

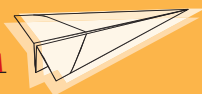
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | WINTER 2015

PITTMED



THE MOST KISSED
FACE OF ALL TIME

A DEATH THAT WOULD SAVE INNUMERABLE LIVES



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BIRDS OF A FEATHER

Migratory instincts start to tingle in the throes of winter. Why not indulge them with Pitt health sciences alumni and friends this March and flock down to the Sunshine State for the 10th annual Winter Academy? Get the bird's-eye view of how personalized medicine can revolutionize the way health care is understood and delivered, and jabber with our scientists and clinicians afterward. Soak up some vitamin D while you're at it—you won't egret it.

March 11, 2015

The Mar-a-Lago Club
Palm Beach, Fla.

March 13, 2015

Ritz-Carlton Resort and Spa
Naples, Fla.

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PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, WINTER 2015

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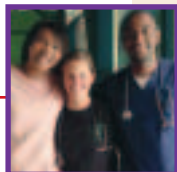
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JASON BITTEL ["Into the Virus"] loves to dig into the nitty gritty of science and nature topics. So we gave him a close-up of a virus's coat for his first *Pitt Med* feature. A lover of sandwiches, Bittel likes to say he "serves up science for picky eaters." He is also a frequent contributor to *Slate*, *National Geographic News*, and *OnEarth*. He collects skulls (much to his wife's dismay), has donated bone marrow, and has shot boars for the National Park Service. Bittel graduated from Pitt's MFA program and lives in Pittsburgh with his wife, son, and two tiny wolves (who may actually be Pomeranians).

STACY INNERST ["The Rush to the Hospital" and "Emily Heart (Map) Pittsburgh"] was one of those tykes who just couldn't sit still. "I started banging on things when I was kid," he says. "My feet were always tapping. I decided I might as well do something productive with it." In addition to working as an illustrator, he plays the drums in two Pittsburgh alt-country bands, Grievous Angels and the Tumblers. Music has been a muse through his visual artistry, as well. Innerst, an award-winning children's book illustrator, made the *Washington Post's* annual list of best titles for his 2013 release, *The Beatles Were Fab (and They Were Funny)* (Houghton Mifflin Harcourt). Now he's working on a new book on George Gershwin and the composing of "Rhapsody in Blue" (Boyd's Mills Press). He was on staff at the *Pittsburgh Post-Gazette* for 17 years.

COVER

The face that would become Resusci Anne's belonged to someone; her story is shrouded in mystery. See p. 40. (Cover: Wikimedia Commons © 2013.)



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For decades, Pitt has been an "intellectual engine" for prehospital care, starting with CPR and the first highly trained paramedics.

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It takes a village to give patients coordinated, multidisciplinary care. See how Pitt's six Schools of the Health Sciences are building integrated treatment communities among professionals-in-training.

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Peering toward atomic resolution. The very little picture will help scientists with the big picture in virology.

IMAGE ESSAY BY JASON BITTEL

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W

*e don't see things as they are,
we see them as we are.*

—Anaïs Nin

Just months ago, I was hardly able to see without my glasses—my vision compromised by myopia since childhood and lately by cataracts. Now, after a surgeon replaced my inborn lenses with synthetic prescription lenses, using contemporary technology that I find amazing given the state of the art just a decade ago, I've gone from 20/200 vision to 20/15. It's been a transformative experience. There's clarity, resolution, and brilliance that I can barely describe. Colors appear as never before. Not only do I see better, I see differently. There is a poetry to this!

I have an inkling now for how Edwin Hubble might have felt in 1919, when he first pointed the enormous muzzle of the Hooker Telescope toward the heavens. At the time, the 100-inch lens was the largest in the world. The Hooker allowed Hubble to pick out stars in Andromeda and other spiral nebulae and gauge their distance from Earth. His work conclusively proved that the universe is larger than our own galaxy. Much larger, of course.

Edwin Hubble's heirs in physics and astronomy carry "the torch of science," as Alfred Noyes put it, to their own "deep-set boundary-mark in that immense darkness of Space and Time." In the life sciences, scientists carry that torch toward the infinitesimal.

We once thought that 200 nanometers—or about half a wavelength of light—was the limit at which we could see the cell's contents in visible light. An optical platform called STORM (stochastic optical reconstruction microscopy), developed by Xiaowei Zhuang of Harvard (who gave a Laureate Lecture here last June), gets around that by switching fluorescent probes on and off to capture overlapping molecules. This approach allows us to see life and the elements that comprise it at about 10 nanometers. The latest Nobel Prize in Chemistry was awarded to microscopists who first surpassed this perceived limit with similar "nanoscopy" systems. Using these platforms, researchers are seeing the most subtle of molecular interactions within cells. And they've discovered organelles that we didn't even know existed before.

Our own school boasts several talented scientists pushing microscopy forward. For instance, James Conway in our Department of Structural Biology studies viruses, including bacteriophages (viruses that infect bacteria—and some believe may be used one day to fight cholera and other pathogenic bacteria in humans), using cryo-electron microscopes. Cryo-EM microscopists preserve the structure of specimens by cooling them to liquid nitrogen temperatures before examining them in the vacuum of the electron microscope. James is now seeing pathogens at 4 angstroms—that's almost atomic resolution. He can even make out chains of amino acids. As he says in our story that begins on p. 30, "It's incredibly exciting . . . I can get a sample, put it in the microscope, and by this evening or tomorrow, I may be the first person to see what a particular virus looks like." And that is likely to translate to novel strategies for combating infectious disease.

Advances in technology pose new questions. (E.g., What is the function of the organelles that we are now seeing for the first time?) The answers are often incomplete and drive us to push the technology further. Research is iterative, and so is my newly enhanced view of the world!

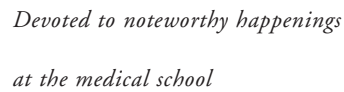
Arthur S. Levine, MD

Senior Vice Chancellor for the Health Sciences

John and Gertrude Petersen Dean, School of Medicine



JOSHUA FRANZOS



In medicine, knowledge comes from experiments and observation. These two sources create different kinds of data—and lots of it—that don't always mesh well. The National Institutes of Health has tapped Pitt to create computational methods that will meld these sources so researchers can better learn what causes diseases.

The work will be done through a new, multi-institute center of excellence with a mouthful of a name: the Center for Causal Discovery of Biomedical Knowledge from Big Data, or CCD. It's one of 11 new NIH-funded centers aimed at turning big data into knowledge (BDzK).

The CCD will develop new computer algorithms to help medical researchers look at the cellular causes of cancer pathways, molecular causes for lung diseases, and how the parts of the brain connect. It will also create new software tools to aid researchers in that work, says Gregory Cooper, an MD/PhD who's vice chair and professor of biomedical informatics at Pitt and director of the CCD.

Cooper is one of three principal investigators on the project, along with Ivet Bahar, PhD Distinguished Professor and the John K. Vries Professor who chairs the Department of Computational and Systems Biology, and Jeremy Berg, PhD director of Pitt's Institute for Personalized Medicine, associate senior vice chancellor for science strategy and planning, health sciences, and Pittsburgh Foundation Professor of Personalized Medicine and professor of computational and systems biology. Collaborating on the CCD are Carnegie Mellon University, Yale University, and the Pittsburgh Supercomputing Center.

Cooper says the \$11 million, four-year project will also train medical researchers on how to use big data tools and models, and analyze their data for causal relationships.

The time for such a center has come, Cooper says. “We have a real opportunity to provide tools to advance biomedical science in the next 10 to 15 years.” —*Michael Fitzgerald*



Bennet Omalu's discovery of chronic traumatic encephalopathy in a former NFL player is a quintessential Pittsburgh story—meds, eds, and tech merging to improve athletes' lives—and Hollywood's come a-knocking. Will Smith will play Omalu, MD/MPH (Fel '00, '02), former Allegheny County forensic pathologist whose autopsy of Steeler Mike Webster sparked debates about football-related head injuries. The movie, *Concussion*, evolved from a *GQ* article by Pitt English prof Jeanne Marie Laskas and was filmed in the Burgh October through January—one of more than a half dozen movies made here in 2014.



Overheard Before the Crisis

A neighbor who just won't turn her music down. Lingering grief after a spouse's death. Sometimes daily stressors are just too much to bear, and their crest doesn't always come during business hours.

In 2008, UPMC and Western Psychiatric Institute and Clinic opened re:solve Crisis Network—a consolidated 24-hour hotline, walk-in clinic, and mobile dispatch that anyone in Allegheny County can use to speak with clinicians and peer counselors during tough situations. We spoke with re:solve's medical director, **John "Jack" Rozel** (Res '04, Fel '05), who's also an MD assistant professor of psychiatry at Pitt.

What set you on this path to crisis psychiatry?

[As a volunteer at a suicide hotline in college], I was just thunderstruck by how much of a difference being on the phone with someone—listening, empathizing with them—often really not saying much, certainly not giving them advice, but saying “tell me about what’s going on,” makes. I’ve really been in the field ever since. And I remember at the time thinking, *Wow, if all I’m doing is listening, imagine if I really knew what I was doing.* I know now, 25 years later, that the most important part is still listening.

What’s a typical re:solve call?

Just like the cardiologist wants to meet someone before a mild angina progresses to a triple bypass, we want to work with people as early as possible. But that also means when someone comes and says, “Hey, I need help from you guys,” that person doesn’t have to be suicidal, that person doesn’t even have to have a psychiatric diagnosis, which sets us apart from other mental health and behavioral health crisis and emergency services out there. We’re really not focused on or especially interested in the diagnosis; we are focused on what’s going on today.

How did re:solve come into being?

What UPMC and WPIC did was spend a lot of time doing focus groups with people living with mental health issues . . . to determine what a crisis center had to be. One of the questions they asked was, If you had a crisis, where would you go? The number one answer was “the emergency department.” Now, an emergency department is great if you have a full-blown emergency or a life-threatening situation. But when you’re feeling really stressed out, we can give you support and help you find your strength. —Interview by Chuck Staresinic; introduction by Robyn K. Coggins

Faculty Snapshots

Professor of pediatrics **Alejandro Hoberman**, an MD, received the Academic Pediatric Association’s Research Award at the Pediatric Academic Societies meeting last year. Hoberman also presented the results of a multicenter study of children with vesicoureteral reflux, or abnormal backward urine flow from the bladder, in children with urinary tract infections. The study showed that giving the kids prophylactic antibiotics in low doses reduced the risk of UTIs by 50 percent compared to placebos.

Juan Carlos Puyana and investigators at four other institutions will use a \$1.6 million grant to expand the use of mobile health and informatics technologies in low and middle income countries. The effort is part of a National Institutes of Health–funded Fogarty International Center program. Puyana’s project will develop an electronic medical record designed for trauma patients in Colombia, Paraguay, and Guatemala. His team will train researchers in information and communication technology and address expertise gaps. Puyana is an MD associate professor of surgery, clinical and translational science, and critical care medicine.

Ericka Fink earned a \$1.87 million grant from the Patient-Centered Outcomes Research Institute to study rehabilitation in children with acute brain injuries. Fink is an MD and associate professor of pediatrics, of critical care medicine, and of clinical and translational science. Her three-year study will compare standard treatment to care supplemented with physical, occupational, and speech therapies within 48 hours of injury. Fink’s team will evaluate whether early rehabilitation therapies improve children’s cognitive, physical, and quality of health outcomes.

The British Medical Association awarded the fifth edition of *Bailey’s Head and Neck Surgery: Otolaryngology* first place in the surgical subspecialties category at their annual book awards, outshining 640 other entries. The “outstanding” text was edited by otolaryngology and communication science and disorders professors **Jonas Johnson**, an MD, and **Clark Rosen**, an MD and founding director of Pitt’s Voice Center. Johnson is a Distinguished Service Professor, the Dr. Eugene N. Myers Professor, and chair of otolaryngology; he also holds appointments in radiation oncology and in oral and maxillofacial surgery. —RKC



Hoberman



Puyana



Fink



Johnson



Rosen

PHOTO BY KIPP MADISON, ILLUSTRATION BY MICHAEL LOTENBERG

Predicting Rejection

Different people have different immune system responses—that’s an obvious but challenging fact to work around, especially in organ transplants in children. Kids’ immune systems are already immature, plus most children who need transplants have a weakened immune response. That makes managing rejection tricky: Dial up immunosuppressive drugs too high, and they can cause lymphoma; drop them too low, and patients risk rejection.

The doctor’s tool to detect rejection has been a biopsy—but there was no tool to predict it. Now Rakesh Sindhi, MD professor of surgery, and colleagues have developed a test that can.

Pleximmune, approved by the FDA this August, is a cell-based test that can predict acute cellular rejection with 80 percent accuracy. Sindhi’s team focused on liver and intestine transplants; tests for kidney and other organ transplants are in development.

“The liver . . . likes to shake hands with any immune system,” says Sindhi, who’s also codirector of clinical pediatric transplantation programs and research at Children’s Hospital of Pittsburgh of UPMC. “The intestine . . . is the exact opposite. Like every organ that sits at the interface of the body and the environment, it’s constantly seeing a bunch of bugs; [so] these organs tend to have lots of rejection”—a staggering 75 percent likelihood of rejection in the first five years after transplantation, in fact.

To develop his risk predictor, Sindhi first tested nonspecific cells against recipient cells using flow cytometry to determine a baseline immune system response. Then he tested donor cells just before transplantation against recipient cells. Express the two results as a fraction, and you get a personalized rejection risk index.

“Sometimes the patient looks fine,” Sindhi says, “but the test tells you otherwise.” —RKC



CATHERINE LAZURE

The Genetics of Autism

No one fully understands the genetic causes of autism, says Bernie Devlin, a PhD who has been studying the subject for 10 years. But researchers are starting to assemble the pieces. “What we are trying to provide are the genetic puzzle pieces to understand the neurobiology,” he says.

To that end, the University of Pittsburgh’s Devlin, a professor of psychiatry, of human genetics, and of clinical and translational science, coauthored two studies published in *Nature* and *Nature Genetics* in 2014.

Researchers know that the genetic architecture of autism spectrum disorder (ASD) involves interplay between common and rare genetic variants. But to what degree might autism be linked to rare variants versus an unusual expression of common ones?

In their *Nature Genetics* letter, Devlin and collaborators reported that after analyzing 3,871 subjects with ASD and their genetic makeup, they estimated that 48 percent of the genetic risk of autism comes from common variants of genes prevalent in the entire population. Each of these has a very small impact on risk, notes Devlin. Yet it’s important to learn more about the roles they play, he says.

What about the other 52 percent of genetic risk? Much of that remains to be characterized, but the scientists’ *Nature* paper points to suites of genes involved in the risk.

Their findings don’t mean much to potential parents just yet, says Devlin. But now another piece of the puzzle is laid out. —Nick Keppler

FOOTNOTE

Search for “anterior cruciate ligament” articles, and you’ll run into familiar names from Pitt orthopaedic surgery. In 2014, faculty from the Pennsylvania Commonwealth System of Higher Education claimed the most authors overall; Pitt faculty published 536 of the PCSHE’s 582 publications. (Freddie Fu authored 275 of those.) All the publications on the subject in Canada totaled 703.



EMILY HEART(MAP)S PITTSBURGH

It's a bit surprising that just last year, there wasn't a cohesive record of where to find automated external defibrillators (AED) in U.S. cities. Lucky for us, Pitt's own fourth-year bioengineering PhD student Emily Bayer found 507 of the heart-jolting devices throughout Allegheny County in October 2014.

An ongoing, multicity crowdsourcing project called HeartMap challenges citizens to find defibrillators in their respective cities and report back, so HeartMap can create a central database to aid emergency services (including 911 operators). A Pitt/University of Washington team of emergency medicine researchers will also be probing the data.

Bayer followed some pretty interesting leads: "It was amazing to learn about all the different types of people who have used these devices to save lives in Pittsburgh—from police officers to Boy Scouts to a ticket scalper who just happened to be at the right place at the right time."

How did Bayer get to claim HeartMap's \$5,000 grand prize? By "setting a goal . . . to find at least 20 to 30 a day and spending two to three hours a night following leads."

—Nick Moffitt

Appointments

Children's Hospital of Pittsburgh of UPMC has recruited cardiologist **Bernhard Kühn** from Harvard University as its director of research for cardiology. Kühn, an MD, is also the third scholar in the Richard King Mellon Foundation Institute for Pediatric Research, a program that allows talented young researchers to pursue promising projects. Kühn's research is focused on new ways to coax heart muscle to repair itself, to prevent and treat heart failure in children.

Robert P. Edwards (MD '84, Res '89) assumed the chair of obstetrics, gynecology, and reproductive sciences this January, after the retirement of longtime professor and chair, W. Allen Hogge. Edwards has been a full professor in the department since 2008 and previously served as its vice chair for clinical affairs, as well as the director of gynecologic oncology research and outreach at Magee-Womens Hospital of UPMC. His work on gynecological cancers and human papilloma virus has resulted in more than 175 peer-reviewed papers and numerous clinical trials.

