thinks perhaps this variability is not a bug, but an advantage that leaves room for adaptation and the possibility to detect and respond to a wider range of incoming stimuli.

Another interesting finding involves the behavior of casting—when a snout sways from side to side, surveying for scents. Urban's team is finding that mice turn their heads invariably toward an odor's source with such speed and accuracy that they must be making a decision with every single sniff. And they sniff *a lot*—almost 15 times per second. "So in 70 milliseconds, they're inhaling, and they're beginning to move their heads in the right direction. That doesn't give much time for the brain to perform this calculation. That's one of the clues we have as to where to look in the brain for neurons that are sensitive to . . . sniff-to-sniff differences in the intensity of a stimulus."

And even if a mouse has one nostril plugged, it's still pretty good at tracking, which means left-right differences don't figure into olfaction as they do in vision—a finding that surprised Urban. His collaborator at NYU is finding the same is true in fruit flies.

Perhaps the biggest surprise of all for the team has been the nature of odor itself. At the onset, the life-sciences folk had figured on a simple bell curve, with the odor strongest in the middle and thinning out on an even gradient—not so. "We were being far too simplistic in how we were thinking about this," says Urban. "Everything is sort of mixing and turbulent all the time, even in a room where you can't feel any airflow." There's work to do yet, but with guidance from the fluid dynamics expert, the team is moving in the right direction—nose to the grindstone. ■

INTO A WORLD

JOSÉ-ALAIN SAHEL ON RESTORING SIGHT

BY ELAINE VITONE

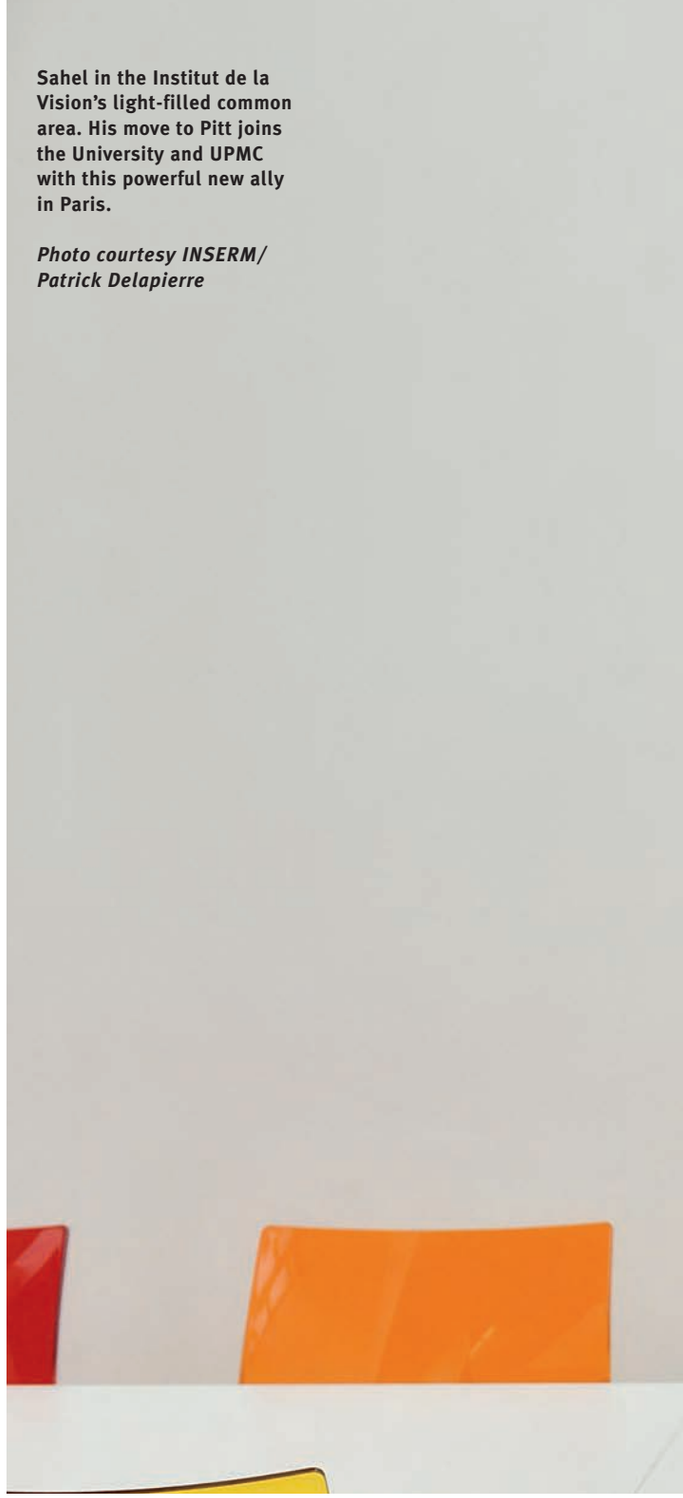
OF LIGHT

What may be the oldest eye hospital in Europe opened in 1260, a few years after the Seventh Crusade. Louis IX of France established the 300-bed infirmary for the poor just to the west of Paris's great fortress. From that dark age of blood and chaos, Centre Hospitalier National D'ophtalmologie des Quinze-Vingts survived into the modern era. (Its current home is still just a short drive from the former fortress, which you know as the Louvre.)

A few blocks from the hospital is an inspired work all its own, a research facility known as Institut de la Vision. Constructed as a patchwork of hundreds of unique panes of glass, their varying sizes and textures playing on the natural light that floods the building, the institute houses a legion of cellular biologists, physiologists, pharmacologists, surgeons, engineers, and others who are working to halt and reverse the effects of diseases that leave millions in the dark.

José-Alain Sahel, who is among the world's leading researchers on blindness, is now Pitt's chair of ophthalmology.

TYPOGRAPHY | ELENA GIALAMAS CERRI



Sahel in the Institut de la Vision's light-filled common area. His move to Pitt joins the University and UPMC with this powerful new ally in Paris.

Photo courtesy INSERM/ Patrick Delapierre

Inherited and acquired blinding diseases of the retina—the part of the eye that's now the largest subfield within ophthalmology—remain untreatable. But that's likely to change soon. Gene therapy and stem cell therapy are in clinical trials, and an electronic prosthetic device was recently approved by the U.S. Food and Drug Administration. At the forefront of these and other biomedical achievements is the founding director of this institute—this empire, as one colleague put it—José-Alain Sahel, who is the University of Pittsburgh's new chair of ophthalmology as of July 1.

Sahel will continue to advise his colleagues in France from his new home. His move here marries Pitt and UPMC to the institute and its academic partner, the Sorbonne's scientific and medical school known as Université Pierre et Marie Curie. And Sahel's many collaborators across the United States and Europe say this union will strengthen each of its member entities: in Pittsburgh, the country's largest payer-provider health care system affiliated with an academic center; in Paris, one of the largest centers of translational research on eye disease worldwide.

Sahel expects they'll make this "marriage" official in the fall, when Yves Lévy, director of INSERM—the French equivalent of the National Institutes of Health—and Jean Chambaz, president of Université Pierre et Marie Curie, are slated to visit the University of Pittsburgh. They'll iron out the details of the partnership in a meeting with Patrick Gallagher, chancellor and CEO of Pitt, Jeffrey Romoff, president and CEO of UPMC, and Arthur S. Levine, senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine, among others.

Sahel is quick to note that his initial decision to leave Paris was for personal reasons—not at all because he was unhappy in his work there. "It's a total blessing. I love it every day. Every minute," he says in a French accent. He's talking via Skype in his book-filled home office on a June afternoon, just before his trans-Atlantic move. (Well, it's afternoon in Pittsburgh, anyway—he's a night owl.)

Sahel had plenty of offers, he admits. But chose Pitt for the truly unique opportunity it presented:

In Pittsburgh, he could build upon the strength and success of Pitt's clinical and research realms—for which he credits his predecessor, Joel S. Schuman, the new ophthalmology chair at New York University's Langone Medical Center, and Levine. ("You don't meet a dean like that [but once] in your life. He's amazing. He knows what translational research is. And his support has been exceptional.") Sahel could also build on the strengths of the city itself: The uniquely collegial relationship between Pitt and its neighbor, Carnegie Mellon University. The growing technology industry, which includes an outpost of Google, as well as Uber's robotic car development operations. The nexus of big data and machine learning, of precision medicine and translational science.

And he was drawn by the urgency of the moment for this region, which has a large elderly population. Macular degeneration—the leading cause of vision loss in the United States—is on the rise. Cognitive loss, dependence, depression, and trauma are all compounded by this as-of-yet-uncurable, age-related assault to the senses.

Without prompting, just about everyone I talked to predicted that Sahel would build a Pittsburgh equivalent to the Institut de la Vision that will attract researchers from all over the world. And when I ask the man himself about this, he says that it is indeed a goal. However, he says, "I like to tell people the future is promising, but it's not today. We have to start working now."

His plan for the present is two-pronged: First and foremost, make changes for patients' immediate benefit by improving access to, and comprehensiveness of, ophthalmologic care—notably for age-related macular degeneration, genetic retinal degenerations, and other diseases of the retina, which require advanced approaches. To do so, he'll leverage Pitt's main clinical and research hub in Pittsburgh's Oakland neighborhood, as well as UPMC's many community clinics. (He's sensitive to the fact that for many people within this patient population, venturing out for doctor's visits isn't easy.) Meanwhile, he'll exploit technologies that can extend Pitt/UPMC's reach even further. "We have an opportunity to build a model of medicine," he says.

Second: Make connections. There's a tendency to view ophthalmology as an island all its own, notes Sahel. But really, it's a part of neuroscience, and relevant to much more.

"The eye is an approachable part of the brain," he says, quoting his mentor, John Dowling. "And a lot of diseases that affect many parts of the body affect the eye, too." Here is an organ with sophisticated vasculature and immunology. Pharmacology is integral to managing eye disease, and biomaterials are becoming increasingly important—for drug delivery, for biocompatible systems. And perhaps most important, in his view, is what happens after the therapy—rehabilitation. Sahel sees treatment as a beginning, not an end. "When a patient comes into your

office, he's not asking you a cellular biology question. He's asking you about his real life."

Scientists from other top institutions are already expressing interest in coming here to work with Sahel—one interviews in Pittsburgh about every other day. Perhaps they have such faith in the next act of Sahel's career because of the compelling story of the previous ones, which he performed starting with far less—virtually nothing, save his talents, notably that of bridge-building. "I built the institute with many people," he says. "So I can do it here—with many people."

When Sahel was 6, the family moved from Algeria to Rodez, in Southern France. In his quick recounting, he focuses more on the upsides of the move and what they made of it than their journey there, which had to have been harrowing amid Algeria's bloody War of Independence. (Rodez was "very cold, but full of very nice people," he says.)

Initially, he had no designs on becoming an eye doctor. The young Sahel went to Université de Paris for his MD and was planning to do a pediatric oncology residency in Strasbourg, 500 kilometers to the east. By then, 1980, he was married, and the family's first child was on the way. So he decided to stay put for a rotation. It was more or less happenstance that he chose to do it in ophthalmology, but within a few months, he was hooked.

"First, the eye is very delicate. It's beautiful, the retina especially." Second, he saw in ophthalmology a rare opportunity to be both a people person and a polymath—a clinician deeply invested in patients' quality and enjoyment of life, and also a student of the world. (His interests are "everything from medicine, to

surgery, to neuroscience, to poetry, to art," he says, referencing blind poets like John Milton and Jorge Luis Borges. "I like that you can be both broad and deep at the same time.") When he did move to Strasbourg, he performed residency rotations in neurology and neurosurgery before starting his core ophthalmology training, ever eager to learn more.

The clinic was frustrating. Half the patients who walked into his office would walk out happy, knowing there was a relatively easy surgical fix for what ailed them—a cataract, a detached retina. But for the other half, he was delivering the devastating news that their sight was slipping away, sometimes shockingly fast, and there was absolutely nothing anyone could do. He resolved to channel that frustration into fundamental scientific questions, so he could be part of the search for answers that might lead to better treatments. Today, we call this translational science, but at the time, it didn't have a name. With zero research experience under his belt, he enrolled in a PhD program at Strasbourg. "Everyone thought it was just nonsense" for a busy surgeon to do such a thing, he says. "But my wife thought, *Well, if you want to do it, just do it.* So I started that."

Sahel realized that if he wanted to study mechanisms of human vision and the diseases that threaten it, he'd have to do so abroad. In 1986 he began a fellowship with ophthalmic pathologist Daniel Albert at Massachusetts Eye and Ear Infirmary in Boston. Meanwhile, Sahel also spent time in the laboratory of Harvard's John Dowling, a founding father of retinal biology. Dowling then appointed him a visiting scholar in the developmental biology department from 1987 to 1992. "It was quite clear to us he was extraordinarily bright," says Dowling. "He had a deep understanding of retinal mechanisms." (It was Dowling whom Sahel called for advice when he was considering coming to Pitt. Having already seen one protégé flourish here—Jeff Gross, a PhD and director of the Louis J. Fox Center for Vision Restoration—Dowling told him to go for it.)

Sahel was invited to stay at Harvard but returned to France for the sake of his toddling young family. Then he built his empire around him, one person at a time.

It all started with a single investigation regarding a group of diseases known as retinitis pigmentosa (RP), a leading cause of blindness around the world. In RP, a person gradually loses her rods, photoreceptor cells responsible for dark-adapted and peripheral vision. As the years pass, the person's field of vision narrows to a tunnel. And then, cruelly, that bright spot in the center goes dark too, as another population of photoreceptor cells called cones—responsible for central and color vision—dies off, as well. Without cones, the patient can no longer read, recognize faces, or see the blue of the sky.

As Sahel was beginning his academic career, a handful of genes had been identified as culprits in RP—but only in rods. None had been found in cones at the time (nor have more than a handful since—and more than 60 RP genes are known today). It didn't make sense.