James Herman, an MD cancer epigenetics researcher from Johns Hopkins University, has

joined Pitt. He is a professor of medicine and coleader of the Lung Cancer Program for the University of Pittsburgh Cancer Institute (UPCI). Some of his research investigates gene silencing and the way that DNA methylation changes can alter gene expression. As a medical oncologist, he will care for patients with thoracic malignancies at the VA Pittsburgh Healthcare System.

Jules Sumkin, a DO, is now chair of the Department of Radiology. Sumkin is the chief of radiology at Magee-Womens Hospital of UPMC and codirector of the Women's Imaging Fellowship, where radiologists are trained on breast imaging techniques like MRI and tomosynthesis—a newer imaging approach that he helped develop—and obstetrical ultrasound. Sumkin holds the UPMC Chair in Women's Imaging at Pitt. He has been with the University since 1986 and began the development of tomosynthesis in 2005. —NM



Kühn



Edwards



Herman



Sumkin

NIH AWARDS*

\$457 MILLION

\$1.46 BILLION

\$185 MILLION

\$2.19 BILLION

2.52 MILLION SQ. FT.

\$525 MILLION

\$702 MILLION

1.35 MILLION SQ. FT.

2014

1998

NIH AWARDS TO FACULTY
TOP 15 EDUCATIONAL INSTITUTIONS
Award dollars in millions.

INSTITUTION	RANK	AWARD
Harvard University	1	\$1,523
University of Pennsylvania	2	\$634
Johns Hopkins University	3	\$630
University of California, San Francisco	4	\$614
University of Pittsburgh	5	\$457
University of California, San Diego	6	\$446
UCLA	7	\$445
University of Washington	8	\$438
University of Michigan	9	\$418
University of North Carolina at Chapel Hill	10	\$396
Washington University in St. Louis	11	\$392
Stanford University	12	\$386
Duke University	13	\$372
Yale University	14	\$361
Columbia University	15	\$350

Source: NIH Web site, Dec. 10, 2014 (Awards by Organization)

GOING UP

It's been 16 productive years since Arthur S. Levine, the John and Gertrude Petersen Dean and senior vice chancellor for the health sciences, was recruited to the University of Pittsburgh. Take a gander at some of these impressive figures on the health sciences. Pitt has made an extraordinary climb during that tenure—ascending as the country has lived through some serious swells and groans (mostly groans) in National Institutes of Health funding. Things won't get easier with clinical revenue streams likely diminishing. Strategic community, industry, and international partnerships have become key. And with long-standing talent and topnotch recruits streaming across campus, Levine is confident Pitt will continue to rise.

—Robyn K. Coggins and Erica Lloyd

—Illustration by Michael Lotenero

* Includes University-wide NIH program funding. Figures on endowments, operating revenues, and research space are for the health sciences schools.

INVESTIGATIONS

Explorations and revelations taking place in the medical school



A century ago, newborns with salty skin often did not last long. They would die of malnutrition from cystic fibrosis. Medical advances eventually addressed the issues of nutrient absorption that the disease creates by damaging the pancreas, and today people mostly think of CF as a lung disease. Yet the disease's roots offer the potential for new discoveries. Pitt researchers recently identified several genetic mutations on the CF gene (CFTR) that do not cause pulmonary problems but can develop into debilitating pancreatitis.

MYSTERY CASES SOLVED

CYSTIC FIBROSIS'S CULPRIT GENE UNDERSTOOD ANEW IN PANCREATITIS

BY NANCY AVERETT

A hundred years ago, the picture of cystic fibrosis (CF) looked quite different. “Back then, when a nursemaid kissed a baby and tasted salt, she knew the baby would die,” says the University of Pittsburgh’s David Whitcomb, who is an MD/PhD professor of medicine, of cell biology, and of human genetics, and chief of gastroenterology, hepatology, and nutrition. Whitcomb is also the Giant Eagle Professor of Cancer Genetics.

CF is caused by abnormalities of the cystic fibrosis transmembrane receptor (CFTR) gene. The CFTR protein forms a channel for chloride and other ions so that they can move in and out of the cells that line certain glands—including sweat glands—and the sinuses, lungs, intestines, and the pancreas.

In fact, the first organ vulnerable to severe damage from CF is the pancreas. CF can cause pancreatic cysts and fibrosis (hence the name for the disease), as well as the inability to secrete digestive enzymes. Today, CF is thought of as a pulmonary disease, but a century ago patients rarely lived long enough to develop lung problems.

As infants, children with CF died of malnutrition because the food they ate could not be digested and passed through the body. “Even though the babies would eat well, they would wither away,” Whitcomb says. This pancreatic disease is also called chronic pancreatitis. Though doctors began treatments for the malnutrition issues using replacement enzymes in the early 1900s, it wasn’t until the 1980s that they were able to coordinate specialized treatments reliably. Then researchers largely turned their attention to the next major organ that CF overtakes, the lung.

However, Whitcomb and collaborators decided to take a second look at the origins of the disease in patients without lung disease. For Whitcomb it was a quest: “My career goal is to understand why some people, for no obvious reason, get chronic pancreatitis, with ongoing pancreatic inflammation and irreversible scarring.” Perhaps a better understanding of CFTR would hold clues.

Here’s how the CFTR channel is supposed to work: Movement of ions results in the movement of water (by osmosis), resulting in hydration of mucus and secretion of fluids.

When the channel isn’t working, fluid secretion is drastically reduced, mucus builds, and organs are damaged. The lungs become scarred because bacteria cannot be removed; the pancreas is damaged because the digestive enzymes become trapped in the pancreas and destroy it; and sodium chloride cannot be removed from the sweat gland, causing salt to be left on the skin after the water evaporates from sweat.

Although CFTR has been known primarily as a chloride channel, Whitcomb and colleagues have been testing the theory that in the pancreas, CFTR functions mainly as a bicarbonate channel. In the pancreatic duct, bicarbonate stabilizes the key digestive enzyme trypsinogen, which is then secreted into the small intestine to trigger activation of the other pancreatic digestive enzymes to dissolve food into a liquid so that it can be absorbed by the small intestine. When bicarbonate flow is compromised, the enzymes are not secreted; they become active in the wrong place and begin to digest the pancreas itself.

The investigators set out to identify atypical CFTR mutations: those that didn’t impede chloride but did affect bicarbonate flow.

Whitcomb, with Pitt mathematics professor Bard Ermentrout, a PhD, first built a mathematical model of the pancreatic duct cells to predict which molecules were critical to bicarbonate movement into the duct. They predicted that the key molecule was CFTR.

The researchers then genotyped patients who had pancreatic disease but not lung disease to see if they had CFTR mutations. “We took 10 years to collect more than 1,000 patients from 30 centers from around the country,” Whitcomb says. “We looked at every genetic change that had ever been reported in the CFTR gene in patients with pancreatic disease

and then tested to see whether or not those abnormalities were popping up in our cases of otherwise unexplained pancreatitis.” They were. The researchers found several CFTR abnormalities occurring in patients who did not have CF but did have pancreatitis.

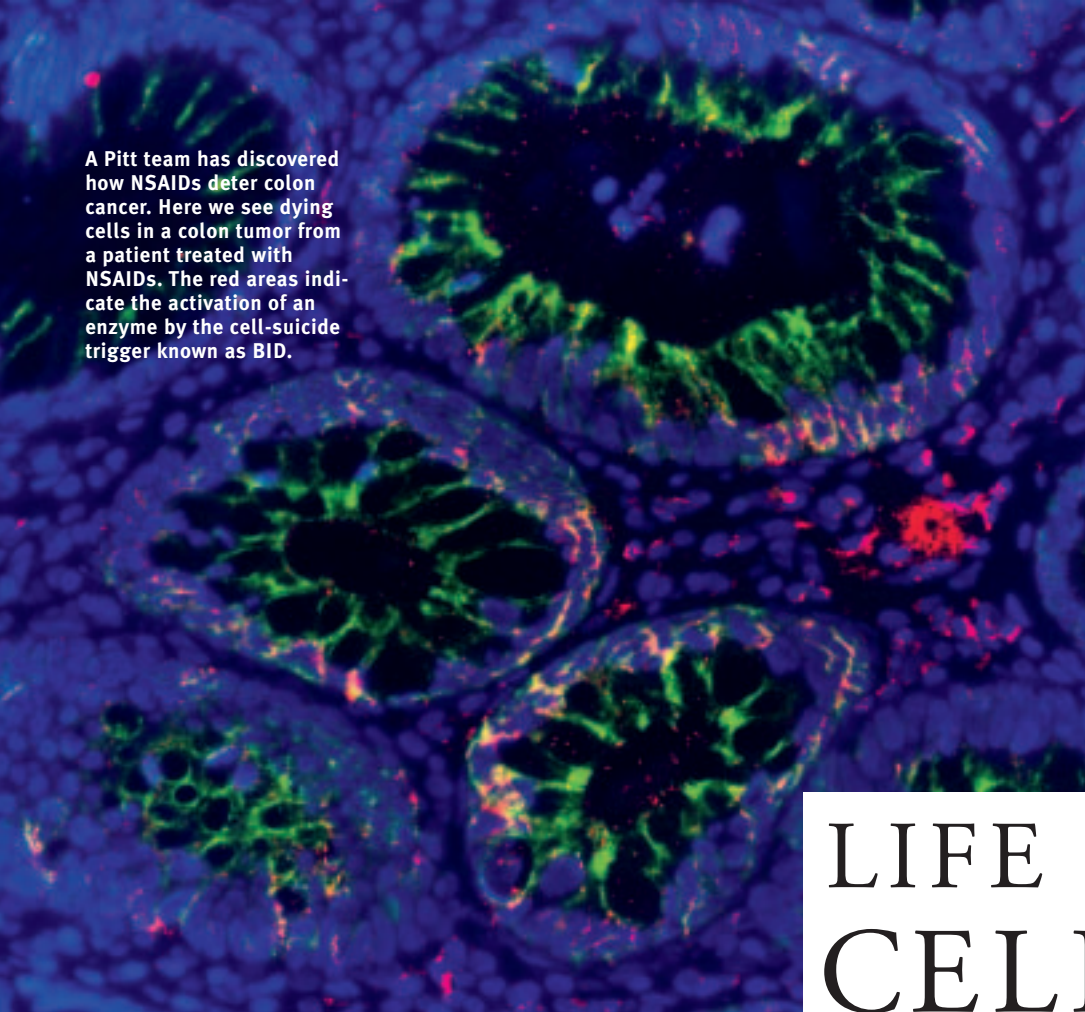
Then, Min Goo Lee, professor of pharmacology at Yonsei University in Seoul, cloned nine CFTR variations, put them into living cells, and measured whether chloride and bicarbonate went through in the normal way. Chloride did; bicarbonate did not—just as predicted by the mathematical model.

Next, Ivet Bahar, a PhD Distinguished Professor who holds the John K. Vries Chair of Computational and Systems Biology at Pitt, built a computer model of the CFTR molecule, marked where the mutations changed the amino acid sequence, and simulated the effect of the altered amino acid on CFTR channel function. In some cases, the abnormalities were near the opening of the channel through which the compounds flow; the channel was wide enough for chloride but not bicarbonate. In others, the mutations interfered with a hinge that shifts a key molecule so that it secreted bicarbonate rather than chloride.

The researchers found patients who had one or more of the nine mutations were also more likely to have chronic sinusitis. Men with the mutation were also more likely to be infertile. Both the sinuses and vas deferens duct of the male reproductive system also use CFTR to secrete bicarbonate.

Whitcomb says the study will allow doctors to identify more patients at risk for pancreatitis earlier and to offer better treatment. Their most recent paper was published in the July issue of *PLOS Genetics*, with Pitt PhDs Jessica LaRusch, Ignacio General, and also South Korean researcher Jinsei Jung as first authors.

“This was a reverse engineering problem,” says Whitcomb, “and it required many different kinds of engineers to figure it out.” ■



A Pitt team has discovered how NSAIDs deter colon cancer. Here we see dying cells in a colon tumor from a patient treated with NSAIDs. The red areas indicate the activation of an enzyme by the cell-suicide trigger known as BID.

COURTESY ZHANG LAB

HOW NSAIDS SEND COLON
CANCER ON A SUICIDE MISSION
BY HEATHER BOERNER

LIFE AND CELL DEATH

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have long been associated with reduced rates of colorectal cancer; now scientists are gaining insight into the whys and hows behind these life-saving effects: suicide pathways, death receptors, and warped genes.

“What our study provides is a clue as to why NSAIDs selectively kill precancerous cells and leave healthy cells alone,” says Lin Zhang, a PhD professor of pharmacology and chemical biology at the University of Pittsburgh and the University of Pittsburgh Cancer Institute, as well as a partner with UPMC CancerCenter. Zhang is coauthor of a paper on NSAIDs with PhD research associate Brian Leibowitz that was recently published in the *Proceedings of the National Academy of Sciences*.

Leibowitz, Zhang, and colleagues started with a mouse model that has a mutation in codon 850 in one copy of the adenomatous polyposis coli (APC) gene—a gene long known to be associated with the development of cancerous polyps in the colon. Then they unleashed NSAIDs on the mouse’s cells.

The NSAIDs attacked cells they’d normally

pass over. Bingo.

The team found that the loss of the remaining copy of the APC gene sends out a signal to NSAIDs to destroy, helping them get rid of cells that might turn into colorectal cancer.

“Here, we show that’s how NSAIDs work, by targeting cells with a specific mutation,” says Zhang. “It’s really exciting.”

They got the same results in human cells.

But how exactly NSAIDs manage to seek and destroy APC-mutated cells that lead to cancer was still a mystery. So Zhang and colleagues set up another experiment to track the progress of NSAIDs in the cell.

The answer, it turned out, was what’s known as BID—the BH3 interacting domain death agonist—which triggers cell suicide, also known as apoptosis. It appears that BID is activated by the so-called “death receptor” pathway, and signals to cells containing the mutated genes to self-destruct.

Once it is activated by the death receptor, BID then activates a protein called Bax, which presses a second self-destruct button—another suicide pathway. Put BID and Bax together, and the cells don’t seem to stand a chance. And although scientists knew how the death receptor and the suicide pathways worked before,

what Zhang and colleagues showed was that BID is the trigger that sets cell death in motion.

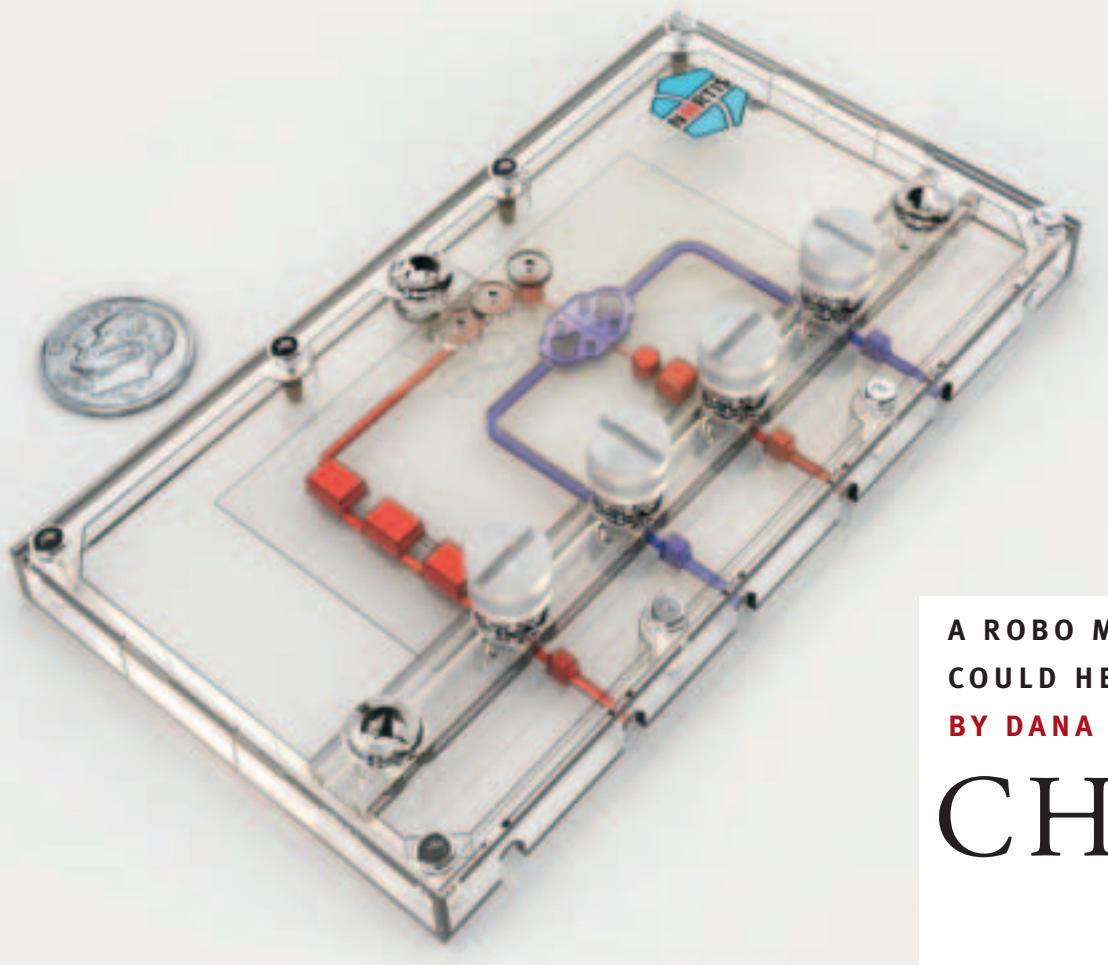
“BID is the cross-talker, the connector in this process,” says Zhang. “It’s the two pathways together that kill the cells.”