And it wasn't fair—we live in a world of light, he says. For that, we need our cones.

"If you protect the cones, people don't become blind. . . . I thought that if we could find a mechanism explaining the loss of cones, that would be great."

At first, Sahel and his institute colleague Serge Picaud chased a neurotoxicity hypothesis. They did find some neurotoxicity at work, and published on that, but it was not enough to explain RP. So next, they looked at calcium overload as another possibility, and published in *Nature Medicine* their findings that, yes, if an overload of calcium burdens the cells, rods and cones die. But that clearly wasn't the whole story, either.

Then the team wondered whether there might be crosstalk between the cells. Did the health of the one population depend on the health of the other? Could the rods somehow be important for the cones' survival?

Sahel and Saddek Mohand-Said, his then-PhD student who is now an associate professor at Pierre et Marie-Curie Université, transplanted isolated rods into an animal model of advanced RP, and found that although it didn't completely stop cone death, it did delay it by half—and not just at the site of the transplant, but all over the retina. Which raised the question: Could there be a diffusible factor, something the rods were releasing that protected the cones? They cultured the two cell types together and found that was exactly the case, publishing their red-letter findings in *PNAS* in 1998.

The team then recruited a molecular biologist, Thierry Léveillard—who's now the director of research at INSERM—and for six years, they systematically cloned every known gene in the retina, then screened thousands of their products before they found what they were looking for: RdCVF, or rod-derived cone viability factor. They showed that when they injected RdCVF into the retina of an animal model of RP, photoreceptor cell death slowed down.

Last year, two decades of work culminated in a *Cell* paper, wherein the team led by Léveillard at last identified the receptor of RdCVF—and revealed exactly why RdCVF is so crucial for cones. Without it, cones are unable to absorb the glucose they need to survive. And their ability to regenerate their outermost segments, which catch and process light, may suffer, as well.

A clinical trial for a novel treatment targeting this mechanism is slated to begin in 2017 (with major and continuing support of Foundation Fighting Blindness). If all goes well, people with RP will soon finally have a way to protect their vision. A single injection of this cell-saving therapy, a vector introducing copies of a gene that's essentially an all-purpose RdCVF factory, is expected to work for several years, slowing cone death and perhaps even reversing it. Best of all, any patient with RP stands to benefit, regardless of which mutation ails him, provided he still has at least 5 percent of his cones intact. And the treatment may help patients with other retinal conditions, as well.

When Sahel started his lab, it was a moonlighting gig—just him and a part-time tech-

"You go to him with some large idea that you would have no clue how to ever [fund] or organize," says Roska, "and he listens. And if he thinks it's a good idea, he just makes it happen. I've seen it so, so, so many times. . . . He builds up trust around him. You know where the money goes. It goes to translational research."

nician making the most of evenings, weekends, and other stolen moments in a surgeon's crammed schedule. Bit by bit, he chased down the money to snowball the Strasbourg group to some 30 people, cellular biologists and ophthalmologic electrophysiologists and others all simmering together in a scintillating interprofessional stew. They cooked up papers, gained momentum, learned from one another, had a ball. And when Sahel accepted a chair position 15 years ago at France's national eye hospital, all but one member of his team came with him.

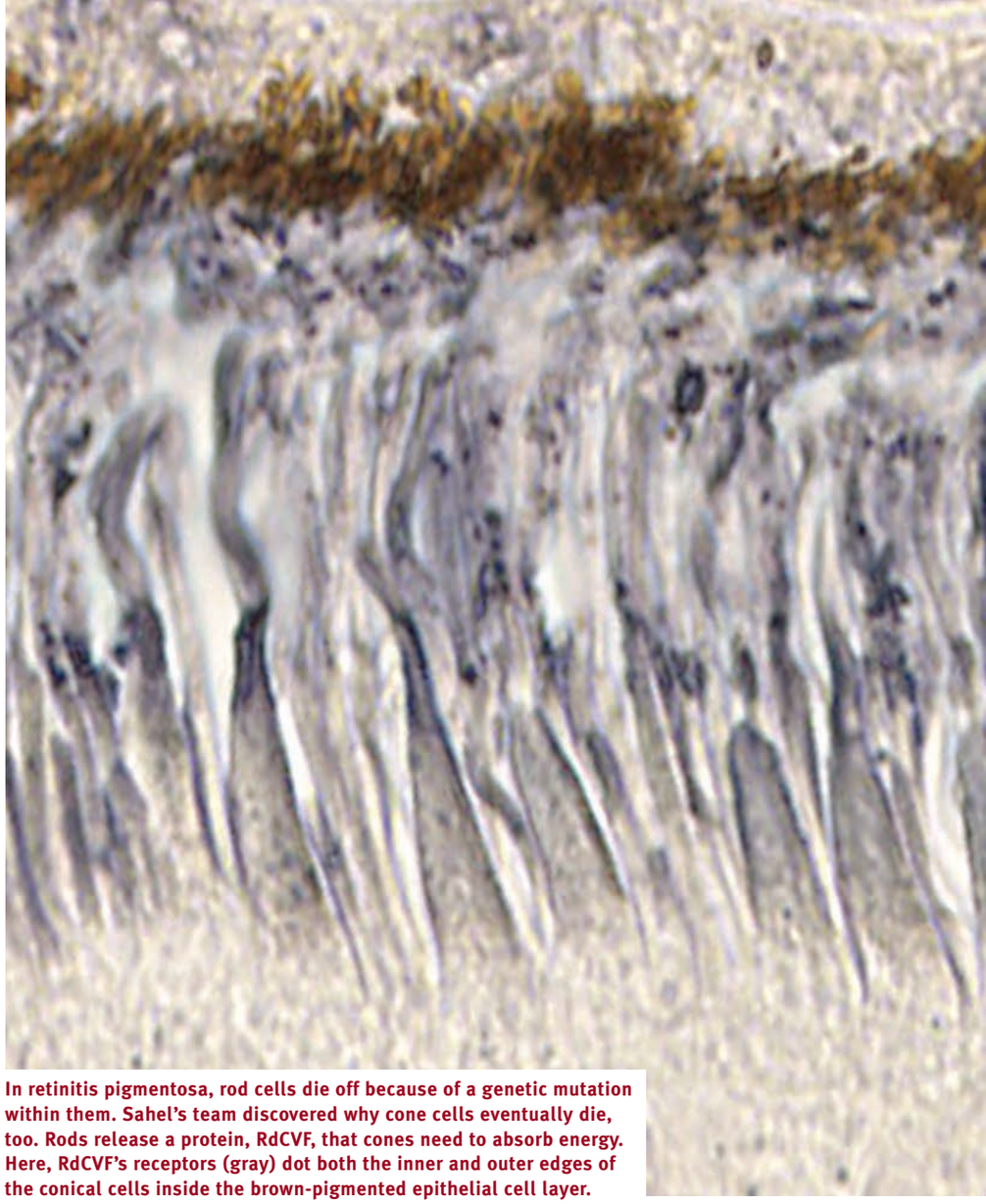
Quinze-Vingts brought Sahel to Paris with the promise of breaking ground on a new research center. But he arrived to find that the money had fallen through. Within a few years, with the support of Quinze-Vingts, he raised it from a variety of government, industry, and nonprofit sources and carved out a magnificent, 120,000-square-foot space that opened in 2008.

And then, just two months later, it burned in a disastrous fire.

Sahel mentions this in our Skype chat only in passing—that his decades-long dream went up in flames. He uses the same soft-spoken, measured, yet incredibly fast cadence with which he recalls any other event in his long and storied career, his mind and mouth moving a kilometer a minute. (He was just as calm on the phone the day after the fire—*No problem. Don't worry. We'll fix it*—says close collaborator and friend Botond Roska, a neuroscientist and group leader at the Friedrich Miescher Institute for Biomedical Research and professor at the University of Basel in Switzerland.)

And fix it they did, reopening in 2010. From their original team of 30 people, Institut de la Vision has since grown tenfold. And by all accounts, their operation is a wonder to behold:

Computer scientists conjure up mathematical models of how the eye works. Developmental biologists refine new treatments using stem cell therapy (Sahel expects they'll be in clinical trials by 2018), as well as efforts to transplant and re-innervate the entire organ of the eye. (Pitt is already a partner and leader in the latter, a long-haul effort that's just beginning—more on that later.) Molecular biologists and geneticists work to pinpoint mechanisms of heritable disorders. A vision function department teases out how information is processed in the retina and the brain. A therapeutics and pathophysiology department develops new treatments for conditions like glaucoma and diabetic retinopathies.



REPRINTED FROM CELL, VOL. 161, NAJATE AÏT-ALI, ET AL., "ROD-DERIVED CONE VIABILITY FACTOR PROMOTES CONE SURVIVAL BY STIMULATING AEROBIC GLYCOLYSIS," PP. 817–832, © 2015, WITH PERMISSION FROM ELSEVIER.

In retinitis pigmentosa, rod cells die off because of a genetic mutation within them. Sahel's team discovered why cone cells eventually die, too. Rods release a protein, RdCVF, that cones need to absorb energy. Here, RdCVF's receptors (gray) dot both the inner and outer edges of the conical cells inside the brown-pigmented epithelial cell layer.

Pharmacological researchers, currently at work on some 140 projects, have 10 drug candidates either in or on their way to clinical trials. And eight startup companies—some of which include Sahel as a cofounder—are cutting their teeth. (One was acquired for $500 million, and two have gone public.)

New patients are entered into a genetic registry and tested for eye-function benchmarks and eye structure, using the latest and greatest imaging devices—including one that can show high-resolution images of the back of the retina, at the level of individual cells. All of this information is funneled into the laboratories, which are busily working on hundreds of different forms of blinding disease. As new treatment possibilities emerge, they go right into the pipeline, says Jean Bennett of the University of Pennsylvania. She laughs, saying, "It's a really incredible empire."

As much of the workspace as possible is shared. Virtually every department is involved in every project. The cafeteria is centrally located. There are no mandatory dinner meetings—but, *mon ami*, while at work, everyone works together, hopefully for the joy of it.

These are things Sahel planned to the letter, with "almost amusing attention to detail," says Roska, "right down to how much light enters the building." But he was on to something: "You can have a lunch with somebody who initially thinks that you're a *complete* idiot," says Roska. "And the next day, he thinks that you are *just* an idiot, and then the third day he thinks that, well, maybe not an *idiot*. And then you start to talk. There is a point where you see light, . . . some place for collaboration. . . . It takes a lot of effort and discussion to find a common point."

"You go to him with some large idea that you would have no clue how to ever [fund] or organize," says Roska, "and he listens. And if he thinks it's a good idea, he just makes it happen. I've seen it so, so, so many times. . . . He builds

up trust around him. You know where the money goes. It goes to translational research."

Sahel, with Oregon Health & Science University's Richard Weleber, was the first to conduct gene therapy trials for Stargardt disease, the most common form of inherited juvenile macular degeneration, as well as for Usher syndrome, which can render people both blind and deaf. And now, he has brought to fruition a gene therapy trial for a mitochondrial disease known as LHON (Leber hereditary optic neuropathy). It's an optic nerve disorder that usually strikes boys in adolescence. They lose vision in one eye, and then weeks or months later, the other eye follows. But with this new therapy—a technique Sahel and Marisol Corral-Debrinski at INSERM developed to transport reparative RNA to the damaged mitochondria—some patients have regained some vision. A new study is now under way at seven sites across the United States and Europe.

For people who have little or no vision left, Sahel and Roska have worked for 10 years perfecting a technique called optogenetic vision restoration. It harnesses dormant cones or other retinal cells, using what are called optogenetic sensors, unique proteins that can transduce light to spark neural responses. Once delivered to the retina (via an injection of a viral vector), the optogenetic sensors target the chosen cell type and kick-start the cells into producing a light-sensitizing protein usually found only in archaea. Then, the patient is fitted with a special set of glasses. Built into them is both a sophisticated camera to capture images of the world around her and a projection system to send these images into her eyes, at just the right intensity and wavelength to stimulate the transformed retinal cells and send meaningful signals to the brain. (A cell phone–sized computer in her pocket links it all together.) This therapeutic approach has the potential to help a range of visually impaired or blind patients, regardless of what mutation they have.

And then, there's the artificial retina, known as Argus II. In a collaboration with the University of Southern California's Mark Humayun, one of the co-inventors of the technology, and Avinoam Safran, an emeritus professor at Université de Genève, Sahel's group was the first in Europe to run clinical trials on the device, which has since been approved by the FDA. This fall, Sahel's team will begin a clinical trial of a new and improved version they designed with Stanford's Daniel Palanker and an institute-incubated startup called Pixium Vision.

Sahel believes it's important that when patients are outfitted with these experimental devices, they aren't just observed for their visual acuity. (In the classic example, flash cards. "Which way is the letter pointing?" and so on.) Rather, they are invited to participate in the research as they practice using their new visual function in a safe environment that mimics everyday life.

Sahel's biggest inspiration for this soup-to-nuts approach to science wasn't a scientist, but twentieth century historian Walter Benjamin, one of the earliest proponents of transdisciplinary teaching in philosophy, history, and art. For Sahel, the borders between academic divisions and departments are fluid, the ends of some studies blurring into the beginnings of others.

But it is all the same thing, and all for the patients.

Sahel has been a unifying force in the field from the start, says Bennett, the physician-scientist at Penn, who first met Sahel more than two decades ago. They were both waiting in the wings for conference presentations on the promise of gene therapy for blinding diseases—a dream on which they would eventually collaborate. "I immediately realized that this was a person who was very, very ambitious, yet incredibly humble and self-effacing, and brilliant, and determined to make a difference in the lives of people who are facing blindness."