Next up for Zhang and his colleagues: Identify the exact molecules to which NSAIDs bind for BID activation. Knowing that should allow researchers to develop small-molecule drugs that bind to those receptors and have the same effects on established cancer cells that NSAIDs have on nascent ones.

Zhang and his team are also searching for other, relatively nontoxic natural supplements—such as dietary components and herbal medicine treatments—that might target the same APC mutations and use the same pathways.

Zhang says he would like to give patients options to prevent cancer before it starts and bring evidence-based medicine to the widely unregulated world of prophylactic supplements.

“Right now, people aren’t sure which natural products have the right mechanism,” he says. “We can provide clues for other products that are well tolerated and can be used for a long period of time to prevent cancer.” ■



Small chip, big change. A team of Pitt researchers is further developing a 3-D, microfluidic model that mimics the structure and function of the human liver's acinus.

**A ROBO MODEL OF THE ORGAN
COULD HELP DRUG DEVELOPMENT
BY DANA YATES**

CHIPPED LIVER

The liver is a master multitasker. The largest internal human organ, it performs hundreds of functions. Among those: fighting infections, producing proteins and hormones, and controlling blood sugar. And, of particular interest to drug researchers, the liver also plays a key role in metabolizing medications. As part of an effort to enhance predictions of drug safety and effectiveness, researchers at the University of Pittsburgh received \$5.8 million from the National Institutes of Health (NIH) to develop a miniature model of a key component of this mighty organ. They are creating what's known as a "tissue chip."

Pitt's NIH funding supports the next phase of the agency's Tissue Chip for Drug Screening program, which is refining existing chips and then combining them into an integrated system to simulate the human body's complex functions.

"We've seen huge advances in this microphysiology systems research during the last two years," says Pitt principal investigator D. Lansing Taylor, a PhD, the Allegheny Foundation Professor of Computational and Systems Biology, and director of Pitt's Drug Discovery Institute. "It will take time," says Taylor, "but there's a good possibility that we

will one day replace animal testing. This is a powerful tool for basic physiology research."

MODEL UNIT

The new liver model will focus on the acinus, the smallest functional unit of the liver. The Pitt team is further developing a 3-D model that mimics the acinus's structure and activities. The chip will simulate nonalcoholic fatty liver disease, primary liver cancer, liver cancer that has spread from the breast, and other kinds of liver damage.

DRUG DE-LIVERABLES

Pitt researchers will integrate their liver chip with other human tissue chips of the kidney and gut—vehicles that are also vital to drug absorption and metabolism. (Those models are being developed at Johns Hopkins University and the University of Washington.)

"Animal [models] aren't very predictive of human disease. In fact, rodents are only 50 percent predictive of a human [liver's] reaction to a treatment. That's basically a coin toss," says Taylor.

According to the National Academy of Sciences, more than 30 percent of medications that show promise in preclinical studies involving animal models ultimately fail in human

trials because they are determined to be toxic. The cells in tissue chips mimic human organs; so scientists are hoping the new technology will let them better predict how well drugs will perform in clinical studies. Those data could reduce the time and money that it takes to develop effective drugs.

THE RECIPE

The process begins by bringing together the fields of nanotechnology, biology, and tissue engineering to make an organ. To develop their model, the Pitt researchers are using cells from resections, surgeries that remove all or a portion of the liver. (Eventually, they hope to use liver cells obtained from stem cells, as well as three other cell types.) The microphysiology systems are built on transparent microchips that feature human cells as well as intricate fluid delivery systems.

HEPATO-TRACKING

The liver platform will have fluorescence-based biosensors that provide real-time physiological readouts and spectrometry measurements that determine toxicity.

The team also will build a database to manage, track, analyze, and model the data collected from the miniature platform. ■



For decades, Pitt has been an “intellectual engine” for prehospital care, starting with CPR and the first highly trained paramedics.

PITT PEOPLE PAVED THE WAY

TEXT BY JENNY BLAIR WITH ERICA LLOYD

ILLUSTRATIONS BY STACY INNERST

THE RUSH TO THE HOSPITAL

Paul Paris (MD '76), a University of Pittsburgh professor of emergency medicine and the ERMI Professor of Healthcare Quality, has spent much of his career studying prehospital emergency care. But he remembers the pre-EMS (emergency medical service) era all too well. In 1972, when he was a medical student at Pitt, a police paddy wagon was called to transport his gravely ill mother to the hospital. At the time, no citywide EMS existed in Pittsburgh. American ambulances then often carried little more than first aid supplies anyway.

Things soon changed. Prehospital care began to take shape. Ambulances began to deliver care as well as deliver patients. Cities founded ambulance services. Many of these advances were sparked here, under the guidance and scrutiny of Pitt researchers.

Just the idea that rescuers should follow a protocol, for example, was preached early by Pitt luminary, the late Peter Safar, MD Distinguished Professor of Resuscitation Medicine. In addition to co-inventing and then advocating for CPR, Safar developed the resuscitation ABCs (airway, breathing, circulation) in the late 1950s. The mnemonic has, in various forms, been the foundation of emergency care ever since.

National standards were born here, too. After a 1966 white paper decried the dismal survival rates for auto and other accidents in this country—trauma victims had a better chance on the battlefield—the nation began to standardize prehospital care. It was Safar and critical care fellow-turned-faculty member the late Nancy Caroline, an MD, who developed a curriculum for paramedics here in the 1970s. She also authored the nation's first textbook for paramedics, which was published in 1979. Her *Emergency Care in the Streets* is now in its seventh edition.

After many an ambulance ride-along, Caroline knew what she was talking about. Between 1967 and 1975, Pittsburgh hosted one of the country's first professional

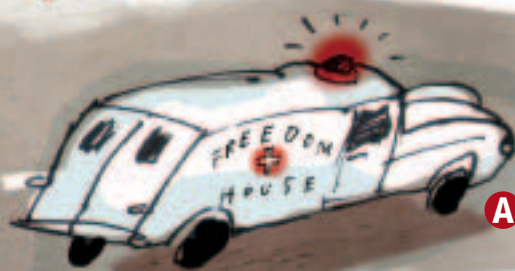


A ROUTE BROUGHT TO YOU

ambulance services offering advanced care. Cofounded by Safar with the Falk Foundation's Phil Hallen, Freedom House Ambulance Service was staffed by African American emergency medicine technicians; they were among the nation's first to be trained to a high standard. Caroline served for a year as its director and frequently joined the paramedics, who served African American neighborhoods (that had been barely served previously) and other parts of the city, as well. When the City of Pittsburgh set up its own EMS program in the 1970s, Pitt's future founding chief of the Division of Emergency Medicine, Ronald Stewart, an MD, signed on as the city's medical director. (Stewart, who is from Nova Scotia, experienced baptism by fire in EMS with LA County's progressive program, of which he was the founding medical director.) Many EMS program leaders throughout the nation cut their teeth here, notes Paris.

The U.S. Department of Transportation adopted Caroline's curriculum for Freedom House in 1977, and recently called it "the foundation for all prehospital advanced life support education today." National curricula, guidelines, and textbooks for first responders continue to come from the efforts of Pitt people, notably the University's Walt Stoy, a paramedic and PhD professor and director of emergency medicine in the School of Health and Rehabilitation Sciences.

Prehospital Emergency Care, edited since its 1997 founding by Pitt's James Menegazzi, a PhD, was the first peer-reviewed EMS journal. By 2010, EMS had gained enough scientific



backing to become an official subspecialty of the American Board of Medical Specialties. Much of that backing came from Pitt faculty. Pitt has been an "intellectual engine" for many EMS advancements, notes Donald Yealy, an MD and chair of the School of Medicine's Department of Emergency Medicine. In some cases, Pitt people invented an idea that caught on; in others, they studied and spearheaded ideas born elsewhere. But every American EMS crew today does what it does in large part because of Pitt.

A AMBULANCES THAT WORKED

When Pittsburgh antipoverty activists teamed up with Pitt's Peter Safar to create the Freedom House Ambulance Service, they didn't skimp on training. Its African American paramedics may have been the country's most skilled, using ECGs and airway equipment at a time when many ambulances carried only first aid supplies or less. Word of their competence got around. (Eventually, police officers would call Freedom House for their own family members in need, instead of calling the police.) The U.S. Department of Transportation has noted that Freedom House technicians were "pioneers in the field of EMS." (The service's director Nancy Caroline would later be nicknamed the "Mother Teresa of Israel," after leaving Pitt in the '70s to build a prehospital program in that country.) A recently placed historical marker on Centre Avenue honors the Freedom House team.

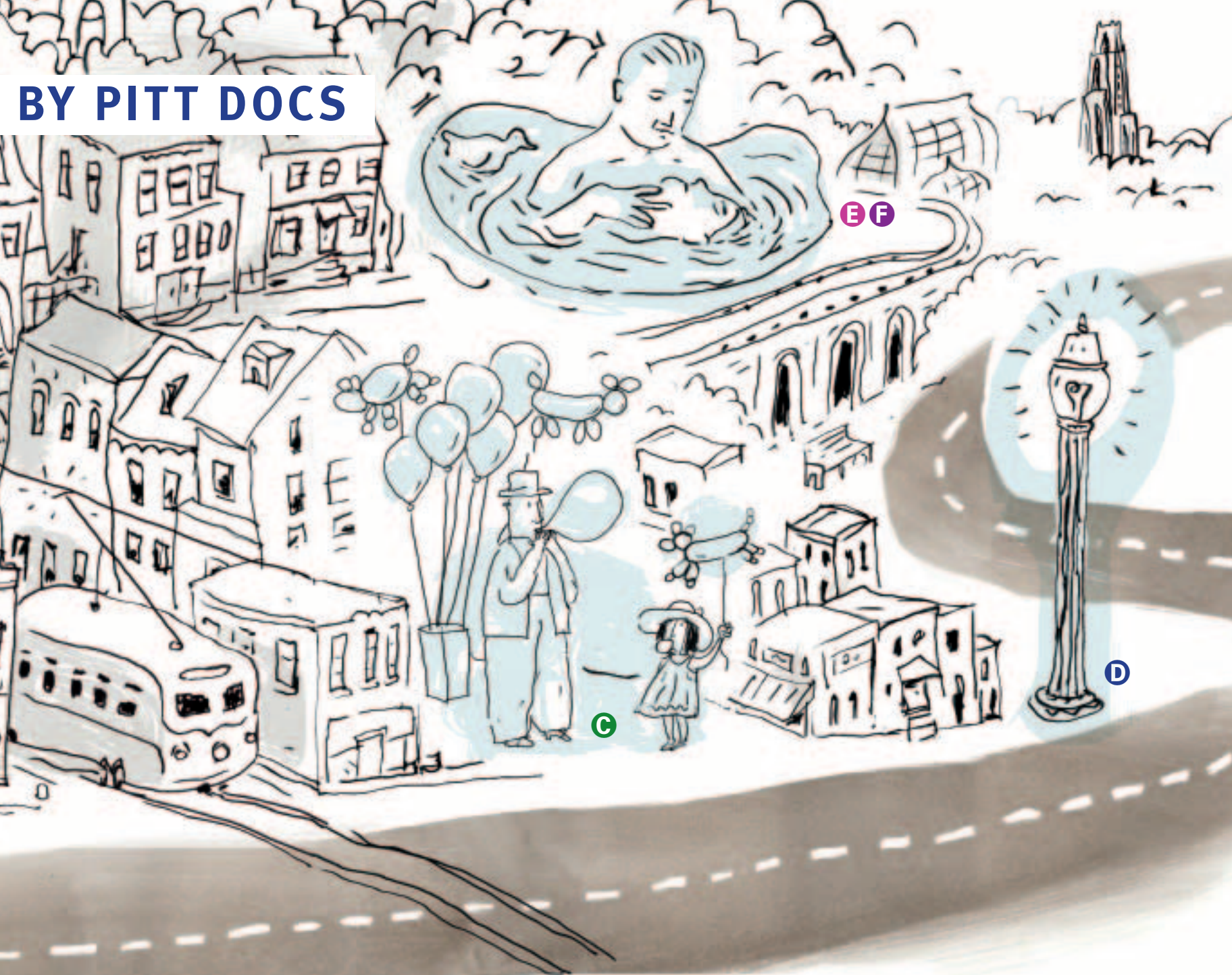
To read more of Freedom House's extraordinary story, see tinyurl.com/freedomh2004

B OXYGEN NATION

The gentle press of a pulse oximeter on a patient's earlobe or fingertip tells paramedics whether a patient's hemoglobin is saturated with oxygen or whether it's time to, say, secure a path to the lungs or give oxygen. Pitt researchers studied and adopted the measurement of this "fifth vital sign" in prehospital care ahead of many other centers, pointing out in a 1989 study of its use in air medical transport that the oximeter was often the only sign the patient was desaturating to life-threateningly low levels of oxygen. Around the same time, pulse ox monitors were becoming commonplace in hospitals. More prehospital studies followed, and the devices are now ubiquitous in medevac helicopters and ambulances.

C EARLY AIRWAY ACCESS

Sometimes the best way to make air enter the lungs is to place a breathing tube. Teaching paramedics how



D LIGHTING THE WAY

Intubation is tricky: You're apt to push the tube down the esophagus instead of the trachea. Ronald Stewart, Paul Paris, and others did the first study of the use of a lighted stylet—that is, a light pushed into the tube itself—for prehospital intubations. They used a surgical light that Stewart shrink-wrapped to keep the bulb from falling into the patient's lungs. In the late '80s, an updated version of the stylet, then found in many paramedic toolkits, captured interest and spurred other airway innovations.

E ABCs & CPR

After publishing a 1958 landmark paper on mouth-to-mouth ventilation, Peter Safar combined that expertise with Johns Hopkins colleagues' findings on chest compressions to develop the ABCs (airway, breathing, and circulation) of resuscitation, the now-iconic system for CPR training. With Norwegian anesthesiologist Bjorn Lind and toymaker Asmund Laerdal, Safar helped create the CPR mannequin Resusci Anne in 1960. (For more of the story behind Anne, see p. 40.) As founding chair of Pitt's Department of Anesthesiology in the 1960s and '70s, Safar advocated so strongly for CPR that he earned

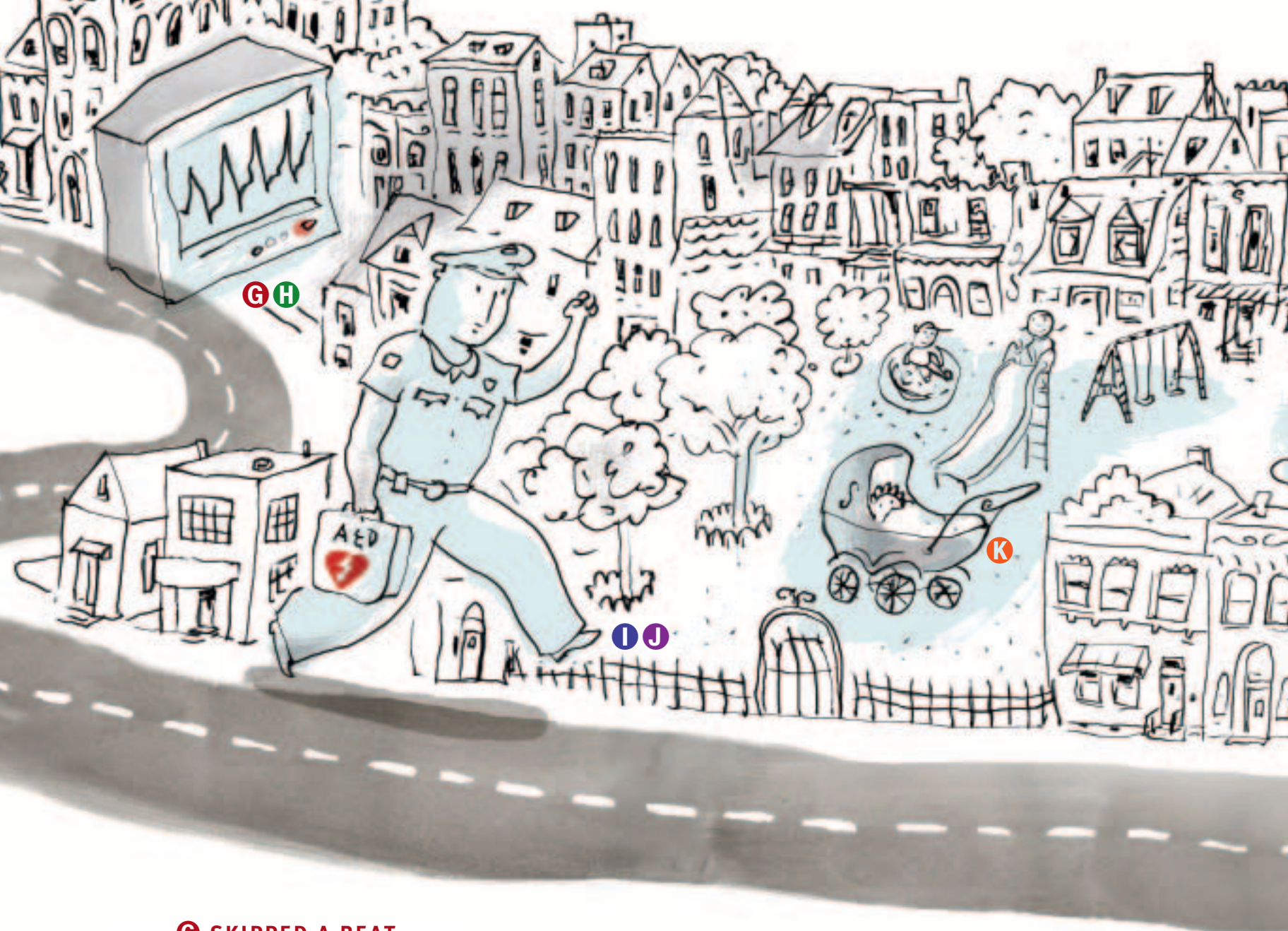
the nickname the "father of CPR." In 1979, he founded what is now called the Safar Center for Resuscitation Research at Pitt.