Bennett and Sahel became acquainted at that international ophthalmology conference—fittingly, she says, in Germany, not far from the felled Berlin Wall. Soon after that meeting, Sahel decided it was time to join U.S. and European forces behind the common goal of turning bench research into meaningful clinical trials. So he scared up funding to host a huge meeting, which he called Curing Blindness: Reaching Across the Atlantic. It was held in the French Senate in Palais du Luxembourg, a grand and gilded space where daylight streams through the domed ceiling.

"First of all, I don't know how he managed to do all that!" she says. "But it really set the pace going forward."

The meeting succeeded in chipping away at old walls of rivalry and ultimately birthing multiple organizations and collaborations.

"I view it as a historic event," Bennett notes. "Everyone [agreed] to move forward, together."

Four weeks after Sahel's arrival in Pittsburgh, we talk again, this time face-to-face in his office at the Pittsburgh Eye and Ear Institute, sandwiched between his many meetings. Among his goals—tap into UPMC and Pitt's strengths and lay the groundwork for new approaches to treatment and research on retinal disease here, from neuroprotection to vision restoration. He's been busy:

Face-time with all of his faculty and staff. Site visits. Chats with Pitt chairs like Angela Gronenborn of structural biology, Lawrence Wechsler of neurology, Peter Strick of neurobiology, Jonas Johnson of otolaryngology, and Gwendolyn Sowa of physical medicine and rehabilitation. With Jeremy Berg, former National Institute of General Medical Sciences director who is Pitt's associate vice chancellor for science strategy and planning (and was just named editor-in-chief of *Science*—see p. 30). And with Martial Hebert, head of Carnegie Mellon's Robotics Institute (a fellow Frenchman who's been in Pittsburgh for 30 years—"We spoke in English," Sahel says, looking down with a smile).

Sahel met with Andrew Schwartz, Distinguished Professor of Neurobiology, and Robert Friedlander, neurological surgery chair and Walter E. Dandy Professor, to discuss future collaborations regarding robotic vision.

He convened with the chancellor and, that same day, with an award-winning app developer.

This afternoon, Sahel will talk with Kia Washington, the young Pitt surgeon whose work *Science* called him to comment on a year and a half ago, before he knew thing one about Pittsburgh.

Washington, an assistant professor of plastic surgery and associate director of the hand transplantation program at Pitt and UPMC, developed the world's first viable model of orthotopic rodent eye transplantation. A multi-institutional consortium with Stanford, Paris, and Harvard is behind this very long-term project; the consortium formed months before Sahel arrived.

"But now the hub is going to be here," he says, "because we're bringing everything together—people like Jeff Gross, head of the Fox Center, Vijay Gorantla, and other experts in optic nerve regeneration, immunology, neuroscience, surgery, biomaterials, many areas."

Coming together like this is what Pitt people have become known for.

And, notes Sahel, "This is what I love to do—to integrate, to view the question as a global question, and then see what pieces we need, and how the puzzle will fit in the end." ■

"GO TO PITTSBURGH"

HOW A CANCER INSTITUTE CAME OF AGE

BY JULIE SCHWIETERT COLLAZO

Louis Bodek, a retired teacher from Northern Cambria, Pa., went to a Walmart Vision Center for what he hoped would be a routine checkup in October 2014.

"I had this little faint gray mark that was in my field of vision, in my left eye," he recalls. "I wanted the optometrist to take a look." Right away, it became clear that the visit would be anything but routine.

"Something's not right there," the optometrist told Bodek.

"He made me get on a better machine," Bodek, 62, recounts. "He groaned when he looked at it. He said, 'Oh boy, I want you to go to Pittsburgh immediately. I'll call for you; they have better equipment.'"

Bodek went the same day to retina specialists in Pittsburgh, and by that evening, he had a diagnosis: ocular melanoma, the most common eye cancer in adults (though far less common than skin melanoma). With a metastasis rate of approximately 50 percent, ocular melanoma is often fatal. A procedure to eliminate the tumor from his eye was successful, but doctors told him the cancer had spread to his liver. They would try to get him in to see the University of Pittsburgh Cancer Institute's melanoma and skin cancer program director John Kirkwood, an MD, who is Pitt's Sandra and Thomas Usher Professor of Melanoma.

COURTESY UNIVERSITY ARCHIVES

Under Ronald Herberman, UPCI became an NCI-Designated Cancer Center in record time.

By Thanksgiving 2014, Bodek had met Kirkwood. "When he walked in, I knew this was a serious man who'd put it all on the line for me. He told me, 'You have cancer. It has spread, and it's at stage 4.' Dr. Kirkwood told me about the 5–10 percent success rate and said, 'Here's what we can do for you.'"

Kirkwood initially put Bodek in a clinical trial on interleukin-2. It fought the cancer, but, says Bodek, "It did a number on my heart."

Kirkwood was leading another trial examining the efficacy of a new class of drugs called immune checkpoint blockers. These drugs work by not allowing cancers to turn on the immune system's built-in brakes. So Kirkwood took Bodek off of interleukin-2 and in its place, introduced pembrolizumab, an immune checkpoint blocker approved by the FDA for certain advanced melanoma regimens in just the past two years.

The introduction of immune checkpoint blockers to cancer care represents "really a remarkable change," Kirkwood says. Prior to this, for melanoma cases that are advanced and inoperable "there was not a single therapy which we knew had an effect upon survival, and only one treatment that had any ability to stop the disease more than 10 percent of the time." One of Kirkwood's current research projects seeks to identify the mechanisms of resistance to immune checkpoint blockers.

Kirkwood has been on the front lines of the fight against melanoma since UPCI's very beginning. The institute turned 30 last year; in many ways, the melanoma program mirrors UPCI's strengths as it's matured—notably advancing research at the bench and seeing that through to its translation into promising new therapies. And there are thousands of stories like Bodek's at UPCI; from across the region and beyond, people facing the diagnosis of almost every type of cancer come to Pitt specialists for world-class care and the chance to be part of experimental therapies.

Kirkwood, who was there in the early days, recalls that the center's origins were indeed quite humble—though the center was founded by Ronald Herberman, an MD who'd been a leading figure in cancer immunology at the National Cancer Institute.

"When I arrived, the Cancer Institute had just about four rooms in the refurbished Eye and Ear Hospital," which, Kirkwood says, was one of the wings of the old Presbyterian Hospital. It had no medical oncologists.

UPCI, now ranked sixth among National Institutes of Health–funded university cancer centers, began in a janitor's closet—depending, that is, "upon which version of the story you believe," says Nancy Davidson, MD director of UPCI; she is also the Hillman Professor of Oncology and a Distinguished Professor of Medicine at Pitt.

In the 2016 fiscal year, UPCI received $147 million in research funding. It's made stronger by, and in turn strengthens, the UPMC CancerCenter network—which includes 40-plus clinical sites today, with 2,000 specialists and 15 disease-focused care centers. More than 74,000 patients pass through CancerCenter doors each year.

How did it rise so quickly?

Already, the University was home to Distinguished Professor Bernard Fisher, MD '43, whose contributions to understanding breast cancer and its progression were changing how people thought about cancer and treating it.

And: "Pitt was famous for its achievements in organ transplantation," says Olivera Finn, a PhD, Distinguished Professor, and founding chair of immunology at the School of Medicine, who's been a member of the UPCI for 25 years. "The goal of the leadership was to catch up and to surpass that fame . . . in cancer research and treatment, as well."

Prominent local families rallied to the cause. After conversations with Pitt's Thomas P. Detre, MD and former senior vice chancellor for the health sciences, George Taber of the Richard King Mellon Foundation set up the funding that permitted the recruitment of Herberman to direct what was then called the PCI, or Pittsburgh Cancer Institute, in 1985. Herberman served in that capacity until 2009, when Davidson, renowned for her breast cancer work at Johns Hopkins, was appointed director. (By the way, based on her research contributions, Davidson was elected president of the American Association for Cancer Research this year.)

In the early years, Kirkwood says, Herberman's team "put out grant proposals every month or two. In quick succession, we got several." By 1988, UPCI had gained the vaunted status of a National Cancer Institute (NCI) Designated Cancer Center, which recognizes excellence in basic science, clinical research, translational science, education, and outreach. Last year, that core grant was renewed once again—with reviewers noting that UPCI's application was "outstanding." Thanks to its substantial translational research activity, the institute has been one of NCI's Comprehensive Cancer Centers since 1990, which is an even more prestigious designation. Today, Pitt faculty hold a total of 166 NCI grants.

During Herberman's tenure, the dream of a new research facility became a reality, thanks to the Hillman Foundation. In 1999, it supported the construction of the Hillman Cancer Center, which would become PCI's home on the UPMC Shadyside campus. The Hillman Family Foundations, providing almost $24 million in gifts for research funding since 2004, have also helped UPCI attract and retain top investigators.

Davidson describes those gifts as "pivotal." She notes that the Hillman Center layout facilitates the relationships between researchers and clinicians—a bridge and other common areas connect clinical and research spaces, which now total nearly 450,000 square feet.

Those close links remain central to UPCI's work: "Everyone uses the same lobby—the researchers, the patients, the nurses, the doctors," Davidson says, "and it helps us keep a focus on why we're all here."

Many of the patients at Hillman, UPCI's flagship center, are probably unaware of just how much the people with whom they cross paths are contributing to the understanding, treatment, and prevention of cancer. Kirkwood says that in the area of melanoma alone, the advances during his time at UPCI have been astounding.

"I really think we can take some significant credit for the fact that we have 10 new FDA-approved treatments for melanoma," he says.

Pitt is home to three SPORE projects (Specialized Programs of Research Excellence)—those are focused on cancers of skin (led by Kirkwood), the head and neck (led by Robert Ferris, an MD/PhD, UPMC Professor of Advanced Oncologic Head and Neck Surgery, and professor of otolaryngology, with former Pitt faculty member Jennifer Rubin Grandis (MD '87, Res '88, Fel '92, Res '93), and the lung (led by James Herman, MD professor of medicine). Make that three-and-a-half—Pitt also shares a SPORE grant on ovarian cancer with Roswell Park Cancer Institute (Pitt's lead is Robert Edwards, MD professor and chair of obstetrics, gynecology, and reproductive sciences). NCI designed these grants to quickly move promising research findings along to therapeutics, "as well as to determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer," according to the agency.

UPCI is home to hundreds of federally supported programs beyond the SPORE initiatives. Those investigations include probing for the best ways to detect breast cancer and using broccoli sprout extracts to prevent oral cancer, to name just a couple. Faculty efforts to understand the basic workings and biology of cancer—including the roles played by viruses, the immune system, and mitochondria—have produced a flood of revealing results (for instance, identifying two of the seven viruses known to cause cancer). Pitt has built a head-turning genome stability group that's just published a string of papers in *Nature* and other top journals; those investigators look at how cancer can unfold when DNA's repair machinery is threatened. And UPCI's clinical trial presence—hundreds at any given time—is dizzying. (An online tool that taps into current trials and findings guides CancerCenter physicians in suggesting the most appropriate evidence-based approaches.) UPMC's own $100 million investment in pursuing personalized medicine focused first on cancer—and helped Pitt gain notice for President Barack Obama's Precision Medicine Initiative.

Just this August, UPCI learned it will receive up to $10 million throughout the next five years from NCI for preclinical research—that means researchers here are now involved in every NCI drug development stage, from screening drugs to determining dosage to all phases of clinical trials.

Nancy Davidson
has led UPCI through seven years of tremendous growth; UPCI investigators received a total of $147 million in funding in 2016.

PORTRAITS BY CIDDE

John Kirkwood
could add "informal memory keeper" to his many roles at UPCI. His team's progress in melanoma through the past few decades mirrors UPCI's strengths.

UPMC CancerCenter also has seven international initiatives. Not surprisingly, UPCI's reach is also global. Davidson points to the work of faculty like Jian-Min Yuan, an MD/PhD and a highly respected epidemiologist who was hired in 2011 to serve as UPCI's associate director for cancer control and population sciences and leader of the Cancer Epidemiology, Prevention, and Control Program. When Yuan, who now holds the Arnold Palmer Chair in Cancer Prevention, arrived at UPCI, he was already the principal investigator of four NCI-funded studies. One of them is a longitudinal study still in progress that tracks more than 80,000 research participants in Shanghai and Singapore.

"Dr. Yuan has been following these people for over 25 years now," says Davidson. "He took people when they were healthy and spent time getting histories, data, and samples from time to time. He was looking at the question: What happens to people that they would become cancer patients?" The significance of this study is profound, Davidson says, because cancer rates are skyrocketing in Asia.

Kirkwood notes that in the field of melanoma, modern research has produced a great deal of information that can be used for early detection, yet the utility of that information is constrained when providers aren't aware of it. So he and his colleagues have embarked on an effort to train more than 500 primary care clinicians in the UPMC system through an online education program, and it's working. Melanomas detected by the program's trained physicians were, on average, half the thickness, and therefore had a better prognosis, as those found by the physicians in the control group.

READY FOR LIFTOFF

In his 2016 State of the Union address, President Barack Obama announced the National Cancer Moonshot initiative—a program led by Vice President Joe Biden that aims to put cancer research on the fast track, to accomplish in five years what is usually done in 10. Pitt people are among the experts from around the country who have been called on to help with the liftoff:

• As a National Cancer Advisory Board member, Pitt's Distinguished Professor of Pathology, Yuan Chang, an MD, will review the Blue Ribbon Panel's recommendations to the vice president on the initiative.

• With Peter Ellis, an MD and director of UPMC CancerCenter's Medical Oncology Network, Nancy Davidson, UPCI director and Hillman Professor of Oncology, has been meeting with representatives of the vice president's office.

• Davidson, an MD, led a congressional briefing on progress in cancer research and the opportunities that lie ahead. She was joined by UPCI's Kara Bernstein, PhD assistant professor of microbiology and molecular genetics. (Davidson also attended the National Cancer Moonshot summit hosted by Vice President Biden in Washington, D.C.)

• UPCI hosted the region's Cancer Moonshot Summit in June. It was organized by UPCI's deputy director and professor of medicine Edward Chu, an MD; Maryann Donovan, PhD research administration associate director; and Linda Robertson, an RN, DrPH, assistant professor of medicine, and associate director of health equity, education, and advocacy. A special guest star also stopped by the summit: the Stanley Cup. (The Penguins' Mario Lemieux, a cancer survivor, has long been an important supporter of UPCI.) ***—Ali Greenholt***

In addition, physicians who did the online training were more likely to detect melanomas. (The study involved 330,000 patients who were screened at UPMC in 2014.) Prevention is occupying Kirkwood's time as much as treatment does these days.

The Eye and Ear Hospital ward where Kirkwood once worked feels a lifetime away now that he is an international melanoma expert at a top cancer center. The fact that such a transition occurred in a few short decades is somewhat remarkable, he admits; but what is even more impressive to him is what UPCI has accomplished, particularly in the past five years.

Now, he says, "we can actually understand what we're doing at ground zero in the tumor, and in the blood, and in other tissues of the body, so as to move novel clinical trials forward in months." Previously, he points out, "this would have taken us many years and, more often, more than a decade, to make progress."

Bodek understands he's part of a clinical trial, but he believes the immune checkpoint blocker represents his best chance, pointing out that pembrolizumab is the same drug former President Jimmy Carter was given to treat melanoma, which had metastasized to his liver and brain. Carter recently announced he is cancer free. "If it worked for a 92-year-old man, maybe it will work for a 62-year-old man," Bodek says, laughing.

"I feel optimistic. I really feel like it's going to come to a good conclusion."

IN ITS PRIME

UPCI TURNED 30 LAST YEAR. DURING THOSE FEW DECADES, IT HAS GROWN TREMENDOUSLY—AND SO HAS ITS ABILITY TO REDUCE THE BURDEN OF CANCER.

GRANTS AND FUNDING

- **$147 MILLION** IN 2016
- RANKED **SIXTH** IN NIH FUNDING AMONG UNIVERSITY RESEARCH RECIPIENTS
- **$10 MILLION** FROM NCI OVER THE NEXT FIVE YEARS TO SUPPORT PRECLINICAL RESEARCH IN DRUG DEVELOPMENT
- **166** CURRENT NCI GRANTS
- **3** UPCI FACULTY MEMBERS HONORED WITH OUTSTANDING NCI INVESTIGATOR AWARDS IN 2015 AND 2016
- FIRST DEEMED AN NCI-DESIGNATED CANCER CENTER IN 1988; SINCE 1990, **ONE OF NCI'S 47** COMPREHENSIVE CANCER CENTERS

RESEARCH PUBLICATIONS

- **5,000** IN LAST FIVE YEARS

FACULTY INVESTIGATORS

- **344**

CLINICAL TRIALS

- **458** ACTIVE TRIALS

ITS CLINICAL PARTNER, UPMC CANCERCENTER, LAYS CLAIM TO . . .

- MORE THAN **25,000** NEW PATIENTS EACH YEAR
- **2,000** EXPERTS
- **40+** TREATMENT CENTERS IN WESTERN PENNSYLVANIA AND OHIO
- **7 INTERNATIONAL CLINICAL INITIATIVES** (IN IRELAND, ITALY, CHINA, COLOMBIA, KAZAKHSTAN, LITHUANIA, AND MYANMAR)

SOURCE: UPCI/UPMC CANCERCENTER

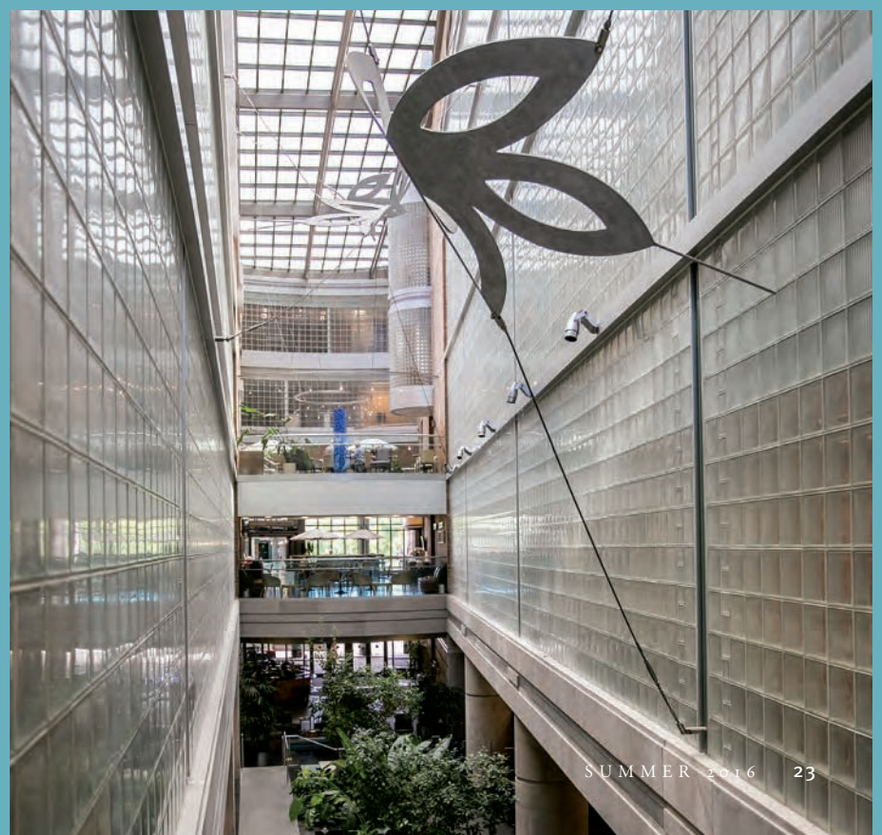
UPCI has aged well. Shown here—scenes from its home, the Hillman Cancer Center. Pedestrian walkways, bridges, and an atrium connect research and clinical areas. Pictured: Immunology research technician Ashley Menk.

NETWORKING

Among the many clinical studies in which UPCI participates are those in the National Cancer Institute's National Clinical Trials Network and the Experimental Therapeutics Clinical Trials Network. For both of these efforts, UPCI is an academic lead. That means Pitt doctors "provide scientific leadership in the development and conduct of clinical trials," according to the NCI.

More importantly, says Edward Chu, an MD and deputy director of UPCI, with hundreds of ongoing clinical trials, "we're able to offer patients an entire continuum of drugs that are being tested at all levels of development." And because of "the breadth and depth of clinical trials that our cancer patients in western Pennsylvania have access to . . . they don't have to go outside our region. They can come right to Pittsburgh." *—AG*

PHOTOGRAPHY BY JOHN ALTDORFER (EXCEPT WHERE NOTED)

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WHEN THE BODY'S CLOCK IS OFF, MENTAL HEALTH SUFFERS | BY SARAH C. BALDWIN

OUT OF SYNC

Colleen McClung's love affair with neuroscience began in the late '90s, when she was a graduate student at the University of Virginia. A professor recommended she rotate in the lab of Jay Hirsh, a biologist who was studying the neurodevelopment of *Drosophila melanogaster*—specifically, the behavioral effects of cocaine on the flies' dopamine receptors. To do that, they first had to figure out how to get fruit flies to take the drug. Their solution? Freebasing. "We vaporized the cocaine," says McClung, a PhD. "When the flies inhaled it, they went nuts—twirling around in circles, walking backwards. It was fascinating!"

In 1998, McClung and Hirsh published a paper in *Current Biology* establishing *Drosophila* as a viable model for studying behavioral responses to cocaine in humans. Around the same time, a fellow graduate student in the lab had made another fruitful fruit-fly finding, which subsequently appeared in *Science*: genes that control circadian rhythms are also implicated in sensitization, a process whereby repeated exposure to a drug increases the intensity of response.

Researchers at Pitt are bringing the mysteries of our circadian system to light. Their discoveries about its role in reward-seeking, decision-making, and mood disorders could help us keep our bodies in tick-tock, er, tip-top shape.

ILLUSTRATION | STACY INNERST

This discovery sparked McClung's interest in the role of circadian genes in behavioral and neuronal responses to drugs of abuse. (At the time, few labs were studying this connection.) During her postdoctoral fellowship at the University of Texas Southwestern Medical Center, she began to explore the genes that make drugs rewarding—this time, in mice. When she looked at mice with mutations in their circadian genes, she found that their response to drugs was altered, just as the flies' had been.

The circadian system—the myriad gears that synchronize body clocks—can affect us in profound ways. Scientists are still trying to grasp the extent of it, but they've learned that disruptions to our body rhythms can make us more vulnerable to addiction and to serious psychiatric illnesses like depression and bipolar disorder. Today, McClung is an associate professor of psychiatry and of clinical and translational science at Pitt, where she and colleagues are decoding the complex interplay between our brains and our inner metronomes. Their findings are turning the clock forward on new approaches to intervention and treatment.

The human circadian system is composed of the suprachiasmatic nuclei (SCN), a pair of small structures tucked in the hypothalamus that act as the brain's central timekeeper, and the genes that make up the biological clock, which are found in almost every cell of the body. The SCN contains thousands of neurons that fire rhythmically in response to light and darkness. The circadian genes in our cells produce clock proteins, whose levels rise and fall on an approximately 24-hour cycle, triggering or suppressing a host of key physiological processes: blood pressure, heart rate, digestion, hormone production, and appetite. The SCN's claim to fame, of course, is regulation of the sleep-wake cycle. Every morning, daylight resets our biological clock by traveling down the optic nerve to the SCN, starting the cycle over again.

In other words, the circadian system is the boss of us. It calls on both internal cues (the clocks in our brain and our cells) and environmental cues (zeitgebers, or "time-givers," such as temperature and light) to tell our bodies what to do and when: Eat. Get some shut-eye. Wake up and hunt down a woolly mammoth.

DYSREGULATION'S DANGERS

A healthy circadian rhythm means rising when it's light out and going to sleep when it's dark. When our circadian rhythms are out of sync with the outside world, the results can be uncomfortable (think jet lag, when your body believes it's 9 p.m. but the clock in your Paris hotel room says it's 3 a.m.) or, over the long term, disastrous, causing adverse health effects ranging from diabetes to depression.

Babies with disrupted rhythms are more likely to experience anxiety in their early teens, studies have shown. Women who sleep poorly during weeks 10 and 20 when pregnant have more complications. And elders are vulnerable, too: McClung recently published a paper revealing startling changes in the circadian system later in life. In a postmortem study of gene expression in the brains of 146 people, she and colleagues found that the rhythm in the clock genes of older people had slowed—588 genes showed a complete loss of rhythmicity. This, she says, might explain some of the alterations that occur in sleep, cognition, and mood in our later years. Interestingly, in brains of people older than 60, they also found a set of genes that gained rhythmicity, indicating the possibility of "some kind of compensatory clock that kicks in," says McClung, who plans to investigate this in future studies.

But if there's one group that has become the poster children for chronic desynchronization, it's teenagers. We know now that puberty brings with it more than just pimples and periods. It also shifts circadian rhythms backward, so that adolescents naturally stay up until the wee hours and sleep in late in the morning.

At least they wish they did. In reality, they face, in McClung's words, "the environmental risk factor that is high school." Teenagers are simply not made to be sitting in a classroom at 8 in the morning. And this clash is exacerbated by yet another complex and all-important process, one that circadian rhythms modulate: reward function. It's the collision of these systems that makes teens acutely vulnerable to problems with mood, substance use, and even addiction.

PLEASURE SEEKING

We experience reward via the brain's mesolimbic pathway. Dopamine, a neurotransmitter that mediates motivation for pleasure, journeys down this path from the midbrain's ventral tegmental area, to the nucleus accumbens in the forebrain's ventral striatum. It's part of our age-old survival system, enabling us to know—and remember—what we find pleasurable so that we pursue it again. This pertains to natural stimuli like food, sex, and social interactions, and also to drugs.

Like McClung, Brant Hasler, PhD assistant professor of psychiatry and psychology, explores how the circadian and reward systems interact at the neurobehavioral level. Hasler, who's on the faculty of Pitt's Sleep and Chronobiology Center, wants to understand exactly how that interaction makes kids more likely to overindulge in drugs and alcohol. In McClung's lab, they've created a sort of rodent high school, where adolescent rats are placed on a treadmill in the morning Monday through Friday and allowed to live according to their natural circadian rhythms on the weekend, paralleling the lifestyle of human teens.

When our circadian rhythms are out of sync with the outside world, the results can be uncomfortable (think jet lag, when your body believes it's 9 p.m. but the clock in your Paris hotel room says it's 3 a.m.) or, over the long term, disastrous, causing adverse health effects from diabetes to depression.

From substance abuse to speeding, our body's internal clock influences a lot more than snoozing.

"One of my working models is that adolescents are suffering from circadian misalignment, also known as social jet lag, where they're forced to adopt early schedules during the week and then shift to the later schedule on the weekend," Hasler explains. "They're bouncing back and forth, traveling across several time zones Sunday night to be ready for Monday morning. This has a number of consequences, including the way we process reward." The findings of the teen rat study, presented this May at the meeting of the Society for Research on Biological Rhythms, suggest that the reward process in the socially jet-lagged teen is, indeed, altered.

To shed more light on how circadian rhythm disturbance and impaired reward function conspire to make young people more susceptible to substance abuse, Hasler is running a novel study in which he's deliberately putting teenagers' rhythms out of whack. During the summer, healthy teens will make two visits to the sleep lab. Each time, they will have spent a week staying up until midnight and rising at 9:30 in the morning—in other words, obeying their body clock. On the "aligned" visit, they'll stay on the midnight to 9:30 schedule for a night; on the "misaligned" visit, they'll follow a week of "natural" rhythms with an 8 p.m.–5:30 a.m. "sleep opportunity." Each of these will be followed the next day by fMRI tests to measure how reward-related activity in their brains has changed.