To read more about Peter Safar's monumental contributions: tinyurl.com/Safar-Oct99

F CPR QUALITY

The right compression depth, full chest recoil, proper speed, and no interruptions: It's not enough just to give CPR; you've got to do it right. Sloppy CPR can doom a patient. Following two studies that warned of poor-quality CPR in American hospitals and Norwegian EMS units, Pitt researchers like Clifton Callaway and James Menegazzi began to study the issue. CPR is much less effective, they found, if defibrillation is involved, if rescuers pause after shocking the heart, or if they're doing it on a moving stretcher instead of the floor. Thanks to insights like these, as well as improved hospital care, survival rates to discharge for prehospital cardiac arrest care have more than doubled in Pittsburgh since the late '90s, from about 6 percent to 15 percent. The nationwide Resuscitation Outcomes Consortium reports similar trends in the past 10 years. That translates to tens of thousands of lives saved a year, notes Paul Paris.

was a far-out idea when Pitt researchers began doing so in the '70s, a time when anesthesiologists weren't sure they liked the idea of even emergency medicine physicians encroaching on what was traditionally their territory. But Ronald Stewart's 1984 study in *Chest* showed a more than 94 percent success rate in cardiac arrest or comatose patients in the field. These days, most cardiopulmonary arrest patients in the United States receive a prehospital breathing tube. Yet Pitt has continued to revisit the wisdom of the practice. In the 2000s, Henry Wang, an MD, then an emergency medicine faculty member at Pitt, pointed out that some medics go years between intubations. Studying field intubations, he found they can interrupt CPR, replace less risky options like noninvasive positive airway pressure masks, and fail all too often. Wang's colleagues, including Pitt's Clifton Callaway, an MD (Res '96), and Jestin Carlson, an MD (Res '10, Fel '12), have been monitoring field intubations with video to help determine what works and what doesn't. "This and other research," says Paul Paris, "has helped define the best tools and indications for airway management."



G SKIPPED A BEAT

Paroxysmal supraventricular tachycardia (PSVT) is a speedy heart rhythm that can sometimes keep the heart from having enough time to fill. To treat dangerous bouts, providers can use a drug called adenosine, which “pauses” the heart briefly. The provider pushes it in fast, eyeing the monitor. The heart flatlines, and the patient experiences what is commonly described as a kick in the chest or a feeling of doom. When the drug wears off a few seconds later, a normal beat often resumes. Brows are wiped. Pitt was the first center to study adenosine for PSVT in the prehospital setting. Now it’s part of standard Advanced Cardiac Life Support protocol and the Pitt-authored paramedic National Standard Curriculum.

H STICKER SHOCK

A pacemaker can save a life in cardiac arrest brought on by a slow heart rate, but it doesn’t have to be the implanted kind. Shocks to the surface of the chest can pace the heart, too, if the electrodes are stuck on soon after the deadly rhythm begins. In a series of studies in the late ’80s, Pitt’s Paul Paris and Ronald Stewart did early investigations of transcutaneous pacing (which uses external pads) in the field. The researchers also subjected brave resident volunteers to the procedure, including Vincent Mosesso Jr. (MD ’88, Res ’91), who is now a professor of emergency medicine and medical director for prehospital care at UPMC. The City of Pittsburgh’s EMS system adopted transcutaneous pacing in 1993.

I FUZZ BUZZ

In an era when automatic defibrillators are in every mall, it’s worth remembering that there was a time when only health care workers were trusted with them. But police often arrive before paramedics at the scene of an emergency. So in the early ’90s, Vincent Mosesso Jr. organized a pilot program for police—one of the first two groups to do so nationwide. The studies found that when police did arrive before EMS and shock patients, the patients were 10 times more likely to survive to hospital discharge than those shocked when EMS arrived. Today, about three-quarters of the country’s state police agencies train officers to operate defibrillators.

J DEFIB FOR LAYPEOPLE

On his birthday in 2001, a Washington, D.C., lawyer named Richard Brown was jumping rope at the gym when he collapsed in cardiac arrest. Trainers leapt to perform CPR, then defibrillated him and restored a normal rhythm. The very automated external defibrillator (AED) that saved Brown’s life was one he himself had urged the gym to get just weeks earlier after a friend had collapsed and died there. Brown is now executive director of the Sudden Cardiac Arrest Association, a patient-led advocacy group originating from Pitt. The organization, formerly known as the National Center for Early Defibrillation, was launched in 2000 by Pitt’s Paul Paris and Vincent Mosesso Jr. as a way to expand

access to AEDs after a pilot program showed that city police could use them effectively (see “Fuzz Buzz”). Sponsors proffered the pros a large grant to establish a national center of excellence, and the association has since offered advice and resources for starting AED programs. As of 2012, roughly a million AEDs were in place around the country, with half a billion dollars spent annually placing more. (Though we are just figuring out where they all are; see p. 6.)

K ALL THUMBS

Rescuers of infants in cardiorespiratory arrest have long been taught to push on the chest with two fingers. Pitt’s James Menegazzi was the first to examine the option of an alternative two-thumb infant CPR method in a series of piglet studies beginning in 1993. The two-thumb method, he found, is easier and delivers a higher blood pressure to the arrest victim. Since 2000, it’s been the American Heart Association’s method of choice for reviving infants when there are two professional rescuers present.

L COMFORT ZONE

While pain management in ambulances still isn’t adequate—recent studies found astonishingly high rates of untreated pain from broken limbs—EMS crews do have good options. For decades, Pitt people have been evaluat-



ing ways to not only save lives, but also make people comfortable and find calm in emergencies. A 1983 Pittsburgh study found that a 50/50 oxygen/nitrous oxide (laughing gas) mix was a safe and effective option for pain relief in ambulances. Yet no company was interested in funding a study on generic nitrous oxide to gain FDA approval. Since then, Pitt faculty members have advocated for paramedics to administer other analgesics, notably fentanyl. Perhaps most importantly, as textbook authors and national leaders on prehospital pain management, Pitt docs encourage EMS personnel to take people's need for relief seriously.

M SKY CALL

If you're struck by sudden chest pain at 35,000 feet, there's a good chance Pitt docs will get involved. UPMC's STAT-MD Commercial Airline Consultation Services is one of only two such centers in the nation, handling hundreds of calls from commercial flights every month. In a 2013 *New England Journal of Medicine* article, Pitt emergency medicine physicians Donald Yealy (Res '88, Fel '89), who chairs Pitt's department, and Christian Martin-Gill (Res '08, Fel '10) reported that most commercial-flight emergencies involve syncope (fainting), breathing problems, or vomiting, and that a doctor was available to help in about half of

all cases. Of 11,920 calls throughout nearly three years, there were 30 in-flight deaths and three early landings for childbirth.

N SO FLY

Headed by Pitt associate professor of emergency medicine Francis X. Guyette (Res '04, Fel '06), the Pitt-affiliated STAT MedEvac program is the nation's largest non-profit critical care transport group, with 17 helicopters; its 36,700 square mile service area includes Baltimore. The program is also a world leader in aeromedicine research. For example, its crew was among the first to test the feasibility of video laryngoscopy for inserting breathing tubes during air transport. And STAT MedEvac can test trauma patients for a spike in lactic acid, which can happen when you're bleeding internally and means you're more likely to require emergency surgery or blood products. (They can give you the blood right there on board and are studying the best way to do this, too.) Their research findings on point-of-care lactate have since been replicated by the Resuscitation Outcomes Consortium. "It's really dramatic what they are doing in the small, hectic environment of a flying helicopter now," notes Paul Paris.

O HIT THE STREETS RUNNING

Twenty years ago, Pitt's Peter Winter, an MD who was then chair of anesthesiology, created a simulation facility for Pitt med students and hospital providers to practice procedures on responsive mannequins rather than real patients. Since then, the Peter M. Winter Institute for Simulation, Education, and Research (WISER) has grown tremendously. WISER continues Pitt's long relationship with Resusci Anne manufacturer, Laerdal, testing and developing new mannequins and software. And the Laerdal family has generously supported WISER through its foundations. Among the very first sophisticated simulation centers in a medical school, WISER has become integral to Pitt med. Many other health sciences students train there too, and so do Pittsburgh paramedics. The Center for Emergency Medicine even shares the building; and WISER's director, Paul Phrampus, an MD (Res '00), has an extensive background assessing and testing EMS providers. As med schools throughout the country have followed suit by building their own simulation centers, their local EMS crews are typically able to practice airway management and other crisis scenarios on simulators, where it's okay to make mistakes. This should translate to better trained emergency responders. ■

AND WHERE IT'S GOING

A PEEK AT HOW PREHOSPITAL CARE MAY BE CHANGING



UPMC emergency medicine residents are probably the only ones in the country who rotate with paramedics. In the '70s, house staff went on calls in Paul Paris's purple Buick Skylark. UPMC now provides a dedicated Jeep.

CUFF 'EM

For heart attacks, limiting the size of the damage to cardiac muscle is a key goal of care. Remote ischemic conditioning is a simple way to trick the body into a smaller heart attack by inflating and deflating a blood pressure cuff. Invented in Europe, the procedure was recently tested for the first time in medevac helicopters by Christian Martin-Gill and colleagues, who found it useful and effective enough to study further at Pitt's Applied Physiology Lab. It might not be long before paramedics put the squeeze on prehospital heart-attack care.

BAREFOOT MEDICS

Community paramedicine is a new field that trains paramedics to enter patients' homes and help them manage chronic diseases—a strategy Paul Paris calls “the next EMS frontier.” Pitt's Congress of Neighboring Communities launched CONNECT Community Paramedics in 2009, partnering with the Center for Emergency Medicine and other key organizations in Pittsburgh.

DON'T STRESS

At Pitt's Applied Physiology Lab, a team of researchers, including emergency medicine physicians Jon Rittenberger and Joe Suyama, studies health questions related to stresses emergency rescuers face, like wear-

ing hot, heavy equipment (a timely topic in the Ebola era). They're examining how fatigue and teamwork affect EMS providers' ability to give care, too.

FEEDBACK LOOP

Did we mention that CPR quality matters? It really, really does. Yet the rescuer often doesn't know moment by moment whether her efforts are actually helping. With a recent \$1.8 million grant from the National Heart, Lung, and Blood Institute, James Menegazzi and colleagues are building a powerful database of electrocardiograms (ECGs) that researchers can digitally analyze in order to track how ECG changes during CPR correlate to patient survival. The aim is to give better real-time feedback during CPR and, of course, save more lives.

BACK TO BASICS

Compressions with or without interruptions for breaths? In 2008 the American Heart Association advised untrained bystanders attempting CPR to stick with compressions alone, because it's simpler. “But it hasn't been tested [to see] whether it's better for patients,” notes Clifton Callaway. The Resuscitation

Outcomes Consortium, which includes Pitt, is pursuing a study comparing both techniques head-to-head (or chest-to-chest, as it were). ■

ROUGH RIDERS

Oddly enough, emergency physicians seldom spend much time in ambulances. But at Pitt, emergency medicine residents go on EMS runs in their very own vehicle. The tradition started after Ronald Stewart and Paul Paris jumped in their own cars to respond to emergencies. Paris recalls the “silly magnetic light that I would throw on the top of my normal Buick.” In 1982, the second year of the residency's existence, he and his colleagues fixed up a vehicle for residents to use in order to respond to certain emergencies, like cardiac arrests. Pitt remains probably the only residency in the country with its own emergency vehicle. (Residents now do these runs in a hospital Jeep instead of Paris's purple Skylark.) As they attempt to save lives in homes, streets, and alleys, Pitt emergency medicine docs get schooled by paramedics on the realities of prehospital care. “Paramedics are so used to the crazy environment and how to get things done,” Paris says. Pitt's Allan Wolfson, an MD professor of emergency medicine and vice chair of graduate education, adds, “It's definitely a favorite rotation.”

Immune cells invade a rodent islet (cell nuclei in blue) in a diabetes-prone mouse. In type 1 diabetes, the islet's insulin-producing β cells (green) come under attack by immune cells (CD4+ T cells in red) when certain aspects of the immune system's "brakes" are lacking. Vignali's lab has discovered several pathways that contribute to this process.

COURTESY MARIA BETTINI, VIGNALI LAB

THE POWER OF NEGATIVE THINKING

MEET DARIO VIGNALI
BY ELAINE VITONE

Two immunologists walk into a bar.

The scientists—a PhD from St. Jude named Dario Vignali and an MD/PhD Yale prof named Mark Shlomchik—catch up over beers, as they often do at these scientific conferences. And then Vignali confides: “I’m considering moving to a major adult cancer center.”

“Well,” says Shlomchik (*speaking of major cancer centers!*), “I’m moving to the University of Pittsburgh as chair of immunology. Maybe you could think about Pitt.”

Joking aside, landing a recruit like Vignali—an eminent scientist who’d been courted many times before—took a lot more than beer. Vignali is now vice chair and professor of immunology at the University of Pittsburgh,

a common language with transplant biologists, molecular oncologists, vaccinologists, and most every other immunology expert you can shake a stick at; and launched his independent research career with basic science papers on autoimmune disease. (In fact, their beer summit was at an autoimmunity meeting.)

And *then* he tackled cancer.

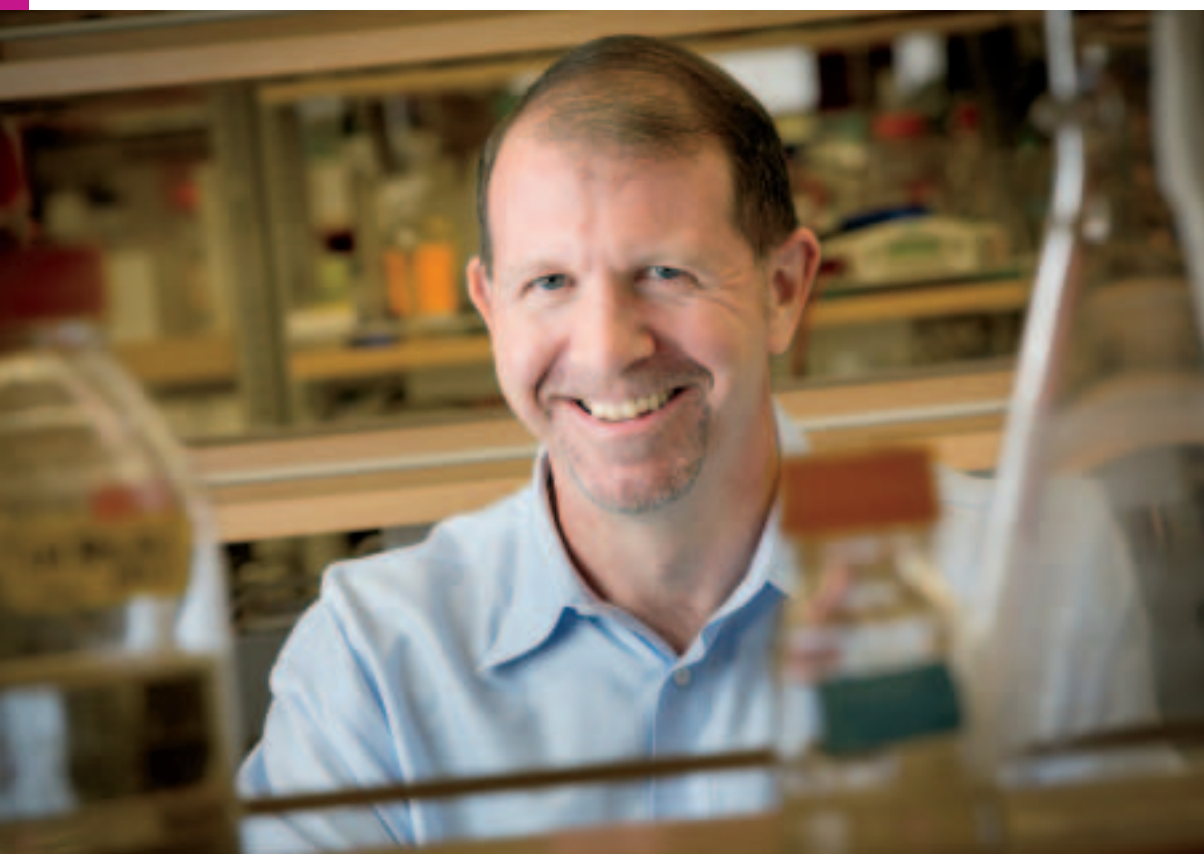
Vignali arrived at Pitt this summer as it was launching Act II of a massive effort to raise the profile of immunology on campus. (Act I was put on by Olivera Finn, PhD Distinguished Professor of Immunology and Surgery, who founded Pitt’s department in 2002.) Using Pitt/UPMC’s cancer immunology program as a model (which was started by Finn in 1991), Pitt plans to strengthen immunology not only in its traditional realms—autoimmune disease, cancer, infectious disease/vaccines, and transplant medicine—but also in its less obvious ones, such as inflammatory diseases of the lung and the microbiome.