Another study, which Hasler calls a "natural experiment," looks at actual drug and alcohol use among college students, who, like high schoolers, regularly cycle through the havoc-wreaking weekday-weekend transition. "We expect that, as their sleep and circadian timing change, their alcohol use behavior will, too," he says. "On Thursday we measure levels of melatonin—a hormone of darkness, signaling biological night." Melatonin, a well-validated marker of circadian timing, enables researchers to gauge what time it is according to each young adult's body clock. "We put them in an fMRI on Friday morning to measure brain response to a monetary reward task. Then they're free to go do whatever they're going to do on the weekend—presumably smoke pot and drink." On Sunday night they come in for another melatonin assessment, followed by a Monday morning fMRI. "We're asking, *Does circadian timing predict how their brains anticipate and respond to reward?*"

One of Hasler's mentors on the misalignment study, clinical and developmental psychologist Erika Forbes, is also keenly interested in reward function in adolescents as it affects mood and addiction. Forbes, who directs Pitt's Affective Neuroscience and Developmental Psychopathology Laboratory and is a PhD associate professor of psychiatry, psychology, and pediatrics, says that the teen brain does not fit on a smooth developmental continuum from childhood to adulthood. "In this period, things look dramatically different from the stage before and the stage after it. Teens are more distracted by pleasant stimuli when

they're engaged in a task, and they show more response in reward areas when there is a reward. They engage in more reward-seeking behaviors—driving fast, trying drugs, doing the foolish things they know better than to do. That's reflected in changes in the brain's reward circuitry."

As in McClung and Hasler's work, the parts of the brain that are key to much of Forbes's research are the ventral striatum, a stop along the reward pathway, and the medial prefrontal cortex, or mPFC, which mediates decision-making about reward—as in, *Should I drink that beer?* Hasler, in collaboration with Forbes and Department of Psychology Chair Daniel Shaw, has found that adolescent evening chronotypes—night owls—are more likely to have problems with alcohol. When anticipating a reward, they show less mPFC reactivity (in other words, their decision-making skills aren't great), while showing more ventral striatum activation during the reward (which means they get more pleasure from the beer). This combination is associated with increased drinking problems. The group has also found that the weekday-weekend shifts in sleep cycles are associated with less reactivity in both regions, possibly contributing to substance abuse and depression: some teens need more of the drug or alcohol to feel good, and their ability to feel good at all is compromised.

The problem is not just with drugs and alcohol. "Adolescents are more sensitive to social context, too, especially with peers or friends," Forbes points out. "Kids drive in a riskier way when they have friends in the car. Risky sexual behavior or substance use is happening in a social context, too. It's not a kid alone in his room, it's a kid trying to get status or who's just excited by being around friends." (Of course, these behaviors are not all attributable to dysregulated rhythms. Pitt's Beatriz Luna, a PhD and the Staunton Professor of Psychiatry and Pediatrics who directs Pitt's Laboratory of Neurocognitive Development, is studying how the adult brain recruits several regions to enhance cognitive control of behavior, while the adolescent brain uses a different pattern of function.)

Because the neural reward system is still developing during the teen years, Forbes says, it's more vulnerable to becoming dysregulated. But that also opens the door to intervention. "As a developmentalist, I love to think there are these moments of opportunity to get in there to take advantage of the brain's plasticity and change things in a positive way."

Four years ago, Forbes published a study with neuroscientist Mary Phillips, an MD/MD (Cantab), who is an expert in neuroimaging technologies, holds the Pittsburgh Foundation-Emmerling Chair in Psychotic Disorders, and is professor of psychiatry and of clinical and translational science. That study was the first to reveal that circadian genes affect the neural circuitry of reward. The two continue to use fMRI to study adolescent-specific reward processing, peering deep into the brains of both healthy and mood-disordered teens, as well as those who don't yet have a mood disorder but who might develop one. (Research has shown that children of depressed or bipolar parents are more prone to develop the disorders themselves.) Their work indicates that lack of sleep, coupled with the dampened response to reward, could intensify some teens' quests for pleasure.

Phillips is particularly interested in comprehending the neural underpinnings of bipolar spectrum disorder. Patients with the disorder are known not only to have a disturbed sleep-wake cycle, but also to process emotion and reward abnormally. They all go together, she says. "People who have aberrant circadian function also tend to be hypersensitive to reward and therefore are highly thrill seeking." She uses a variety of neuroimaging techniques to "drill down" and observe in real time the brain regions and structures associated with these processes—as well as the white matter connecting them.

Phillips and McClung are using a mouse that simulates human mania via a mutated circadian gene, given to her lab by renowned neurobiologist Joseph Takahashi, to understand the neurocircuitry of one phase of bipolar disease (the mice don't get depressed).

"They're hyperactive and impulsive like bipolar patients in manic phase, who often go on shopping or gambling sprees or abuse drugs. Anything that's rewarding, these mice find more rewarding," McClung says.

GETTING ON PACE

Phillips, with professor of psychiatry and psychology Alison Hipwell, a PhD, is also scanning the brains of 3-month-old babies to get baseline data on early neurocircuitry and temperament. "It could be that between 3 and 9 months something crucial happens that determines a human being's temperament—and that can be changed," she says. "The younger you are, the more malleable the brain is. The brain is developing until age 25, in terms of white matter maturation. So if you can go in and do something to right a wrong or change the path in a good way, that could stop a lot of suffering." While that's a ways off, Phillips says that we can use this knowledge "to guide strategies to help improve longer-term outcomes in otherwise disadvantaged young children."

This is not work for a lone wolf, notes Phillips.

Plumbing the seemingly infinite mysteries of the human brain to improve therapeutic and preventive measures requires multiple perspectives, she says: "People get very focused on their own area and they drill down and drill down, and they don't put their head above the parapet and see what's out there. We have to think about the overlaps, the similarities. … Until you talk to everyone it's difficult to get the big picture." ■

In McClung's lab, they've created a sort of rodent high school, where adolescent rats are placed on a treadmill in the morning Monday through Friday and allowed to live according to their natural circadian rhythms on the weekend, paralleling the lifestyle of human teens.

People and programs that keep the school healthy and vibrant

THE O'MALLEY RALLY

BY ALI GREENHOLT

Four students from the Class of 2016 received this year's Bert and Sally O'Malley Awards for Outstanding Medical Student Research. The O'Malley couple, Pitt alumni (MD '63 and BS in Education '59, respectively), established the award in 2009 for med students who carry out basic and clinical research.

Eric Etchill and mentor Matthew Neal, MD assistant professor of surgery, took a closer look at massive blood transfusions. Etchill reviewed literature on plasma-to-red-blood-cell ratios in transfusions and found that the high ratio used in trauma patients may not be beneficial for non-trauma patients.

Why do patients with human papillomavirus–related head and neck cancers respond better to chemotherapy and radiation than their HPV-negative counterparts? **Bhavana Chapman** and Pitt mentor Saleem Khan, PhD professor of microbiology and molecular genetics, found one possible reason: They identified a type of RNA expressed at higher rates in HPV-positive cancer patients that affects the migratory ability of the cells.

Having relatives with sickle cell disease has put both **Olubusola Oluwole**'s head and heart into improving quality of life for those with the disease. Oluwole and mentor Enrico Novelli, MD assistant professor of medicine, dug into poorly understood complications of the disease, namely the development of cognitive deficits that may be influenced by anemia or a patient's nutrition.

Brian Ahn and mentor Hideho Okada, now a professor of neurological surgery at UCSF, were curious about a clinical finding: People with asthma, eczema, and other allergic hypersensitivities are less prone to malignant brain tumors called gliomas—but chronic antihistamine use appears to reverse this relationship. Ahn tested the immune cell population of mice deficient in histamine and found that certain blood cells were inhibiting cancer-fighting cells. Their results also point to a histamine-producing enzyme called HDC as a potential biomarker for glioma survival in humans.

IN A HEARTBEAT

APP FOR LIFE

BY MICAELA FOX CORN

When someone goes down after a sudden cardiac arrest, it's only a matter of minutes before irreversible damage or death takes hold. Each minute without an appropriate intervention like CPR reduces the chance of survival by 7–10 percent. And there's no way to know when and where a sudden cardiac arrest will strike.

This public health issue inspired two Pitt emergency medicine experts to team up with City of Pittsburgh officials and the Henry L. Hillman Foundation to bring a game-changing mobile application to the region. Called PulsePoint, the app helps people respond during that small window of opportunity.

PulsePoint uses location-aware technology to notify ready and willing citizens—CPR trained or anyone inclined to help by following the app's instructions—about emergencies in their area. Any PulsePoint user within walking distance of a cardiac arrest will get the S.O.S. about as quickly as 911 operators do (the app's software is integrated with software at emergency call centers around the city). Users can then arrive on the scene, even before medics in some cases, to perform CPR, initiate hands-only chest compressions, or apply an automated external defibrillator (AED). The app also tells users where the nearest AED can be found. All this helps to improve bystander response and increases cardiac arrest survival rates.

You can download PulsePoint for free.

The trek to get PulsePoint to Pittsburgh began in 2015, when then–emergency medicine fellow Leonard Weiss joined forces with David Salcido, who had recently finished his Pitt PhD in epidemiology. Weiss had caught wind of the lifesaving app in other cities and wanted to bring it here, but he needed funding. Salcido, meanwhile, had been studying sudden cardiac arrest and the likelihood of re-arrest after resuscitation. As part of that work, Salcido had also established the Pittsburgh site of HeartMap, a national endeavor to identify and catalog the location of every AED in cities across America. Salcido compiled Pittsburgh's crowdsourced cartography into an online public database, resulting in an ongoing, centralized registry of the heart-jolting machines, which made them easier to maintain and study.

But just knowing where AEDs were wasn't enough to solve the survival problem of sudden cardiac arrest, and PulsePoint was an expensive pilot test for the city. So, Weiss (Res '15, Fel '16), now a clinical instructor in emergency medicine, and Salcido (MPH '08, PhD '14), a research assistant professor of emergency medicine, put their heads together.

Working with Allegheny County Executive Rich Fitzgerald, Councilman Daniel Gilman, and Mayor Bill Peduto, as well as Pitt's emergency medicine department, they secured $200,000 from the Henry L. Hillman Foundation—enough to buy the license for PulsePoint and support a larger umbrella effort to improve outcomes for out-of-hospital cardiac arrests called the Resuscitation Logistics and Informatics Venture, or ReLIVe. On July 7, the City of Pittsburgh officially launched the app.

As the app gains users, Salcido says, researchers can begin mining data for answers to key questions like, How can we optimize those first few critical moments following cardiac arrest? Are there enough AEDs in a particular area?

Ultimately, it will be up to good Samaritans to step in, Weiss says. Effective bystander intervention can triple a person's chances, and "anyone can help." ■

Berg is the word.

MARTHA RIAL

SCIENCE'S CHOICE

BERG TO EDIT VAUNTED JOURNAL

The University of Pittsburgh's Jeremy Berg, a PhD, has begun a five-year term as editor in chief of the *Science* family of journals. He was unanimously elected by the American Association for the Advancement of Science's (AAAS) Board of Directors and appointed to the position July 1.

Those who know Berg say his energy, curiosity, and creativity make him a natural fit for the high-profile role. Though he'll be commuting to Washington, D.C., during his *Science* tenure, he will continue as Pitt's associate senior vice chancellor for science strategy and planning in the health sciences, Pittsburgh Foundation Professor, and professor of computational and systems biology and of chemistry. He'll transition from director to a senior advisor of Pitt's Institute for Personalized Medicine.

As former director of the National Institute of General Medical Sciences at the National Institutes of Health, Berg was well known for encouraging multidisciplinary collaboration and for dismantling research silos. Adds former NIH director and colleague, Elias Zerhouni, "Jeremy always listens to all points of view in an authentically kind and open way. He builds consensus around strong principles of scientific excellence without expedient compromise, which attracts universal respect."

Zerhouni says that Berg is a "great choice for *Science* and science."

The following Q&A appeared in the June 13, 2016 *Pitt Chronicle.*

—Introduction by Micaela Fox Corn
Interview by Jane-Ellen Robinet

What makes *Science* stand out among other journals?

Science has a long and distinguished history. The journal was founded in 1880 with financial support from Thomas Edison and became associated with the American Association for the Advancement of Science in 1900. Unlike most journals, *Science* publishes papers in a very wide range of scientific fields, and many of them are quite important scientifically. For example, Eric Betzig and colleagues published a paper showing that individual molecules could be imaged using special microscopic techniques, and he shared the Nobel Prize in Chemistry about a decade later. Publishing in *Science* is also very competitive. Only about 7 percent of the submitted manuscripts are accepted for publication. Its weekly readership is estimated to be 1 million.

Science is also a major forum for science news and for discussions of scientific policy issues, both national and international. The journal is unusual, if not unique, in that scientists, administrators, congressional staffers, and other diverse groups read or are at least aware of *Science.*

What appealed to you about this opportunity?

First, I have had an interest in science policy since relatively early in my career. Before coming to Pitt, I spent almost eight years as director of the National Institute of General Medical Sciences, the component of the NIH that is most focused on basic science. The position as editor in chief of *Science* is a tremendous vantage point for following developments in the science policy arena and for contributing to the discussion from an influential position.

Second, I have very broad scientific interests, and this role is a tremendous opportunity to learn about cutting-edge science in many fields.

Third, publishing, including scientific publishing, is facing many exciting challenges. For example: How can one find the right balance between wide accessibility and sustainable business models? How can one take advantage of modern media to communicate science at all levels? I will have the opportunity to work with others at *Science* and AAAS on these and other issues.

Finally, I am drawn to public service. This position provides a great opportunity to serve the scientific community and the public. A robust scientific enterprise is crucial to solving some of society's most pressing problems, including economic development.

What do you hope to accomplish during your editorship?

I do not have a highly specific agenda at this point. I need to learn more about initiatives already under way at AAAS. In addition to *Science,* I will be responsible for three other journals (*Science Translational Medicine*, *Science Signaling*, and *Science Advances*). AAAS is also launching two new journals, *Science Immunology* and *Science Robotics*, in the coming months. Maintaining or getting these journals on solid footing will be an important initial goal.

One theme that I expect to inform my editorship relates to interactions between different scientific disciplines and sectors. Of course, there are often great scientific opportunities at interfaces between fields such as physics and biology, for example. Yet it is also striking how different the cultures of different disciplines can be.

What are three of the most significant issues facing the field of science today?

One of the biggest issues is public trust. Science and scientists had been one of the most trusted groups in the country in the past. Now, scientists are often regarded as a special interest group on par with many other groups. It will be crucial to enhance the public trust in science through effective communication and handling issues within the scientific community in a forthright way.

The second issue is sustainability of the scientific enterprise. This is particularly true for biomedical science, which underwent a period of rapid growth, driven in large part by a doubling of the NIH budget from 1998 through 2003. Since then, the NIH appropriation has lost considerable buying power when inflation is included, yet large numbers of graduate students and postdoctoral fellows have been (and are being) trained. The enterprise needs to transition from rapid to more slow and steady growth.

The final issue is data management. Many scientific experiments now generate vast quantities of data: images, genome sequences, analytical data, and so on. How can these data be effectively stored and shared? Should there be central repositories or should each individual laboratory or institution be responsible? These are complicated issues.

How will you address these issues during your tenure as editor?

The most important tools for addressing all of these issues and others are analysis and transparency. The scientific method can be applied to such questions of culture and policy. To what extent has public trust in science and scientists fallen? Why has it occurred? A good example involves recent discussions that many scientific results are not replicable, which came largely from some papers from industry investigators who had difficulty reproducing published results. However, further analysis reveals that the reasons for lack of reproducibility can be varied. . . . As with any ailment, it is important to get the diagnosis correct before deciding on a treatment. Transparency is key to this process. *Science* provides an important outlet for sharing the analyses, the data, and differences in interpretation or opinion to move toward effective resolution of such issues. ■

The author with her grandmother. "Gram" was like a second mother to her.

TOUGH TALK

DIFFICULT CONVERSATIONS IN THE ICU AND BEYOND

BY ROBYN K. COGGINS

When my grandma had a sudden catastrophic stroke, her emergency physician, thankfully, did not mince words. I was the first family member to arrive at the hospital, so at just 18 years old, I became her medical surrogate. A nurse led me to a family consultation room where the doctor said in no uncertain terms that Gram would not survive the night and, because she'd requested no heroic measures, there was nothing more to do. Did I think she'd want a priest to visit her? Were there other family members on their way?

I wasn't sure how to answer whether my grandma wanted a chaplain. She wasn't religious . . . but a prayer couldn't hurt, right? As I sat next to Gram later, stroking her arms, holding her hand, speaking my last words to her, the only things that troubled me were the brown fluid draining from her catheter and the hose snaking from her mouth. She hadn't wanted either of those interventions, I later learned, but the doctors had inserted them as a kindness to us, her family, so we could say goodbye. I've never begrudged them that judgment call. She spent less than 12 hours in the hospital and made it to 88—an end-of-life circumstance that's hard to beat.

My grandma had signed a do not resuscitate order and left instructions for where paramedics would find it (rolled into a plastic tube in her freezer). Thus, unlike so many of her contemporaries, she didn't receive rib-cracking CPR; she wasn't whisked away to futile surgery or noisy intensive care. Maybe she was uncomfortable in the hospital, but nearly her entire family was able to attend her death, and I don't think she would have minded that trade-off.

It's hard to know, even when a patient is conscious, what exactly the right move is during a serious illness. The brain tumor is no longer treatable—what next? Your options are to take opioids that make you nauseated or be in pain—which do you choose?

Such decisions get at one ultimate question: What does the patient and her family value, and how can medicine align with that answer? In many cases, it's hard to articulate exactly what you or your loved one wants, which demands that the physician become an interpreter and a guide.

"The same thing we do in medicine is what you do when you analyze a novel—you look for what's there, what's said," says Douglas White, an MD, who holds the UPMC Chair of Ethics in Critical Care Medicine at Pitt. It's the doctor's job to examine the person's character and consider, "What is the patient complaining of? What are they not complaining of? How are they saying it? And what clues might we get as to what's going on?"

White says his undergraduate literature degree prepared him for his work as director of Pitt's Program on Ethics and Decision-making in Critical Illness because he's always been asking those kinds of questions. As a doctor, he's spent his entire career researching the different ways health care providers approach situations that resist easy analysis. Lately, his focus has been on divergent prognosis perceptions in the ICU. About 500,000 deaths per year in the United States occur in ICUs and "things don't often go well," which he calls "a perfect recipe for something worth studying."

She hadn't wanted either of those interventions, I later learned, but the doctors had inserted them as a kindness to us, her family, so we could say goodbye.

In a study of doctors and surrogate decision-makers in four ICUs, published in the *Journal of the American Medical Association* this May, White and colleagues found that in more than half of cases, doctors and surrogates substantially differed in how they perceived the patient's prognosis. (Interestingly, both groups' estimates were better than chance, though the doctors' were overall still more accurate.)

All patients were adults in the ICU for at least five days, on mechanical ventilation, and unable to make decisions for themselves.

PHOTOGRAPHS COURTESY ROBYN K. COGGINS

To determine prognosis estimates, White's team separately asked doctors and surrogates, on a scale of 0 to 100 percent, "What do you think are the chances that the patient will survive this hospitalization if the current plan of care stays the same?" (Ultimately, 57 percent did survive.)

They also asked the surrogates, "If you had to guess, what do you think the doctor thinks is the chance that your loved one will survive this hospitalization if the current plan of care stays the same?" If the surrogate's and doctor's estimates differed by more than 20 percent, the team marked them as "discordant." Just over half of the prognoses were discordant, with surrogates being more optimistic than the physicians in 80 percent of those cases.

Some earlier research had suggested that family members don't accurately understand the doctor's explanations of prognosis, leading to this discord. To see whether this hypothesis was correct, White's team also interviewed the surrogates, asking them to elaborate on their prognosis answers. This is where things got interesting.

One of the most common answers among optimistic family members was that the doctor didn't understand. One surrogate said, "I feel that my brother's a fighter, and I know him [better than the physician]." Others felt they needed to keep hope alive, a kind of magical thinking like willing your plane not to crash during a turbulent flight. Some surrogates held religious views—a belief that God is ultimately in charge or that a miracle could happen—or they felt the doctor was too pessimistic.

"This finding," White et al. write, "raises concerns that one of the fundamental assumptions of shared decision-making—agreement between parties about the likely outcomes of treatment—is often not achieved."

But what does a little positive thinking or prayer hurt?

"If this were just a coping mechanism that didn't have consequences for anyone else, it would be fine," White says. But "one of the strongest predictors of families having a very difficult time with the grieving process—having a disorder called complicated grief—is that they felt that they were not prepared for the possibility that the patient would die."

Being too optimistic can be bad for the patient, too. "This lack of understanding or appreciation of the gravity of the prognosis may actually lead to more burdensome treatments at the end of life that those patients wouldn't choose for themselves," White says.

In another study, published last October in *JAMA Internal Medicine*, White and colleagues also found that the religious and spiritual needs of patients and family members are not being adequately addressed in the ICU. Of 249 recorded conversations between surrogates and doctors, only 16 percent broached the topic of religious or spiritual concerns—and those talks were usually spurred by surrogates. When spirituality did come up, most health care professionals deflected to treatment plans or didn't directly address the subject at all. One simply responded with a deep sigh.

"I try to take a somewhat charitable view of [this result], and I do not think these are physicians who are anti-religious or callous," says White, who describes himself as spiritual but not religious.

Rather, "I [think] these findings suggest that these physicians likely don't have a good set of skills to manage these very complex conversations. Religious conversations are very different from conversations about how to treat pneumonia. And they certainly are not the focus of medical education in any substantial way."

Why are these conversations so difficult, and why do doctors avoid them? For one, they're emotionally draining for everybody. Additionally, "doctors have a really hard time listening—they like to talk," says Winifred Teuteberg, an MD associate professor of medicine in palliative care and medical ethics. She arms colleagues with the strategies needed to initiate these discussions.

"[Goals-of-care] conversations are rewarding and important," Teuteberg says, "but they're tough. And imagine what it must be like for the patient, whose life is at stake." (It should be noted that palliative care—sometimes called supportive care—is not limited to end-of-life conditions: transplant and oncology patients, those on dialysis, patients with AIDS or sickle cell disease, among many others, can benefit from a decrease in symptom burden.)

Like many doctors, Teuteberg didn't learn how to talk to laypeople about subjects like code status in medical school, but once she became a resident, she was suddenly expected to know how to broach them. With a grant from the Beckwith Institute, Teuteberg started CardioTalk at Pitt—the nation's first-ever structured training program for cardiology fellows and faculty in palliative care communication skills, incorporating role play, simulation, and didactic lessons. (Pitt's Kathryn Berlacher, director of the cardiology fellowship program, and Eva

One of the most common answers among optimistic family members was that the doctor didn't understand. One surrogate said, "I feel that my brother's a fighter, and I know him [better than the physician]."

Many people say, "I don't want to be a vegetable"—Gram backed that up with documentation. This photo was taken in the spring of 2004, shortly before she died of a stroke.

Reitschuler-Cross, both MDs and assistant professors of medicine, are her partners in developing CardioTalk.) Teuteberg says that just giving docs a few pointers makes them "horribly relieved" and more prepared to ask patients tough questions.

In addition to her training and inpatient consulting at Magee-Womens Hospital of UPMC and UPMC Shadyside, Teuteberg works at an outpatient clinic for heart-failure patients at UPMC Presbyterian. Because heart disease is the leading cause of death in America, this large population is especially in need of the symptom management that palliative care can provide.

"Let's say I was playing basketball, and I threw my knee out, and I go to see an orthopaedic surgeon. I'd want the surgeon to tell me what [she] thought—should I have surgery or not?" she says. With difficult decisions, such as those at the end of life, however, physicians often expect the patients to tell them what to do, in a well-meaning attempt at shared decision-making that could be seen as passing the buck.

"The patients don't know enough—they don't know enough detail about the options to make those decisions, plus you're then putting the full burden of the decision on the patient or on the family member: *Do you want me to pull the plug on your mother? Well of course I don't want to pull the plug on my mother—what's best?*"

Teuteberg's heart-failure patients are often anxious, depressed, and profoundly fatigued; they also need to come to terms with the life limitations their condition can bring. What she trains cardiology fellows and faculty to do is ask questions and listen: Which symptom is most bothersome to you right now? What's important to you in everyday life? How would you feel about having a feeding or breathing tube? Eventually, the mosaic of answers becomes a plan.

In a 2015 study published in *Gynecologic Oncology*, Teuteberg and colleagues found that a palliative care consultation improved patient pain, eating, fatigue, depression, anxiety, nausea, and breathing, often as early as the next day. Many other studies have found improvement in other populations, as well.

But there aren't enough palliative care doctors for every patient who needs them, so more providers need to come to the clinic equipped with these skills. Pitt's Julie Childers (MD '05), an assistant professor of medicine, leads system-wide communication training courses for oncologists, geriatricians, nephrologists, critical care fellows, surgeons—really any interested providers.

And Teuteberg is committed to improving care beyond individual conversations, too. As medical director for community supportive services at UPMC, she's "built fabulous technology solutions to try to help people do a better job after you've had the discussions," says Robert Arnold, an MD, medical director of the UPMC Palliative and Supportive Institute, the Leo H. Criep Professor of Patient Care, and professor of medicine and of psychiatry. (Arnold's also cofounder of VitalTalk—a broader educational communication program that became a model for CardioTalk.)

Beginning this summer in certain electronic health systems at UPMC, a pink tab with POLST (Pennsylvania Orders for Life-Sustaining Treatment), goals of care decisions, code orders, and the content of any related conversations will appear prominently in charts, so patients' wishes are more likely to be met.

A little guidance early on will go a long way, Teuteberg thinks; yet, she says, "There's always uncertainty. I think there always will be." ■

CLASS NOTES

JOHN ALTDORFER

Paul Caplan with his daughter, Roberta

'30s

Reflecting on his life recently, **Paul Caplan** (MD '36), who is 103 years old, leans back on the sofa in his Oakland apartment. He recalls starting out at Montefiore, the only Pittsburgh hospital that would employ him at the time as a Jewish physician. Treating soldiers wounded on D-Day on Omaha Beach. Traveling for 20 years as the Pittsburgh Symphony Orchestra tour physician. Building a thriving internal medicine and arthritis practice. And retiring at 96.

Seated beside Caplan is his daughter, Roberta Caplan (Educ '71), who, by the way, choreographed the 1971 Scope & Scalpel production. She reminds her father of other ways he and his wife, Gertrude Forman Caplan (Educ '41), made their mark, including endowing a research grant for the Division of Rheumatology and Clinical Immunology, funding an award to support a fellow at Pitt's Rheumatoid Arthritis Center, and establishing a scholarship for Pitt students to work with Shakespeare-in-the-Schools.

But Caplan, a former clinical assistant professor of medicine and a master of the American College of Rheumatology, prefers to remember the patients he treated—and the privilege it was to be part of their lives, saying, "I never worked a day in my life."