“[Pitt] is going to be an exciting place,” says Vignali. “In the next five years, we’ll probably have one of the largest expansions of immunology in the country.”

In the early ’90s, cancer immunology research was still somewhat phenomenological and descriptive, Vignali says. “A tumor grows. You look inside. There are a bunch of [immune] cells. But why is the tumor not being cleared? ... I felt that, until we really understand the immune system, we’re not going to be able to manipulate the immune response to cancer.”

To pay the bills through his graduate studies at the London School of Hygiene & Tropical Medicine, Vignali worked as a technician in a lab that studied the immune response to a parasitic worm and the deadly infectious disease it carries, schistosomiasis. It turned out to be a productive day job. “Infectious disease models are terrific for studying the immune system,” he says.

If you’re an immune cell, “know thyself” is a fundamental imperative. For every passerby you come upon, recognizing “self”—healthy bodily cells—versus *personae non-gratae* like viruses, bacteria, and cancer, is crucial. So, for each of his two postdoctoral fellowships, Vignali trained with a scientist who was expert at the mechanisms of



ANNIE O'NEILL

Vignali joined Pitt's faculty in 2014.

as well as coleader of the cancer immunology program and codirector of the Tumor Microenvironment Center at the University of Pittsburgh Cancer Institute (UPCI).

Many of Vignali's papers in recent years were at the forefront of a sea change in oncology known as cancer immunotherapy, which *Science* named breakthrough of the year in 2013. But Shlomchik is quick to point out that Vignali is not “just” a cancer researcher.

Vignali got his PhD in infectious disease immunology; did postdoctoral training in fundamental molecular processes, giving him

In his new scientific home, Vignali has two labs: one in the Immunology Department, where he studies certain pathways of what's known as immunoregulation, and another at the Hillman Cancer Center, where he's applying his benchside insights to new cancer therapies.

One reason Vignali chose Pitt is that, at a time of dwindling federal research dollars, many immunology departments are shrinking—but thanks to the investment of the School of Medicine, as well as UPMC, Pitt immunology is growing.

this self-knowing: Günter Hämmerling at the German Cancer Research Center, who uncovered some of the basic mechanisms used by the immune system to recognize “self” and distinguish “self” from “foreign,” and Jack Strominger at Harvard, who isolated and solved the structure of some of the molecules known as MHC (major histocompatibility complex). (Peter Doherty, who recruited Vignali to St. Jude in 1993, won a Nobel prize for showing that it’s MHC molecules, in fact, that define that process of self-knowing.)

Vignali’s Harvard mentor remembers

ance your blood sugar. In your immune system, there’s stimulation—to fight off pathogens—and the yang to its yin is regulation, ever keeping your immune response in check. Without efficient immunoregulation, we’ve long known, a body can attack itself: It damages its own pancreas in type 1 diabetes; its central nervous system in multiple sclerosis; and a host of organ systems in lupus.

On the flip side, scientists have long suspected that when the immune system is subdued, it leaves the door open for cancer. In animal models as in humans, we’ve seen tumors spark and spread like a gas fire when

a molecule called LAG-3; its potential is directly informed by Vignali’s work.

It wasn’t an easy road. For many years prior, studies along these lines were considered dangerous academic territory. See, everyone had a sense that immunoregulation was important. Everyone suspected some kind of specialized “brakes” must be at work—regulatory T cells (Tregs), or suppressor T cells, as they were called back then, explains Lotze. “But the immunogenetics, in a series of unfortunate studies, failed to confirm their existence.” Tregs remained the Bigfoot of immunology.

“Suppression became a dirty word,” recalls Vignali. “It was just labeled phenomenology, and many questioned whether it really existed.”

him as efficient, precise, and extremely hard-working. “He’s a self-made scientist,” says Strominger, adding that Vignali is a technological innovator, as well. In 2006, Vignali’s lab first detailed, in *Nature Methods*, a new way to develop mouse models for studying T-cell biology. Vignali’s process allows scientists to express various immune proteins, like T-cell receptors (which are used by T cells to identify MHC molecules), and employs a retrovirus as a gene vector. The old way of creating mouse models could take several years. These retrogenic mice, as Vignali dubbed them, can take as little as six weeks to develop, from start to finish.

Strominger is one of a host of scientists now using retrogenic mice to study a range of diseases. “He improved the technology enormously,” Strominger says.

In the early ’90s, when Vignali was just starting out, the big buzzword in molecular immunology was costimulation. A long list of cell-surface molecules known to play some part in fine-tuning and revving up the immune response—in applying the gas, if you will—was growing.

But very little was known about the other side, the brakes.

Medicine is full of binaries like this: triceps versus biceps to control your arm; insulin versus its opposite, glucagon, to bal-

the immune system is compromised. So for decades, cancer researchers have attempted to compensate for these imbalances with immune-boosting cancer vaccines—and Pitt teams, notably that of Finn (immunology’s founding chair emerita), have been testing these experimental techniques.

As Finn wrote last summer in *Cancer Immunology Research*, cancer vaccines have largely proven unsuccessful at treating cancer. However, these studies have opened new possibilities in cancer prevention research and pointed the way to an entirely new approach to cancer treatment. This is because these past two decades of cancer vaccine research have helped to uncover new insights about how cancer develops in the first place.

Namely, by slamming a foot on the brakes. Cancer cells actually boost immunoregulation.

In the past five years, the FDA has approved three cancer drugs that take aim at this mechanism—that stop the foot from hitting those brakes. “It’s the power of negative thinking,” says Michael Lotze, MD professor of surgery, immunology, and bioengineering and assistant vice chancellor, health sciences. These drugs, he says, are the most promising things to happen to cancer research in decades. Another drug in this class that’s currently being evaluated in clinical trials targets

“Suppression became a dirty word,” recalls Vignali. “It was just labeled phenomenology, and many questioned whether it really existed.”

But that made it all the more appealing for Vignali.

When he started his St. Jude lab, he began using the LAG-3 molecule as a study control for his experiments, just because it happened to be structurally similar to the molecule he was studying called CD4. But he noticed that LAG-3 happened to have “very interesting inhibitory properties,” he says. He’s been studying them ever since.

Vignali found that when LAG-3 is removed from a mouse with a genetic predisposition to type 1 diabetes, the disease goes into hyperdrive. LAG-3 seemed to be a crucial part of the immune system’s brakes. He would go on to publish extensively on this and other pathways implicated in diabetes and other autoimmune diseases, and eventually in cancer.

Some 20 years ago, immunoregulation became not so dirty anymore when Tregs’ existence was finally confirmed. A flurry of interest surrounded Tregs; Vignali, at first, opted not to follow the pack. “Then, sort of ironically, we got dragged into it,” he says with a laugh.

As it turned out, T cells—the immune

system's infantry—are turned off by LAG-3. A scientist who played a key role in this discovery, Johns Hopkins's Drew Pardoll, didn't know much about LAG-3 (very few people outside of Vignali's lab crew did) when the molecule's intriguing abilities first caught his attention. As it happened, Pardoll and Vignali had met just a year prior when Pardoll was touring St. Jude labs. So in 2002, Pardoll gave Vignali a call. "And [Vignali] said, *Yeah, absolutely. Happy to send you our antibodies*, which are always very useful tools to study a molecule," recalls Pardoll. More than a decade later, they're scientific collaborators, copatent holders, and close friends. Pardoll is even a scientific godfather of sorts to Vignali's second-eldest son, who's working in Pardoll's lab at Hopkins.

The team found that when LAG-3 is blocked or deleted, T cells divide like

detailed how IL-35 could turn T cells into highly potent immune-response quashers.

Most recently, Vignali's team discovered a Treg-surface pathway with promise as a target for cancer. Preliminary findings (published in *Nature*) suggest that the pathway appears to be important to Tregs' astounding durability in what's called the tumor microenvironment. What's the tumor microenvironment, you ask? Good question.

Cancer doesn't happen in a vacuum. In its natural habitat—a living, breathing host—tumor cells are interspersed with connective tissue, blood vessels, and a multitude of immune cells of various stripes, some of which are defending the body and others that have been co-opted to contribute to its demise. Cancer-host crosstalk is dynamic, evolving, and complex.

Most often, though, scientists tend to

"We said, *Gee, what would it take for you to move here?*" recalls Ferris. "And he said, *One thing I've always wanted to do is really focus on the tumor microenvironment.*"

Well, Ferris replied (*speaking off*), as it happened, he'd recently gotten the green light—and some greenbacks—to finally pursue that very same goal.

As codirectors of Pitt's Tumor Microenvironment Center, Ferris and Vignali lead a multidisciplinary effort to essentially meet tumors where they are—which is all over the place, in a constantly shifting biome in terms of genomics, metabolism, oxygen, and inflammation. UPCI teams are studying cancers in mice—and comparing that activity to what's happening in Hillman Cancer Center patients a few dozen yards away. They're enlisting Pitt experts from all walks and recruiting a few

Studying this big, biomolecular picture, the whole physiological enchilada formally known as the tumor microenvironment, is like "looking at the community rather than the individual."

crazy. And when the researchers administered Vignali's LAG-3 antibodies to a mouse model of immune regulation in the lungs, the antibodies blocked immune-regulation-causing disease.

Even better, mice that lack LAG-3 do not suffer crushing autoimmune disease, as one might fear. As it turns out, LAG-3 is specific only to inflammatory sites—like a tumor.

And if you administer LAG-3 antibodies along with antibodies to another known immunoregulatory receptor, PD-1, you get even more bang for your buck. These encouraging results, published in *Cancer Research* in 2012, are the bases of clinical trials now under way.

While hunting for ways to target Tregs, in 2007 Vignali discovered that an important product of these cells, called IL-35, is one of the few cytokines that regulate rather than excite the immune response. His team published its initial findings in *Nature* in 2007. In a *Nature Immunology* paper, Vignali et al.

focus on one particular aspect of a cancer cell and how it responds when, say, a given pathway is removed. Vignali is interested in complementing this approach with a bigger-picture perspective: What's the impact on the body when a pathway becomes unstable? How do bodily cells then, in turn, affect the cancer?

Studying this big, biomolecular picture, the whole physiological enchilada formally known as the tumor microenvironment, is like "looking at the community rather than the individual," says Vignali. "That's what we've felt was lacking. That's what we wanted to do."

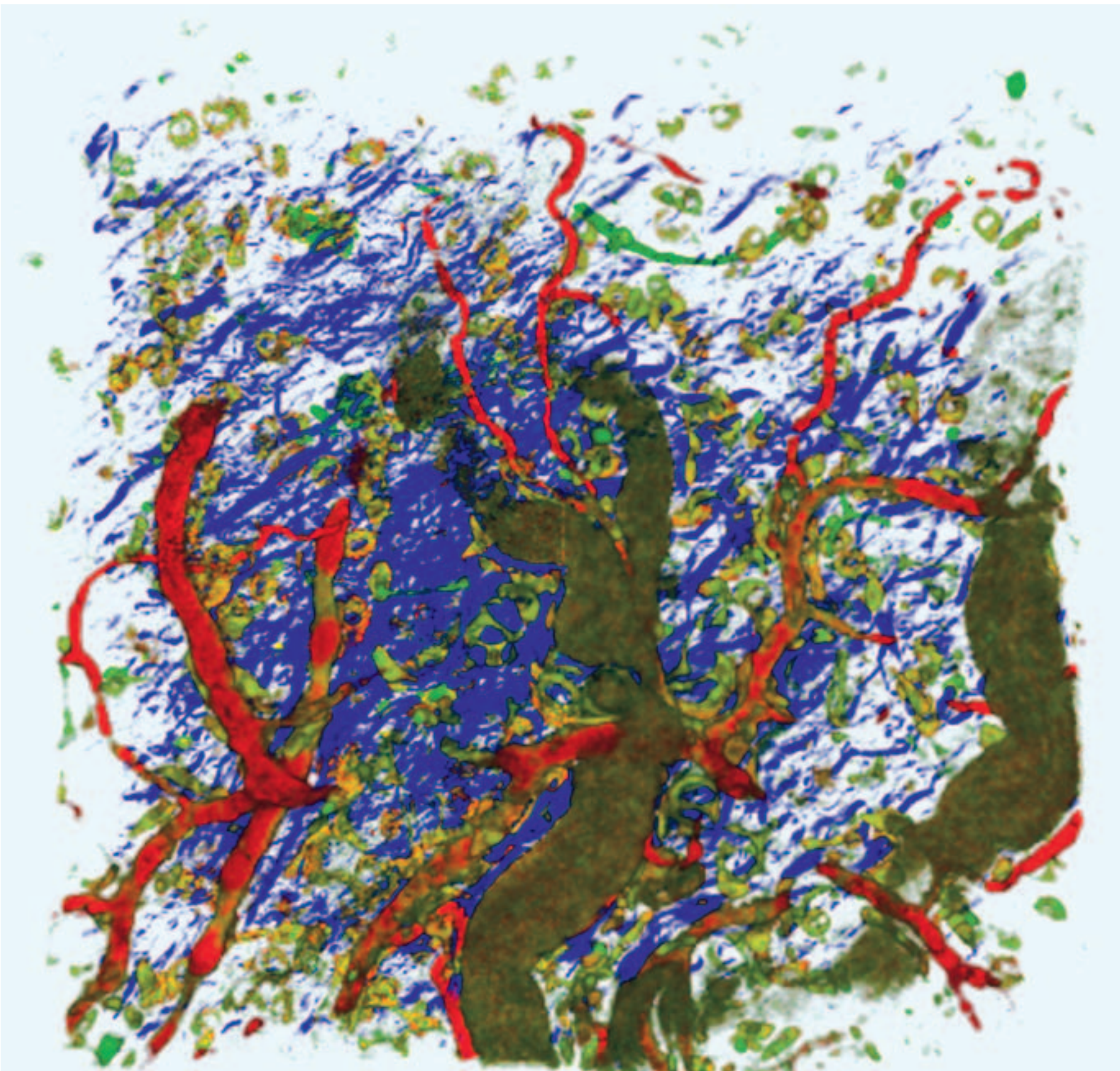
As Vignali was scoping out Pitt, he got to talking and e-mailing with Shlomchik and with Pitt's Robert Ferris—an MD/PhD and UPMC Professor of Advanced Oncologic Head and Neck Surgery and chief of the Division of Head and Neck Surgery within the Department of Otolaryngology (among other titles).

new ones, too. (The first recruit, assistant professor of immunology Greg Delgoffe, a PhD who did his postdoc with Vignali at St. Jude, arrived last summer.)

"We need to move past the animal models and move [the study of the disease] into humans as quickly as possible," says Ferris.

An immunologist, an oncologist, and two pharmaceutical company researchers walk into a bar . . . and, casually and unceremoniously over beers, the pharma researchers show Vignali and Pardoll a small, empty vial encased in a solid block of plastic for posterity. The label indicates the vial was designed to hold LAG-3 antibodies—the first ever produced for human use. The company would also explore how the antibody's efficacy might be boosted by combining it with other drugs.

Today, a promising class of therapeutics is being tested in patients. And that's no laughing matter. ■



Rendering of immune cells infiltrating a rodent melanoma. During tumor growth, regulatory T cells (green) invade the tumor (blue) and use a number of mechanisms to prevent the host's immune system from attacking the tumor (vasculature in red). Vignali's lab has discovered several pathways that contribute to this process.



A team at Children's Hospital of Pittsburgh of UPMC evaluates X-rays to decide next steps in care. The pediatric intensive care unit (PICU) at Children's emphasizes a team-based, multidisciplinary approach to rounds and treatment—and this approach is believed to contribute to its low mortality rate. Pitt's Schools of the Health Sciences want this culture to go viral.

PHYSICIAN, KNOW THYSELF, AND OTHERS TOO
BY ROBYN K. COGGINS

IDENTITY TRIUMPHS

The blue, green, and red teams round through Children's Hospital of Pittsburgh of UPMC's pediatric intensive care unit early on a Friday morning. On the blue squad: Rajesh Aneja, MD medical director of the PICU; fellow Jessica Wallisch, an MD; pediatric resident Catherine Polak, an MD; and three observing Brazilian fellows. They stroll genially through the multicolored corridors, expanding the team as needed—a respiratory therapist for this patient, a transplant consult for that one.