'60s

In this often noisy world, **Lawrence L. Feth** (PhD '69) believes it's increasingly important to better understand what he considers our "primary communication channel"—hearing. Feth, a professor of speech and hearing science at Ohio State University and a National Institutes of Health–funded investigator, recently coauthored a paper about a model that does "a better job at predicting the ability of human listeners to respond to sounds." Feth says although some of his work is more abstract, he also conducts "practical" research, like finding ways to improve a clinician's ability to hear in a loud hospital environment. His fascination with sound and technology began when he got an amateur radio license as a teen. Although this sparked an interest in electrical engineering, he later realized that his true passion lay in psychoacoustics research. "Somewhere along the line, I moved from being interested in antennas to being interested in ears," Feth says. "So, different kind of antenna."

'70s

When a significant number of patients weren't getting relief from neuropathic pain using FDA-approved medications, pain management specialist **Barth Wilsey** (MD '73) knew it was time for a change. "Some patients would tell me that the medications I prescribed weren't helpful and that they'd instead been going to a marijuana dispensary, because this herbal medicine alleviated their pain." So Wilsey, an associate physician at the Center for Medicinal Cannabis Research at the University of California, San Diego, investigated. Wilsey and colleagues picked apart which strengths of delta-9 tetrahydrocannabinol in cannabis are effective in treating neuropathic pain and also assessed side effects (e.g., cognitive impairment, psycho-activity). Their work was the subject of a *Discover* magazine feature story in October 2015.

Wilsey

'80s

Daniel Lattanzi's (Obstetrics and Gynecology Resident '82) practice extends far beyond Pittsburgh, where he's a Pitt assistant professor of obstetrics, gynecology, and reproductive sciences and codirector of the Ob-gyn Global Health Program at Magee-Womens Hospital of UPMC. In Haiti, he has helped establish working health systems. His work has also taken him to Guyana's Georgetown Public Hospital, which treats some of that nation's most underserved pregnant women, mothers, and infants. Lattanzi trains both UPMC and Guyanese physicians onsite. "As a result," says Lattanzi, "we've seen maternal deaths decrease . . . right before our eyes. We can save a woman's life."

'90s

Simon Mears (Neurobiology PhD '94, MD '96) is an orthopaedic surgeon and professor of orthopaedic surgery at the University of Arkansas for Medical Sciences in Little Rock, where he also serves as the medical director of musculoskeletal services. In this role, says Mears, "I take care of a lot of patients with arthritis who need joint replacements," many of whom are elderly. His focus on the treatment of geriatric patients is taking him around the globe: Mears serves as president of the International Geriatric Fracture Society, an organization that works to advance geriatric fracture care globally. As the winner of a fellowship sponsored by the American Orthopaedic Association, Mears recently toured orthopaedic centers in Austria, Switzerland, and Germany.

William Yancy Jr. (Internal Medicine Resident '98, Chief Resident '99) has devoted nearly two decades to the study and treatment of obesity at the Department of Veterans Affairs and, most recently, at Duke University, where he is associate professor of medicine and director of the Duke Diet and Fitness Center. In a study published last year in *Annals of Internal Medicine*, Yancy and his coauthors showed that patients may benefit from having an expert shape their diet practices as opposed to being left to individual choices.

'00s

For emergency medicine physician **Henry Wang** (Emergency Medicine Research Fellow '02, Clinical Research MS '06), patience pays off. This past December, Wang began an NIH-funded, randomized trial of paramedics in 30 agencies across the United States. "Essentially I've been waiting 15 years to do this," he says, noting that it builds on research he conducted at Pitt's Institute for Clinical Research Education when he was a grad student. In the trial, paramedics will treat a total of 3,000 cardiac arrest patients in need of oxygen, either with

a standard endotracheal intubation or the newer King laryngeal tube, to determine which method is the safest and most efficient outside of the hospital setting. Wang is an adjunct associate professor of emergency medicine at Pitt as well as professor and vice chair for research in the Department of Emergency Medicine at the University of Alabama at Birmingham.

Cope

As a medical officer at the Centers for Disease Control and Prevention, **Jennifer Cope** (MD '04) is the subject-matter expert for free-living amoeba infections. Such infections—including the infamous brain-eating amoeba *Naegleria fowleri*—have begun to respond to treatment with miltefosine. During Cope's first summer at the CDC in 2013, the successful administration of miltefosine saved an infected girl's life, and she made a full recovery—making this patient the first U.S. survivor of *N. fowleri* in more than 30 years. "It was great to be a part of that milestone," says Cope.

Rouzan Karabakhtsian (Gynecologic and Breast Pathology Fellow '06) is an associate professor of pathology at the Albert Einstein College of Medicine and an attending pathologist at Montefiore Medical Center. In January, she coauthored a paper in *Modern Pathology* showing an association between MRI-detected lobular neoplasia—an atypical increase of cells in the breast lobule—and breast cancer. An MRI from the study made the cover. Karabakhtsian also co-edits the anatomic pathology abstracts section of *CAP Today* and is a founder of the Armenian American Pathology Association. She presents widely, both nationally and internationally; recently she spoke on a cost-effective model for starting new histology labs in developing countries.

Kasi

'10s

As a kid in high school, **Pashtoon Murtaza Kasi** (Internal Medicine Resident '13) would help his physician parents with their research. Today, the oncology/hematology fellow and assistant professor of oncology/medicine at Mayo Clinic is author of a book on research and 57 journal articles. Some of his clinical trials focus on individualized cancer treatments. "Previously, we only had surgery, radiation, and chemotherapy as three tools in our toolbox," Kasi says. "Now, we have the option of immunotherapies and targeted therapies that act on one particular aberration." Such approaches, Kasi notes, are personalizing treatments as cancers evolve within patients. Recently, Kasi accepted a staff position in gastrointestinal oncology with a focus on colorectal cancers at Mayo Clinic's Jacksonville, Fla., campus. His work made the cover of the *Wall Street Journal* in March.

—John Altdorfer, Imaz Athar, Jessica Boddy, Rachel Mennies, and Susan Wiedel

NATALIE SHAW

LET SLEEPING KIDS LIE

COURTESY NIEHS/STEVE MCCAW

Shaw

A butterfly undergoes metamorphosis inside a chrysalis. A tadpole transforms while swimming around a pond. For humans, the big change happens beneath a comforter.

"The brain is what controls puberty, and when it turns on, it releases hormones that then tell the ovaries or the testicles to make estrogen or testosterone, respectively," says Natalie Shaw (MD '04), a researcher at the National Institute of Environmental Health Sciences in North Carolina.

"And the neat thing is that we think the brain first turns on those signals while kids are asleep," she says. The intricacies of how this works remain murky, but Shaw's work suggests that slow-wave sleep, the deepest sleep, is important. As a pediatric endocrinologist, Shaw seeks to discover what triggers puberty and how sleep communicates with the reproductive centers of the brain. Unraveling these mysteries may have important implications for kids who don't get enough sleep (like sleep apnea sufferers) or kids for whom puberty is delayed.

Shaw is also part of a group at Massachusetts General Hospital conducting research on Kallmann syndrome, a genetic disorder characterized by delayed or absent puberty, infertility, and an inability to smell (or, rarely, the absence of the entire nose). Defects in the two very different systems—reproductive and olfactory—occur together because the brain cells responsible for starting puberty begin life in the nose and must migrate along the olfactory system "highway" to reach the brain.

Shaw credits the endocrine program at Children's Hospital of Pittsburgh of UPMC for encouraging her early interest in the field and says the city is still near and dear to her. "I miss it and try to visit often," says Shaw. *—Jason Bittel*

MAA SAYS, "A BLACK-CODE AFFAIR"

GEORGE THOMAS MENDEL/CIDDE

TOP PHOTO: Professors Georgia Duker and Joan Harvey with McGarry. BOTTOM: Cisneros, Thomas, and the Fridmans.

"We were a very close class—everybody hung out together," said Pitt assistant professor of medicine Holly Thomas (MD '09) as she hovered over the Class of 2009's yearbook. She and her husband, pediatrician Gabriel Cisneros (MD '08), gathered with nearly 70 others, who hailed from classes ranging from 1958 to 2019, on a drizzly night this May to reminisce, nosh, and mosey around the Andy Warhol Museum.

The shindig, sponsored by the Medical Alumni Association, welcomed classmate extraordinaire Ryan McGarry (MD '09) back to the 'Burgh. McGarry was in town to speak at the School of Medicine's commencement. He also gave talks at Pitt related to his role as executive producer of the new CBS series *Code Black*, which is based on his award-winning documentary of the same name.

Also around the yearbook: Hilary Fridman (MD '09), an academic hospitalist at the VA Pittsburgh Healthcare System and clinical instructor of medicine, and her med school sweetheart, cardiology imaging fellow Yaron Fridman (MD '09). The Fridmans shared stories of McGarry's party-planning prowess: As class president, he organized an epic semiformal in a surprise location that wasn't revealed until the guests arrived. They emerged from school buses with blacked-out windows to find themselves at Heinz Field.

This spring's quasi-reunion was organized by MAA to hold folks over for a spell. The annual Medical Alumni Weekend has moved to the fall—mark your calendars for September 23–25. (For information contact Ashley Knoch at akk57@pitt.edu.)

While you're at those fall festivities, stop and say hi to Kelsey Thayer, the MAA's first-ever assistant director. And in the meantime, stay in touch with your alumni association through Instagram (@PittMedAlum) and Twitter (@PittMedAlum). *—Robyn K. Coggins*

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Hoyson

GREGORY M. HOYSON

OCT. 3, 1956–DEC. 27, 2015

From the time he was a Pitt med student, Gregory Hoyson (MD '82) had an ability to form strong connections with people, says Jan Madison (MD '85). It was Hoyson she called when she moved back to Pittsburgh after her training and needed a pediatrician for her son. "I had such trust in Greg as a person and knew he'd be the right choice."

Hoyson, 59, died of colon cancer in his McCandless home last winter.

Madison, president of the Medical Alumni Association (MAA), notes that as an MAA board member of six years, Hoyson served with commitment and enthusiasm, regularly attending meetings and assisting in fundraising events. Previous President Brian Klatt (MD '97) says Hoyson was instrumental in raising the profile of the MAA. "I had hoped he would serve as its next president. He had deep devotion to his family, his profession, and his patients."

Hoyson's bond with Pitt med spanned 37 years, from student to resident at Children's Hospital of Pittsburgh of UPMC to clinical associate professor of pediatrics. He also served as chair of pediatrics at UPMC Passavant and on the executive medical committee at Children's.

—Pamela Goldsmith

Jannetta

PETER J. JANNETTA

APRIL 5, 1932–APRIL 11, 2016

"Imagine being Tasered in the face—for hours, sometimes days," Charlotte Kemerer says of trigeminal neuralgia, a chronic facial pain disorder that's been known to drive sufferers to suicide. When she turned to UPMC for help, she didn't know to what extent she was coming to the right place.

Peter Jannetta—who headed neurosurgery at Pitt for some 30 years, starting in 1971—had made a discovery back in his residency at UCLA while he was dissecting cranial nerves. He devised a procedure known as microvascular decompression that would eventually deliver many people from the torture of trigeminal neuralgia—but first, he had to convince a very skeptical profession of the appropriateness of the approach. A. Leland Albright (Fel '76, Res '78), one of Jannetta's first residents, recalls, "[Colleagues] scoffed. But the way he convinced people was to have the top neurosurgeons in the world come, one by one, to operate with him. Then they'd go back home and do it in their patients."

Jannetta trained more than 150 surgeons and operated alongside countless residents and med students, including Pitt's Paul Gardner, who treated Kemerer. Gardner (whom Kemerer calls "magnificent") first had her try medication, but that turned her into a "zombie." After the surgery, the pain was gone, and she knew she'd be okay.

"This literally saved my life. Nobody understands, unless you've had it, how horrible the pain is. …[Jannetta's procedure] has saved thousands of people from that pain."

—Sarah C. Baldwin

INDRAVADAN N. PANDIT

JAN. 20, 2016

Birthdate withheld at family's request.

From his boyhood in Visnagar, India, medicine was the obvious path for Indravadan Pandit (Res '70, Fel '71), says his daughter Neha Pandit. It enabled him "to help people on an individual basis, to be true to who he was, even if it meant studying under the streetlights at night and using outdated books." At the local temple, he made sure there were always fresh flowers and food for people to take. And he continued giving to others throughout his life, volunteering at Pittsburgh's food bank until he was 77.

Pandit, director of the catheterization laboratory at UPMC Shadyside, died in January.

As chair of the American Association of Physicians of Indian Origin Charitable Foundation, Pandit gave back to Visnagar, which was 90 minutes away from the nearest hospital. He organized the construction of a new hospital and also established mobile medical units to bring free medical care and immunizations to area villages. Pandit was also a founding member and board chair of the Hindu Jain Temple of Pittsburgh.

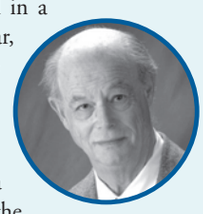
"He was such a loving man who didn't ask for anything in return," says Neha.

—Susan Wiedel

Pandit

PETER M. WINTER

AUG. 5, 1934–MAY 14, 2016



Winter

As a teenager, Peter Winter served in a medic unit during the Korean War, after which he decided to pursue a career in medicine. "He was interested in scientific research, I think, for a lot of the same reasons he was interested in the outdoors," says his son, Chris Winter, "a sense of exploration and adventure and the unknown."

Winter chaired anesthesiology and critical care medicine at Pitt from 1979 to 1996, succeeding Peter Safar, who taught him the importance of multidisciplinary approaches to anesthesiology. Winter made innovations in neurological, cardiac, and transplant surgery; nearly eliminated anesthesia-related deaths at Pitt; and about doubled his faculty and trainees. Raymond Planinsic and William McIvor, both professors of anesthesiology, express gratitude for Winter's commitment, not only to building a highly respected department, but also to their personal development as doctors.