Each team orbits with an electronic medical record cart, Wallisch sometimes putting a foot on its wheeled base like a kid riding a shopping cart, while expertly coordinating a ringing phone, a pager, and requests from staff.

Midway through blue rounds, “Dr. Raj,” as everyone calls Aneja, and the team stop at a young girl’s room. White patches of tape cover her motionless face; tubes from her mouth graze her smooth right cheek. (Details have been changed to protect patient privacy.)



Rounds at Children's include nurses, nurse practitioners, respiratory therapists, pharmacists, social workers, residents, fellows, and attendings. Family members also attend rounds.

PHOTOGRAPHY | MARTHA RIAL

"Cardiac arrest at home, six days ago," Aneja explains, his voice somehow soothing. The girl's nurse, Erica LeBlanc, an RN, stands near the door, ready to update the team on her progress overnight.

"Still no gag? Cough?" Aneja asks.

"I wouldn't say she necessarily coughs; it's more of a gag," LeBlanc clarifies.

"She doesn't have a pupillary response or a corneal," Wallisch adds, which prompts resident Polak to present on yesterday's tachycardia, the girl's fluid buildup, and her slowly decreasing blood pressure. Then it's respiratory therapist Brian Stiles's turn to detail another litany of information while Aneja jots notes and Wallisch types the data into the electronic medical record.

Some of the team pores over graphs housed directly in the records, while others look to

is what we do oftentimes here, requires lots of talented people all working together."

No physician—or nurse or physical therapist—is an island. There's too much medical knowledge to retain, too many cascading decisions to make, too much for any individual to do in a day. The team approach helps keep Children's PICU mortality rate exceptionally low, around 2 percent. Everyone is present, everyone has the same expectations and knows the next steps.

Over on the blue team, Aneja and company are sussing out a treatment strategy. "So the main issues now are, one, you need a long-term plan. It seems like she's gonna survive this. And we need to formulate [that] plan of care after discussion with Mom," Aneja says.

This case comes with an added complication: Nurse LeBlanc has contacted both

girl has been given about half that dose since she arrived and is scheduled for it again this afternoon.

"So you want me to not give this lower dose? Wait first?" asks Nurse LeBlanc.

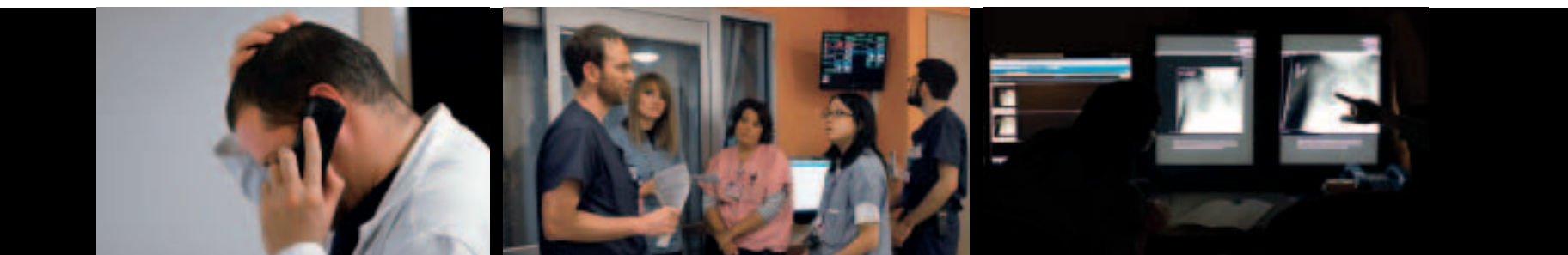
"Can we give 2 mcg/kg extra clonidine? Can we, Carol?" asks Aneja.

"Oh, we can order 2 mcg/kg."

"Carol will make it happen!" Aneja announces, and the crew seems satisfied.

Vetterly and her fellow pharmacists are vital in the PICU, where children are frequently on a cocktail of medications. She computes dosages on a small calculator and considers potential treatment interactions while others present on the patient. It's common for attendings to totally defer to her expertise—pharmacists often manage and prescribe all of a patient's meds here.

As the team moves to its next patient, Kayla Stalma, an RN, teases Aneja about never work-



the screen above the patient's door displaying biological data. They're debating next steps until the girl's parents can give input on a care plan. Throughout rounds, other parents in fuzzy slippers and old rock band T-shirts appear sleepily outside rooms to listen to the day's updates and add their own observations and questions. No parents wait at this bedside.

The PICU is "open," meaning the team coordinates care between different specialists and professionals, rather than one person dictating treatment. As Robert Clark, MD chief of pediatric critical care medicine, puts it: "It's more of an orchestra here than it is a solo act." After his red team rounds, he explains the interplay between each member of the staff, dimples cratering his cheeks, his voice soft:

"[In] children [you] might have a domino effect," says Clark, who's also professor of critical care medicine and pediatrics as well as associate director of the Safar Center for Resuscitation Research. "Any sort of intervention you might do, there's a consequence that affects other organ systems or parts of the body. . . . Managing that, managing family dynamics, managing disease processes in the face of development, managing multiorgan failure, which

parents, but a custody dispute has stifled communications. Regardless, the team wants to consult them before moving forward. They decide that Aneja will try calling the parents today; maybe hearing from the doctor will spur conversations. Later, a social worker—a 24/7 linchpin of collaboration in the PICU—will stop in to further facilitate talks between the medical team and the family, whether in-person or in a conference call. Social workers like Gwen Harcar listen to family concerns and connect them with much-needed support and coping resources. (They often listen to doctor concerns too—everybody needs a good listener, after all.)

For now, the team focuses on keeping the girl stable. "Let's hear from the pharmacist on this," Aneja says. He wants to increase the girl's clonidine, a drug that helps control the storm in the sympathetic nervous system often seen after brain injury in cardiac arrest. It helps in lowering blood pressure and also acts as a sedative. "What's the upper limit?" he asks Carol Greco Vetterly, PharmD clinical pharmacy coordinator.

"Oh, 25 migs [mcg/kg] per day is the highest. There's lots of room," she replies. The

ing—this is his first day back after a few weeks away.

"The docs are awesome," Stalma says later. "We call them by their first name; they listen to the nurses. They hear you."

"It's a group effort."

It's tempting to simply say that the PICU exemplifies teamwork—which is true. But these professionals are doing something more remarkable than a double play or producing a stage drama; they're working together in a communicative, interdependent way within a system that's historically been hierarchical and fraught with egos.

Interprofessionalism—defined by the World Health Organization as "when multiple health workers from different professional backgrounds work together with patients, families, carers, and communities to deliver the highest quality of care"—falls in that hard-to-quantify space between intention and action, hearing and listening. It's an art, and a difficult one. Because who doesn't think she's a team player? Who isn't aiming for high quality care?

But if becoming better and better is the goal, as it is at Pitt, how do we start conversations among well-meaning, well-educated people to make collaborative, PICU-like scenarios a broader care reality?

The PICU's emphasis on collaborative care, or interprofessionalism, or multidisciplinary work—whatever one's preferred term of the many that describe it—has been a long time coming.

A 1972 Institute of Medicine report chronicled the need for this kind of care after a conference called Educating for the Health Team. It noted that health workers . . . *are proliferating in random fashion; each defines certain functions for itself either by self-arrogation or by delegation but almost never in collaboration with other health professionals; new professions appear to fill in the gaps left between the perimeters of existing professions; educational programs duplicate each other, as do facilities; many, many small programs appear in response to local needs.*

Like the little Dutch boy plugging holes in the dike, health science professionals had been acting quickly, if a little shortsightedly, to address

interprofessionalism as well as communication and problem-solving skills.

A few years ago, Pitt's six Schools of the Health Sciences anticipated the need for interdisciplinary work and sought to make their students' training, and Pittsburgh's clinics, look more like the collaborative PICU.

For the past eight years, a 12-person working group across the schools has been identifying opportunities to work together and try out small-scale reforms—from student mixers to forums to curriculum shifts. Susan Meyer, a PhD and pharmacy's associate dean for education who is administrative leader of the working group, serves as a touchstone and advocate for interprofessionalism at Pitt. Professor of psychiatry and of health policy and management Loren Roth is also a longstanding champion of the effort.

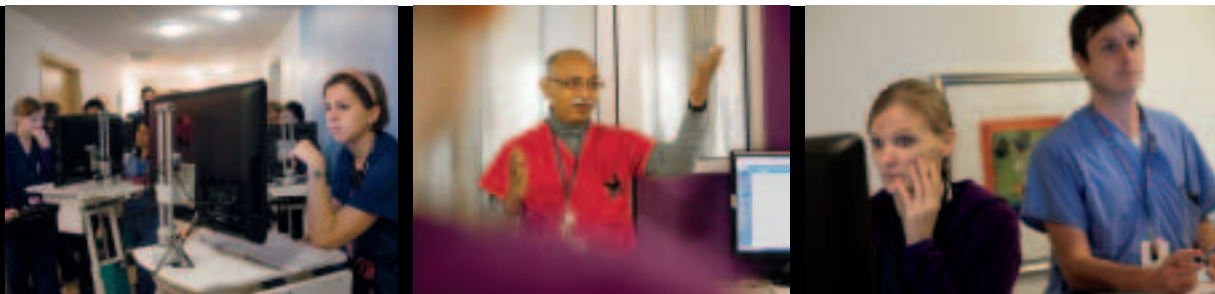
been separated by history and convention and the nature of identity formation. All those things have acted until now to prevent what is necessary team behavior and equal respect to all, period."

He says that as medicine shifts from an ethos of treating disease to preventing it, there's an increasing need for skills other than and in addition to a physician's.

Though less common today, old-school bully doctors disrespecting nurses is only one example of obstacles to interprofessionalism in practice.

What if studies show that surgery and physical therapy for chronic back pain have about the same efficacy? Which path does the care team choose, and who decides? Even in the PICU, the team waited for Aneja before beginning rounds, and treatment decisions were

Structured patient handoffs to the PICU started about six years ago, according to chief of pediatric critical care, Robert Clark. "You can try to read notes and come up with an impression, but it's not the same as sitting across from [team members]," he says. "A lot of that can make an impact, since the stakes are higher here." Electronic medical records have helped create a more complete data picture, but they can't capture the interpersonal art of medicine: "You can't put nuance into an electronic medical record," Clark says.



the problems arising in their respective fields. They needed more fingers; they needed someone to truly fix the leaks—a broad, long-term view. Contemporary clinicians and educators have been challenged to overcome this history of scattered experts, disjointed protocols, and intercultural misunderstandings.

About half of all American adults now have some type of chronic medical condition—like heart disease, diabetes, or hepatitis. And nearly a quarter, or 60 million, have multiple, ongoing health conditions. The resulting panoply of interactions and complications needs to be treated together. As the Boomers age, as researchers gather ever more immense clinical data sets for better treatments, flying solo won't be an option, even in private practice where MDs are typically seen as the boss.

On the national level, the Affordable Care Act incentivized "accountable care organizations"—multiprofessional efforts to treat Medicare patients—on the theory that an ounce of coordinated prevention and care should make for many pounds of cure (and savings). The Liaison Committee on Medical Education recently—finally, some might say—updated its standards to ensure that all accredited medical schools teach

Roth, MD/MPH associate senior vice chancellor for clinical policy and planning for the health sciences, might even object to the fact that we have to list the six schools: dental medicine, public health, nursing, pharmacy, health and rehabilitation sciences, and medicine. His definition of interprofessionalism includes a more diverse roster of members, like ambulance drivers, janitors with keys to facilities, interior decorators who make patient rooms comfortable, IT professionals who build record systems—really anyone who, however indirectly, helps patients. He balks at separate alumni magazines, separate buildings, and language that divides the schools.

Roth got to thinking about interprofessionalism in his former position as UPMC chief medical officer and senior vice president of quality improvement, and now he's part of the interprofessional working group that meets in the Falk Library of the Health Sciences, which this reporter erroneously characterized in conversation as "neutral ground."

"Neutral ground," Roth scoffs. "Between the warring parties, we have to have neutral ground? I just don't see it that way. We're all health care professionals, and I think that we've

ultimately his call. Could he cede some of his clinical autonomy to a nurse or rehab specialist?

Or take, for instance, an MD graduate who never encountered the increasingly common setting where a nurse practitioner treats most of a clinic's patients. Without training in such a situation, the MD could feel unmoored, underprepared, perhaps even hostile as she enters an unfamiliar role.

Resolving these professional conundrums comes down to identity and self-awareness: It means knowing where you and your colleagues fit within a larger system. It means being able to step up when your expertise is needed and step down when someone else knows best.

"What you really hope," Roth says, "is that as the evidence comes in, [interprofessional efforts] are evaluated objectively. Costs is one way. The patient experience is another. Disease outcomes is the third." He's reciting the so-called Triple Aim of care—a pyramid of values that the working group and others use to explain their reformative standards.

"And the challenge of an academic institution," adds Roth, "is to actually try to collect that data and to analyze [them] in such a way that a practice can be developed rationally."

Everette James, a JD and MBA, wants to give educators those analytics. James is director of the Health Policy Institute, Pitt's nearly 35-year-old effort to turn health science expertise into applied research and legislation. He's also the former Pennsylvania secretary of health, newly honored M. Allen Pond Professor of Health Policy and Management, and associate vice chancellor for health policy and public planning.

This summer, James and Meyer directed All Together Better Health VII. The international conference on interprofessional practice and education was the first-ever held in the United States. Professionals from across the globe exchanged ideas for new models of care and education.

"It elicited a lot of connections on campus," Meyer says. "Because it was here, it was an opportunity for a lot of our people to present their work. They're finding out about each other and what's available. I've gotten calls from groups . . . who want to evolve the culture more. So it really has made connections among

and night shifts.

Another incubator is using an electronic "dashboard" to alert geriatrics staff when patients tip into categories at high risk for serious medical events based on their vitals and other data.

Many of these more than a dozen incubator sites focus on transitional moments—as care responsibilities move between staff or parts of the hospital, or from clinic to home—and use technology in new ways to aid clinicians on a larger scale.

Working group member Hollis Day, MD associate professor of medicine and an advisory dean at the med school, suggests that clinics lacking a particular expert can create a "virtual team" of advisors to solve patient problems. But she's especially interested in how educators get the art of collaborative diagnosis and treatment into the curriculum.

"Just because you work next to a nurse does not mean that you work *with* a nurse," says Day. "And so I think unless we are incredibly explicit about what we are doing and why, and

training is that students from the different professions stayed in the room to observe one another, rather than performing their parts separately and reconvening. The result?

Wow, I had no idea that occupational therapy did this!

I really liked the way the pharmacist asked these questions.

Turns out health care workers of all stripes often have little idea what other practitioners actually do. Even faculty participants sometimes say they're surprised by their colleagues in other schools.

"This is totally different than anything we were taught," Day says. "You're taught about your profession and how to teach to your profession. You're not taught necessarily how to teach a PT [physical therapist] or an OT [occupational therapist]."

But lots of Pitt people are trying to learn. Perhaps the longest arm of the working group's reach is the annual half-day Interprofessional Forum mandated for all first-year health sciences students. October's forum filled a Scaife Hall auditorium to the aisles with an estimated 650 attendees. Of course, getting strangers to mingle is not so simple. But each

Nurses and respiratory specialists steward much of the care at Children's PICU, and doctors-in-training at Pitt are increasingly learning to cede some power and follow care plans designed by other health care experts, like pharmacist Carol Greco Vetterly (far right, in white).



people and stimulated more activity."

Pitt is part of the Nexus Innovations Incubator Network—a health care reform-backed undertaking of the National Center for Interprofessional Practice and Education, based at the University of Minnesota. Through data sharing and relying on the "wisdom of teams," the Nexus, an 11-state network, hopes to launch America into a more connected era of health care.

"It's a really important feedback loop," says James. "We've got to make sure that our education and training programs stay abreast of changes and that we adjust [them] to make sure our graduates are ready to go and practice."

Pitt's Nexus trial sites at Falk Trauma Clinic and the intensive care units at UPMC Presbyterian and Montefiore are testing out new staffing configurations, particularly integrating "advanced practice providers"—nurse practitioners, physician assistants, and other highly educated clinicians—for drop-in hours

how we are integrating and helping each other out, then that message is not necessarily passed on to the students."

Day heads Pitt's Standardized Patient Program, a training venture that gives health sciences students and faculty a chance to hone their clinical skills. Standardized patients (SPs) are actors trained to present with symptoms, a backstory, and behaviors to test specific skills in a realistic setting.

In interprofessional SP sessions last May, Day would give a didactic lesson on, say, translating medical jargon to plain English, then present a case that puts those skills to the test. One simulation tackled the case of an ill elderly patient who fell, injuring her jaw. Students entered a mock examination room, greeted the woman, and got to work—just as a health professional would. They took her medical history, asked follow-up questions, and looked for social and environmental factors that might prolong her illness. What's unique about Pitt's

student received a color-coded packet denoting assigned seating, which resulted in mixed student groups.

On stage, faculty from all six schools presented a case study of an older man who had fallen at home, needed medication adjustments, but was wary of taking too many pills. The profs spoke to the standardized patient as though they were really treating him. There were some starkly different approaches between professional groups. Medicine suggested putting the man in a nursing home, to the shock of occupational therapy students, who are taught to help others "age in place" when possible. Students got a chance to discuss these treatment divergences with the people sitting next to them.

"It was really obvious from the Interprofessional Forum that it's not possible for one person to take care of a patient," says first-year PharmD student Nayanika Basu. "There's no way you could think of all the ways your knee moves and the drugs you have to take specifically for your legs. There's no way [one person] can have all that knowledge."

The event was informative; yet Basu—and many other students we spoke to for this story—said she'd like interprofessional opportunities in a smaller, more intimate setting where establishing bonds is realistic. Approaching someone in a packed auditorium is tough. "The med students can be kind of intimidating," Basu says. Frankly there isn't much interaction between the budding dentists and pharmacists who share Salk Hall, let alone between pharmacy and medical students or public health scholars who inhabit different buildings, she says.

So maybe some of the divide is geographic—a university campus can seem fragmented and insular once students are deep in their studies. Or maybe it's a lack of urgency and imagination on everyone's part. Whatever the cause, the training of health care professionals is still largely divided into instructional silos; and there are subtler separations like field-specific jargon and uniforms that uphold old hierarchies.

Closing these divides takes more than a half-day seminar, which is why Day organized those smaller refresher SP sessions last spring for more

advanced students from the six schools. The working group also presented to the health sciences board in May with suggestions for further expanding their efforts.

Meyers, Day, and the rest of the working group want to train students in ever more collaborative settings arranged by functional strengths, rather than traditionally perceived abilities. And they try to lead by example.

Day's favorite case of interprofessionalism in action: a man she treated on a geriatrics unit who couldn't stand without passing out. Physical therapists and their students, nurses and student-nurses, two med students, pharmacists, Day, and family coordinated his medication, physical activity, and social support. They were able to create the right conditions for a successful walk halfway down a hall.

"It was the most beautiful thing I had ever seen," Day says, beaming.

"He was so happy, the family was so happy, the students and the therapists were so happy because they all worked together. . . .

"And that's what sticks in your mind about

why this is so important."

Second-year med student Alyssa Bruehlman says there's lots to overcome. "So many of us, especially getting into medical school, were taught that you really were on your own. It's difficult to get out of that mindset," she says. "As I'm simultaneously trying to succeed to become a physician, I've also got to learn these skills that help round me out as a team member." A new group she helped found, Primary Care Progress @ Pittsburgh, will give her more opportunities to practice with other health sciences students.

Enacting interprofessionalism comes down to a shift: toward shared values, clear and flexible roles, and, above all, communicating well. That shift requires interrogation of the self: How do you come across to colleagues as honest, accurate, and respectful?

Roth says the answer is simple: "You have to have a will to do it. You have to believe that it's worth a try." ■

UTILITY PLAYERS

With the rise of interprofessionalism, more medical facilities are seeking out nurse practitioners and physician assistants (PAs) for their own know-how. Where physicians have become too encumbered to attend to some of their traditional tasks, duties like taking medical histories, giving physicals, and writing prescriptions can be taken on by other skilled players. (The PA master's has been deemed the most desirable advanced degree by both *Forbes* and *Money* magazines.)

Pitt alum Thomas Piemme (MD '58), coauthor of *The Physician Assistant: An Illustrated History* (who helped bring about that profession), explains that the value of PAs and other similar positions is strongly related to shortages in primary care. "We are training too many physicians to be specialists," he says.

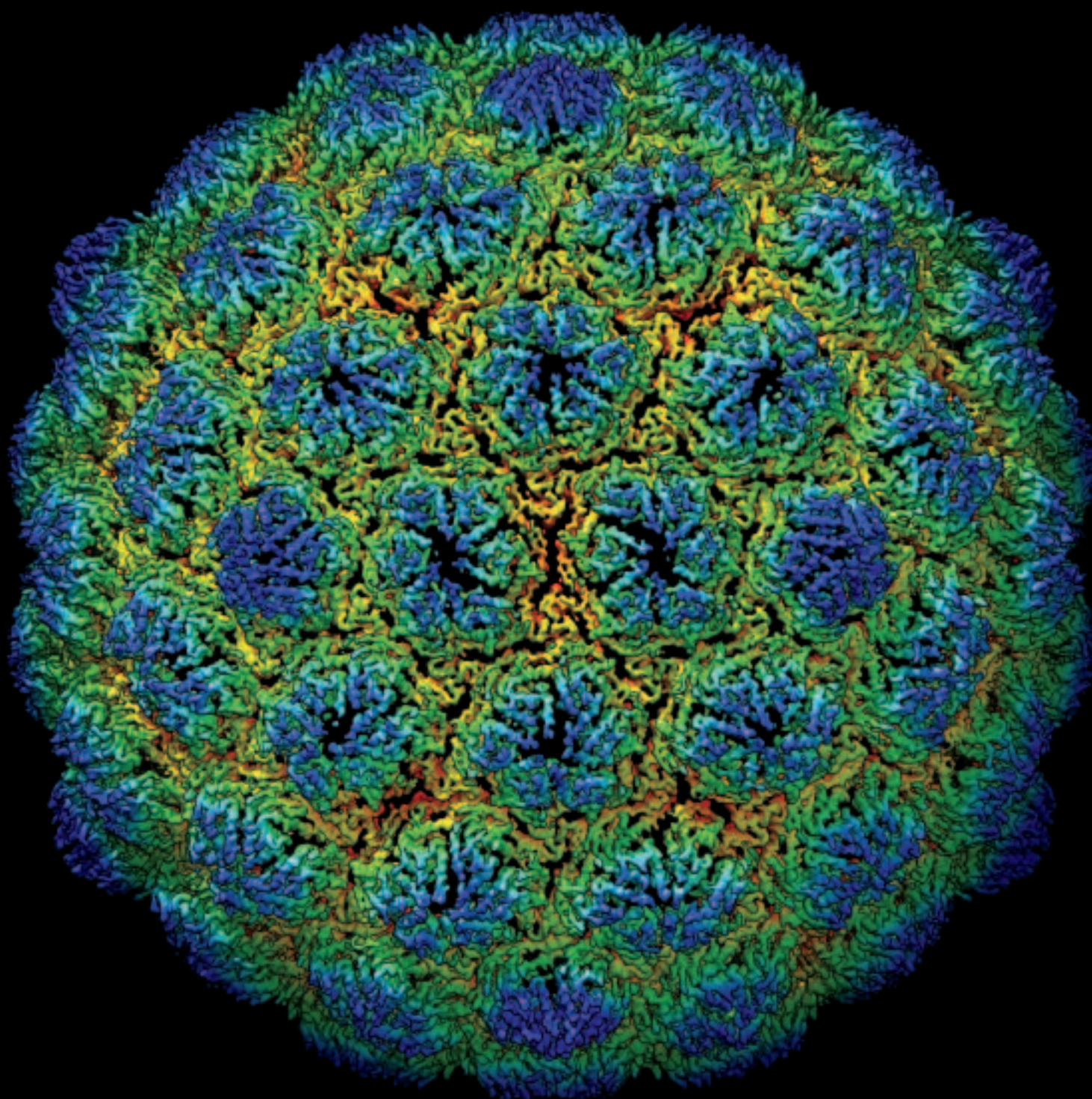
Yet advanced practice professionals can benefit specialties and specialty sites as well. In a surgery practice, for instance, Piemme notes, "a PA can take care of patients postoperatively." Likewise, a nurse practitioner can order lab tests and interpret the results, a nurse anesthetist can manage anesthesia, and a physician assistant to a surgeon can suture an incision, allowing the surgeon to get ready for another case. According to the Institute of Medicine, this coordination promotes a much safer, and more efficient and effective, means of care, because teams are less apt to make mistakes.

While physicians still captain many teams (and that's no longer a guarantee), they aren't necessarily the best at every medical job. As the health care field changes, so does the roster. —Nick Moffitt



Getting all six Schools of the Health Sciences together at once can be tough. The annual Interprofessional Forum, captured here by Mike Drazdzinski/CIDDE, is one way Pitt gathers everyone together in their first year of classes to learn from one another.





PEERING TOWARD ATOMIC RESOLUTION

BY JASON BITTEL

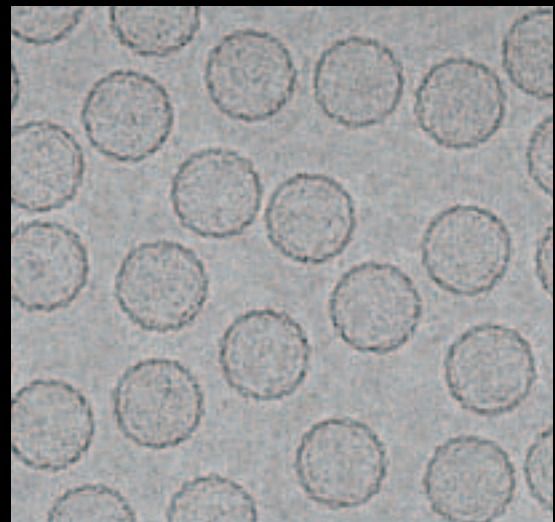
INTO THE VIRUS

James Conway is a PhD associate professor in the Department of Structural Biology at the University of Pittsburgh School of Medicine, and his is a world of the mostly invisible.

Conway specializes in cryo-EM, or cryo-electron microscopy (so-called because specimens are examined at liquid nitrogen temperature, which preserves their structure in the vacuum of an electron microscope). For a decade, he's been training his lab's three microscopes at the protein shells (capsids) of viruses.

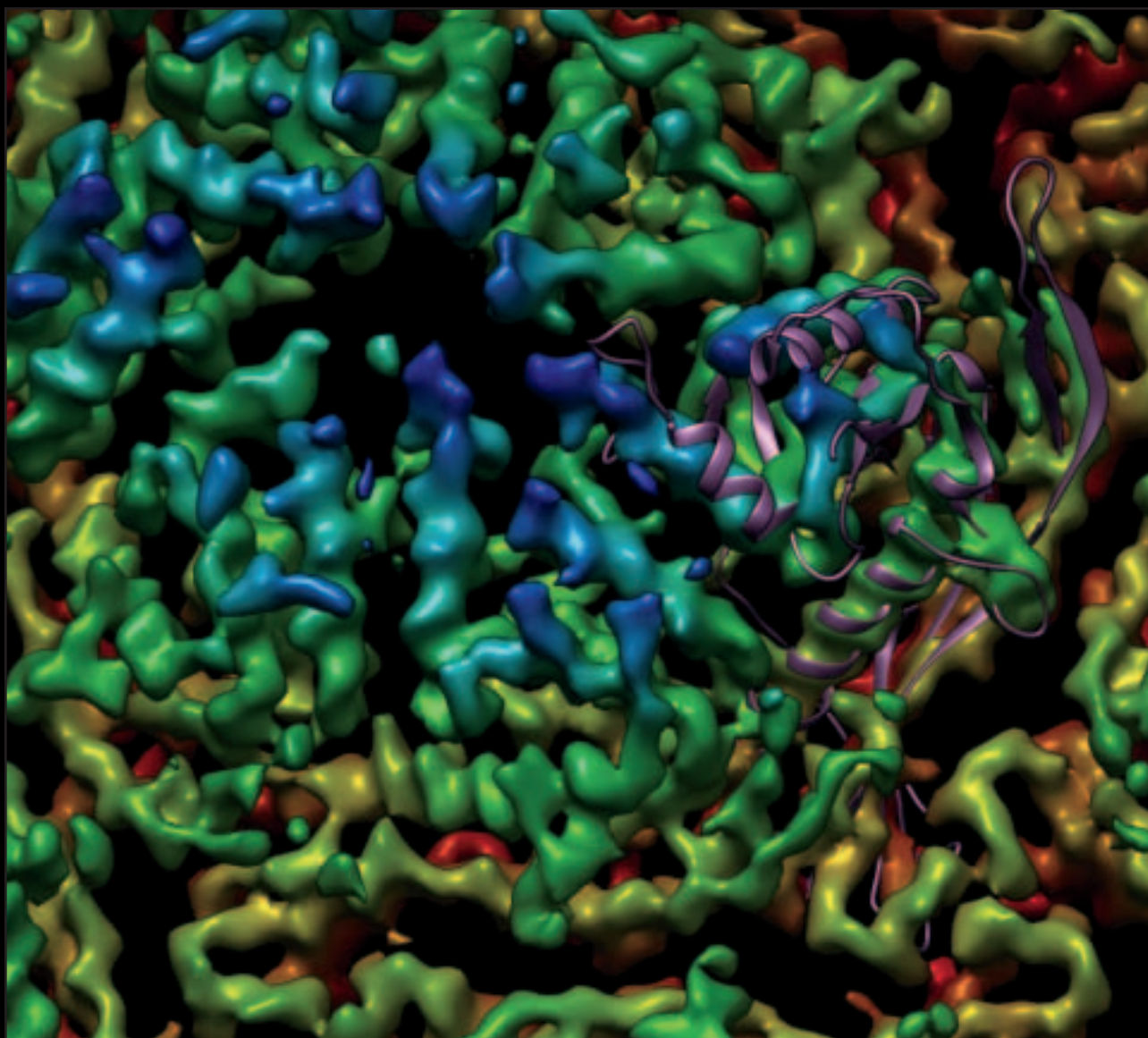
Since the first virus was discovered back in 1898 we've been trying to develop better ways to get a good look at the parasites. In the 1930s, the first electron microscopes (which use a beam of electrons to create an image instead of visible light) brought us closer than ever before. Breakthroughs in mathematics in the '60s allowed us to take the images from those advanced microscopes and translate them into three-dimensional structures.

Today, a trinity of technologies has evolved to the point that Conway and his colleagues are coming close to mapping the very atoms that make up viruses and other infinitesimal bits of matter.



Bacteriophages are viruses that prey upon bacteria. (Their name comes from the Greek word *phagein*, which means "to eat" or "to devour.") It may seem counterintuitive, but Conway's cryo-EM microscopes can actually see smaller particles, like phage D3 pictured above and to the left, more clearly than larger ones. "The quality of the images is the same," explains Conway; it's just that larger capsids are more difficult to work on. The gray image shown above is indicative of what Conway actually might see—what cryo-EM produces. The colorful images presented on the opposite page and elsewhere in this feature are modified with the freely available molecular graphics software, UCSF Chimera. From the preparation of grids to the angle of the image, there are a thousand things that can go wrong with each shot. That's why three-dimensional models are best created after Conway has taken, on average, tens to hundreds of thousands of images.

PHAGE D3 IMAGES (PP. 30-33) COURTESY: JAMES CONWAY, DEPARTMENT OF STRUCTURAL BIOLOGY.
ROBERT DUDA, ROGER HENDRIX, DEPARTMENT OF BIOLOGICAL SCIENCES.



Perhaps the most important among these technologies is the field emission gun—a powerful tool that creates a focused beam of electrons. In the 1990s, the introduction of the field emission gun transformed cryo-EM by drastically improving the signal-to-noise ratio and spatial resolution of specimens. It also allowed electron microscopes to achieve resolutions down to 10 angstroms (Å) and below. For reference, scientists consider 3 Å to be truly atomic—or at the level that lets us perceive individual atoms. Conway's lab recently managed to see bacteriophages (viruses that infect bacteria) at about 4 Å.

"It's incredibly exciting that we're now heading toward atomic resolution with the new technologies," he says. "I can get a sample, put it in the microscope, and by this evening or tomorrow, I may be the first person to see what a particular virus looks like."

Automation has also propelled the field forward. One of the electron microscopes in Conway's lab can take up to 2,800

images a day, a boon when you consider that tens of thousands of images are required to stitch together a three-dimensional model like the colorful images on these pages.

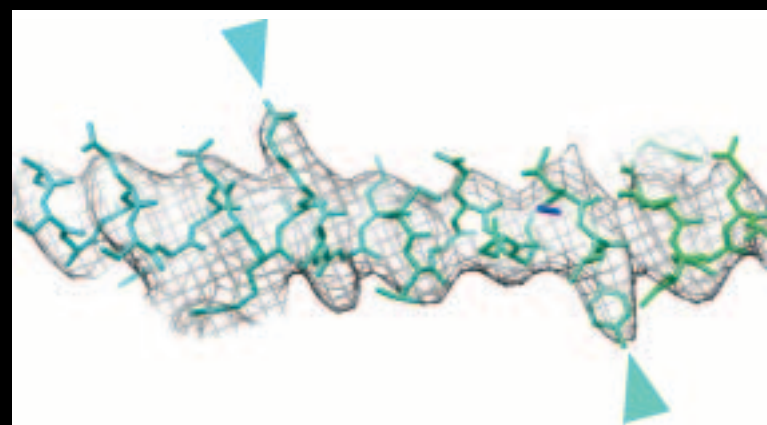
Most recently, a new type of camera has allowed the microscope to collect electrons directly rather than having to convert electrons into photons much like an old television set would.

Getting to the near-atomic isn't cheap. The new camera system costs close to half a million dollars. (The one in Conway's lab is currently on loan.)

Of course, seeing the virus clearly is only part of the objective.

"Understanding how the virus assembles, its architecture, how the virus interacts with its environment and host receptors and antibodies—that gives you the basis on which to start designing something useful as a therapy," says Conway.