Perhaps Winter's greatest legacy is creating the Peter M. Winter Institute for Simulation, Education, and Research (WISER). What started in 1994 as a two-room simulation laboratory in Montefiore is now a sprawling 16,000-square-foot facility with seven satellite sites. "Prior to this, there weren't really good ways to train on how to manage patients who had difficult airways," says McIvor, associate director of the institute. Today, using dozens of human simulators that cough, cry, bleed, breathe, and monitor student performance, WISER trains thousands of health care providers.

—Ali Greenholt

IN MEMORIAM

'40s

N. BRUCE TANNEHILL SR.
MD '42
APRIL 9, 2016

'50s

JOHN C. HAIRSTON JR.
MD '54
APRIL 21, 2016

ROLAND T. KEDDIE
MD '57
MAY 22, 2016

BARRY C. HARRIS
RES '59, '65, FEL '68
APRIL 16, 2016

'60s

J. DARRELL SHEA
RES '67
JAN. 20, 2016

RAIS A. BEG
RES '68
OCT. 12, 2015

TERENCE MCAULIFFE
FEL '68
MAY 7, 2016

DAVID C. NORRIS
RES '69
MAY 26, 2016

'70s

RICHARD A. PROPPER
MD '76, RES '80
MAY 31, 2016

'80s

KAREN A. KRUGER
FEL '83
DEC. 31, 2015

'90s

HARRY BONET
FEL '92, '93
FEB. 10, 2015

DWAYNE A. MCQUITTY
FEL '96
APRIL 18, 2016

FACULTY

RAYMOND E. FELGAR
PHD '90, MD '92
APRIL 18, 2016

JACKSON WRIGHT JR. TAKING AFRICAN AMERICAN MEDICINE TO HEART

BY SHARON TREGASKIS

UNIVERSITY HOSPITALS CASE MEDICAL CENTER

Why do racial disparities in health outcomes exist? Wright's research has unveiled some surprising answers.

Author and orator Booker T. Washington was just 59 years old when he was hospitalized for exhaustion and difficulty breathing. "Racial characteristics are, I think, in part responsible," his physician told the *New York Tribune* in November 1915, just days before Washington's death. Readers of the time understood the statement as a veiled reference to syphilis, fueling speculation that the emancipated slave, a champion of morality and virtue to advance racial progress, had died a hypocrite.

A century later, Jackson T. Wright Jr. (MD '76, PhD '77), an emeritus professor of medicine at Case Western Reserve University, put the issue to rest with a review of Washington's original medical records—including the blood test that had confirmed for Washington's own physicians that he never had syphilis. Actual cause of death? Malignant hypertension. (Wright presented his findings at a historical clinical pathology conference at the University of Maryland in 2006.)

In Washington's day, doctors knew little of the fatal cascade of organ damage precipitated by hypertension. Today, we know a lot more about this disorder, and physicians have a wealth of weapons in their arsenal for prevention and management of the disease. We also know that high blood pressure is an epidemic among African Americans. What role do characteristics related to ethnic heritage play?

As program director of the William T. Dahms MD Clinical Research Unit and the Clinical Hypertension Research Program at Case Western, Wright untangles the biological, cultural, and medical roots of racial disparities in kidney disease and hypertension. Last year, the American Heart Association recognized his labors with its 2015 Clinical Research Prize.

"One of the objectives of mine has always been to obtain credible data in African American patients so we'd better understand why racial differences in health outcomes exist," says Wright, who was two years into his PhD studies in pharmacology when he decided to earn a medical degree, in part to advance the clinical applications of his research. "At the time I started training, most of the data in black patients was either anecdotal reports, very small studies, or opinion. There were almost no well-controlled scientific studies."

Four decades later, Wright has authored more than 200 peer-reviewed papers detailing the prevalence of hypertension among African Americans, revealing contributing factors, and—because his work has shown that African Americans respond differently to some drugs—offering treatment guidelines.

He has also served as a principal investigator for multiple long-term, National Institutes of Health–funded clinical trials, including the 1,100-participant, 21-center African American Study of Kidney Disease and Hypertension Trial (AASK); the 42,400-participant Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT); and the Systolic Blood Pressure Intervention Trial (SPRINT), the latter of which was published in the *New England Journal of Medicine* in November 2015 and prompted changes in hypertension guidelines.

In 2013, *NEJM* published a report coauthored by Wright revealing a variant of the *APOL1* gene that speeds the progression of kidney disease and is more common among black people. And yet, he says, relatively few racial disparities in kidney disease and hypertension owe to genetic explanations. Rather, patterns of diet, exercise, stress, income level, toxin exposure, access to health care, and other aspects of life in America that correlate with race likely have an outsized effect.

The study of racial differences in disease presentations, especially in populations at highest risk, provides critical information that benefits all populations with the disease, says Wright. He notes that simply asking patients whether they consider themselves black remains a potent predictor of risk for hypertension and its consequences.

"Even though the answer may not necessarily define the genetic makeup of the person, it clearly in many instances defines their risk of developing and suffering from a disease." Why that is remains an important unanswered question. ■

COURTESY RACHEL REGINA

Gugu Mofokeng (center) with former coworkers holding "No Gugu, No Work!" signs.

SIGHT FOR SORE EYES

Thirty-eight-year-old Gugu Mofokeng has dedicated her life's work to others, and people seem inclined to dedicate themselves to her in return. "No Gugu, No Work!" was her coworkers' rallying cry on her last day at WhizzKids United, a South African clinic and youth center that uses soccer as an educational tool. They dreaded losing their teammate.

In 2012, Mofokeng started losing sight in her left eye because of epithelial downgrowth, a condition in which certain eye cells grow out of control, causing great pressure and pain. After several unsuccessful treatments, Mofokeng's vision deteriorated to the point at which she could only distinguish light from dark.

The Class of 2017's Zachary Dong heard about Mofokeng's condition from his aunt, Krista Dong, an MD and a colleague of Mofokeng's. He coordinated a team that included Deepinder Dhaliwal, an MD and professor of ophthalmology; Scott Drexler, an OD and assistant professor of ophthalmology; and Joel Schuman, an MD and former chair of ophthalmology. Together, they managed Mofokeng's epithelial downgrowth, fitted her for special contact lenses and glasses, and treated her frequent headaches. More than 100 people pitched in funds and other resources (including *gratis* care and attention from UPMC staff) to make Mofokeng's trip possible.

Mofokeng returned home with pain-free vision. "Coming back, I noticed and appreciated the different shades of green in the hills and trees in my town," she notes. Mofokeng now works for a program helping young people with HIV and tuberculosis.

"I may never get a chance to show kindness to the people who showed me kindness, [but] I have made it my business to show kindness all around me," she says. *—Ali Greenholt*

CALENDAR

FOR ALUMNI & FRIENDS

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

ORIENTATION LUNCHEON FOR THE INCOMING CLASS
AUGUST 19
11:30 a.m.
University Club, Ballroom B

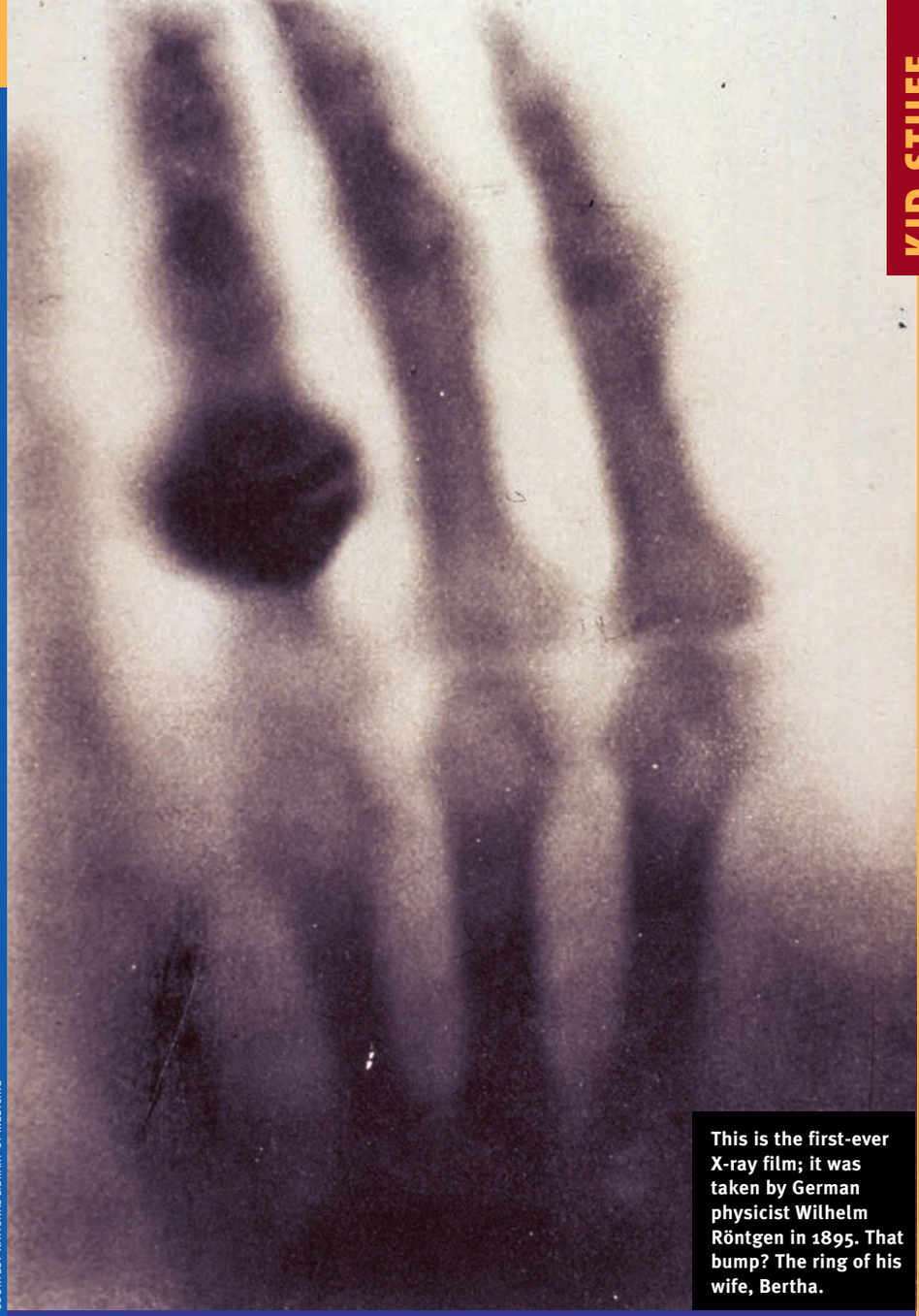
MARSHALL S. LEVY, MD MEMORIAL LECTURE
SEPTEMBER 2
9 a.m.
Lecturer—Mariana Kaplan, MD
Chief, Systemic Autoimmunity Branch
National Institute of Arthritis and
Musculoskeletal and Skin Diseases
Scaife Hall, Room 1105AB
For information: Linda Sadej at 412-383-8123
or sadej@pitt.edu

ARIZONA PITT ALUMNI & FRIENDS RECEPTION
SEPTEMBER 8
6 p.m.
Mod Phoenix
For information: Rachel Edman at 412-864-1957
or rge6@pitt.edu

WILLIAM S. MCELLROY DISTINGUISHED RESIDENT AWARD RECEPTION
SEPTEMBER 23
6 p.m.
Phipps Conservatory
Recipient—James D. Kang (Res '92)
Chair, Department of Orthopaedic Surgery
Brigham and Women's Hospital

MEDICAL ALUMNI ASSOCIATION REUNION WEEKEND
SEPTEMBER 23–25
Reunion Classes:
1956, 1961, 1966, 1971,
1976, 1981, 1986, 1991,
1996, 2001, 2006, 2011

MEDICAL ALUMNI ASSOCIATION HOMECOMING TAILGATE
OCTOBER 8
Three hours before kickoff
Heinz Field, Red Lot 6



COURTESY NATIONAL LIBRARY OF MEDICINE

This is the first-ever X-ray film; it was taken by German physicist Wilhelm Röntgen in 1895. That bump? The ring of his wife, Bertha.

FOR REAL! TWEEN SCIENCE

If you've ever had a bad tumble, you've probably had X-rays taken. Using an extra-powerful version of light, an X-ray machine lets doctors get a gander at your skeleton. Just like a flashlight beam can shine through a window but not a wall, an X-ray beam passes through stuff that's made of lightweight atoms (soft tissues like skin, fat, and muscles), and it's absorbed by stuff that's made of heavy atoms (like bone). Typically tissue looks gray, and bone looks white. A plate underneath your body captures the full image—and exposes the black empty spaces where the bone has been broken.

There are different kinds of X-rays, too. Mammography, partly invented by Pitt med alum Robert Egan, can find cancerous growths inside breast tissue. We're still waiting for someone to invent X-ray spectacles, though! *—Lela Nargi*

Big thanks to Pitt's chair of radiology, Jules Sumkin, for illuminating this subject.

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MAKING TRACKS

We've got a good thing going here: 16 years of award-winning stories. And now, you can take *Pitt Med* on the go—in your car, on your morning jog, and anywhere you might wander.

To get more mileage out of our trunkful of tales, we've launched a new Read Aloud feature for Pitt Medcast, a podcast series from these editorial offices. Our first foray: "Let's Talk About Sex," a journey through biology that isn't binary, and the challenges it brings. And up ahead: "When Fred Met Margaret," a trek through Mister Rogers' neighborhood that signposts the indelible influence of Pitt's own Margaret McFarland. We hope you'll tune in as we take this show on the road.

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