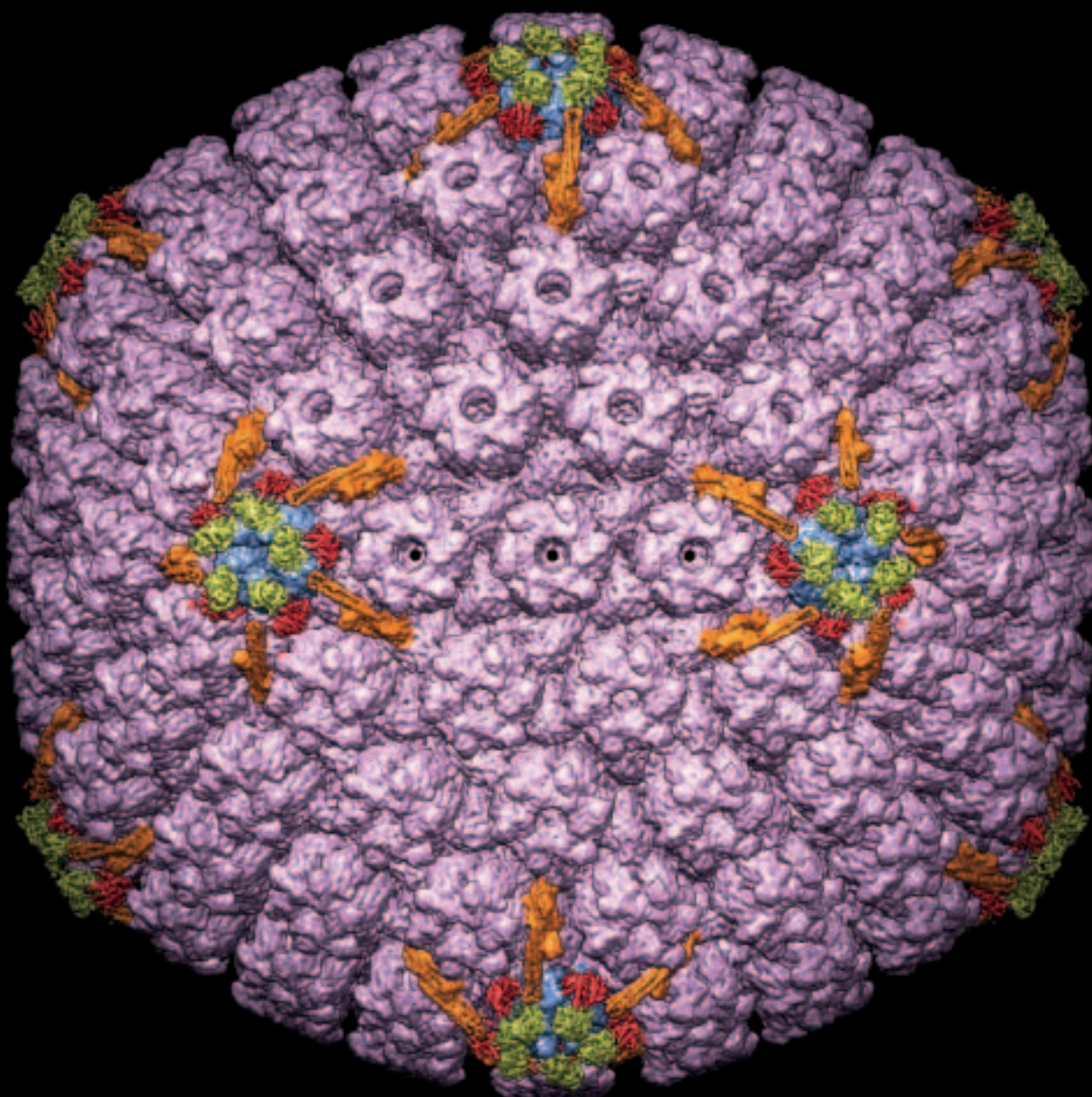
"But until you know how the pieces fit together, you can't even really start." ■



Above, from a close-up of a phage D3 protein helix, you can see how an atomic model (sticks) fit into the cryo-EM density (chickenwire). The shell of phage D3 is made up of 540 copies of the major capsid protein, which is, in turn, created by 20 different kinds of amino acids stringing together. Each of those amino acids has distinct side-chains, which give them their specific chemical and structural character. The way that proteins interact, and eventually assemble as building blocks or enzymes, is wholly dependent on the nature of those side-chains. Being able to “resolve” such blueprints of structure tells scientists a lot about function. Conway’s team has resolved D3’s side-chains.

The panel on the opposite page illustrates how far the field of cryo-EM has come. Just a few years ago, this same image would have looked like a bunch of “blobs and sausages” (that’s the technical term, says Conway). Instead, the proteins here appear more like corkscrews—right-handed corkscrews, to be specific. Conway explains, “For the first time, we’re really seeing secondary structure, not just a blob of the right length or a smooth tube of the right length. We’re seeing an actual chiral helix.” (In other words, he is able to see the direction of the spiral.) The purple ribbon above is a protein crystal structure identified from bacteriophage HK97 (so named because it was identified in Hong Kong), which infects *E. coli*. Notice the way it fits almost perfectly onto the helices of phage D3. “We’re seeing that we have a tremendous correspondence between this virus and the other virus,” says Conway.

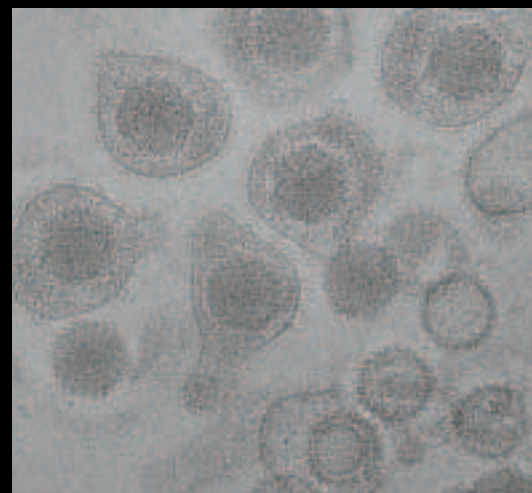
PURPLE “RIBBON” IMAGE OF BACTERIOPHAGE HK97: RETRIEVED FROM PROTEIN DATA BANK (ENTRY 3E8K)



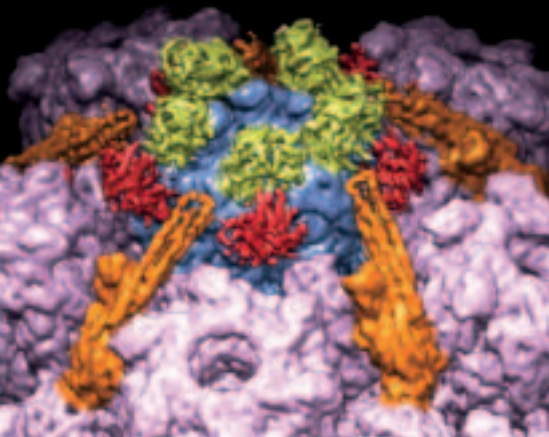
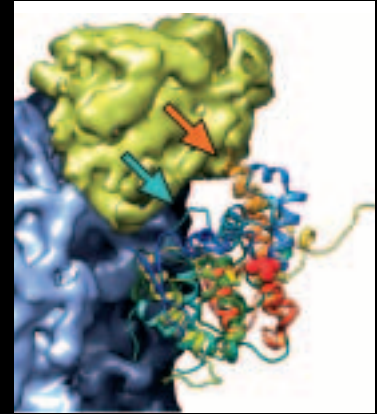
Behold the complex brilliance of a herpesvirus capsid (above and right). When people use the word “herpes” they are usually referring to HSV-1 or HSV-2, but a large family of viruses actually comprise *Herpesviridae*. Eight types are known to infect humans, including varicella zoster virus (the cause of chickenpox and shingles), Epstein-Barr virus (think, mononucleosis), and Kaposi’s sarcoma–associated herpesvirus (the cancer-causing KSHV is known for its opportunistic infections in AIDS patients and was discovered by Pitt’s Yuan Chang and Patrick Moore). According to the Centers for Disease Control and Prevention, about 90 percent of adults have been exposed to one kind of herpes or another. This makes it an extremely interesting virus for research, says Conway.

HERPESVIRUS CAPSID IMAGES COURTESY: JAMES CONWAY, ALEXANDER MAKHOV, ALEXIS HUET, DEPARTMENT OF STRUCTURAL BIOLOGY. FRED HOMA, JAMIE HUFFMAN, DEPARTMENT OF MICROBIOLOGY AND MOLECULAR GENETICS.

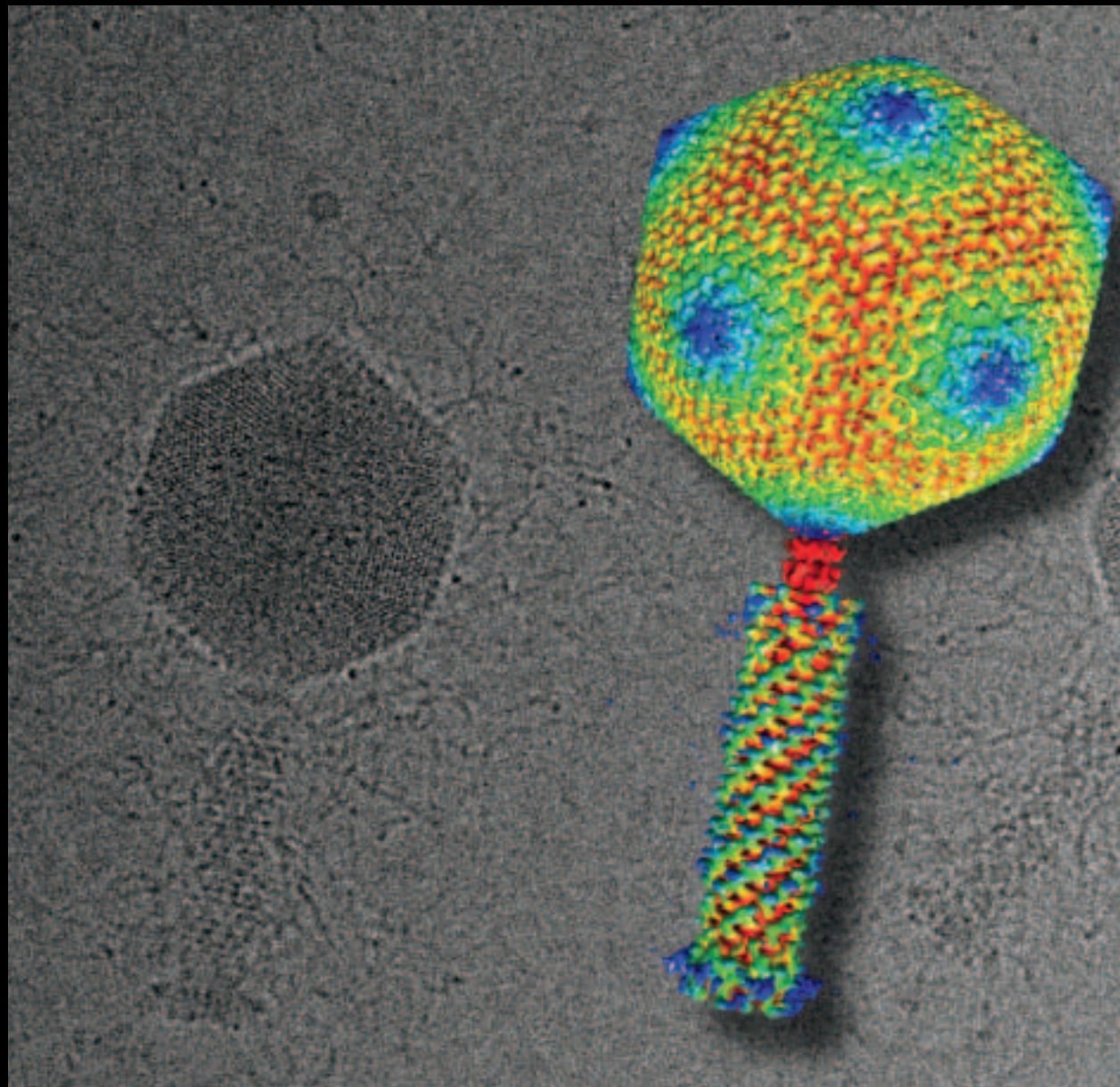
PHAGE 121Q (SHAPE OF MAGNIFYING GLASS, OPPOSITE PAGE) IMAGES COURTESY: JAMES CONWAY, ALEXIS HUET, DEPARTMENT OF STRUCTURAL BIOLOGY. ROBERT DUDA, ROGER HENDRIX, DEPARTMENT OF BIOLOGICAL SCIENCES.



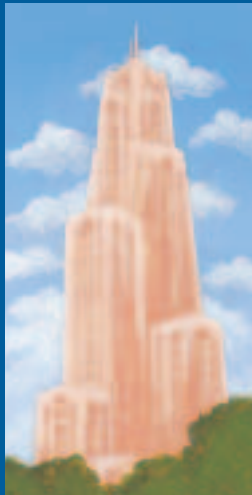
At 6 Å, the image to the right offers a rare glimpse into the way proteins interface on a herpesvirus capsid. Here, the red, burr-shaped protein (UL25) from the starfish-shaped constellation (shown lower left) has been replaced with an atomic structure obtained through X-ray crystallography—a field complementary to cryo-EM requiring proteins or protein fragments that can be crystallized. While this may look like no more than New Year’s confetti to most of us, to Conway it represents an opportunity to short-circuit the virus. The arrows point to sections where protein UL25 interacts with protein UL36. Perhaps scientists can develop a drug that mimics UL36 and binds with the confetti strands instead of UL36. Such a drug would have the advantage of being extremely specialized and unlikely to get in the way of any of the other cellular processes on which our bodies depend. With nonspecialized drugs, says Conway, “the medicine might be as bad as the disease—or worse.”



Compared to other viruses, the herpesvirus capsid is both massive and multifarious. We’re only just beginning to understand how it functions. Learning more about the capsid’s surface could yield more effective virus-fighting therapies. For instance, imagine a drug particle coming into contact with the vast wasteland of purple shown to the left. There are lots of places to land, but what should it target? The image above shows a starfish-shaped collection of proteins that we know to be responsible for maintaining the DNA stored inside the capsid. These proteins are crucial to the virus’s success—that also means they’re ripe for exploitation.



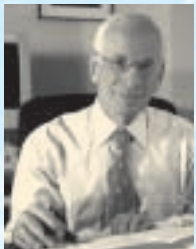
Phage 121Q, before and after: The gray image in the background shows the phage as Conway eyes it using cryo-EM. On the right, Conway has superimposed what that same particle looks like after a modeling makeover. This image shows the full bacteriophage particle, tail and all. When the phage finds a suitable host, it’s the tail that actually attaches to the cell and serves as a corridor through which the phage can pump its DNA.



CLASS NOTES

'50s

Middle ear disease (otitis media) is the second-most commonly diagnosed infection in children—but as recently as a few decades ago, “it was totally neglected” by researchers, says **Charles**



Bluestone

Bluestone (MD '58, Intern '59). In 1975 he founded Children's Hospital of Pittsburgh of UPMC's Department of Otolaryngology. This summer, as he retired after 50 years of service, Children's named Bluestone an honorary staff member, and Pitt named him Distinguished Professor Emeritus of Otolaryngology.

Bluestone trained 60 fellows, most of whom are now in academic medicine and several of whom are department chairs. He's also coauthor of the “bible” of the field, *Bluestone and Stool's Pediatric Otolaryngology*, now in its fifth edition. “This thing is a monster,” he says, placing it on his desk with a thud. “It should be online.”

An author of more than 250 articles and 27 books, he's still working—each month, Bluestone collects ENT literature from PubMed and posts it to the Society for Middle Ear Disease Web site, which he founded in 2012.

'70s

Frank Rudy's (MD '74) interest in pathology and laboratory medicine began early—he interned at the Harrisburg Hospital lab in high school and college. The former chair of the Department of Laboratories at PinnacleHealth System credits his Pitt training for turning his interest into a passion. Rudy has since paid it forward by educating hundreds of physicians on test interpretation and use. In 2014, Rudy received the Laboratory Accreditation Program Service

Award from the College of American Pathologists at a ceremony in Chicago. This national award recognizes his efforts to improve patient safety.

'80s

Robert Brolin (Surgical Resident '80), a charter member and former president of the American Society for Metabolic and Bariatric Surgery, recently won the organization's 2014 Outstanding Achievement Award. The codirector of Metabolic and Bariatric Surgery at University Medical Center of Princeton at Plainsboro, N.J., former professor of surgery at Rutgers Robert Wood Johnson Medical School, and self-described “Bahnsen boy” (a tip of the hat to former Pitt surgery chair Hank Bahnsen) has performed more than 3,200 bariatric procedures. “I think that [Pitt] is a major contributor to my success.” And he wants to make it very clear that, even though he no longer lives in the Steel City, he remains a huge Steelers fan.

'90s

Margaret Larkins-Pettigrew (MD '94, Obstetrics and Gynecology Resident '98), associate professor of obstetrics and gynecology and of reproductive biology at Case Western Reserve University, is a founding member of WONDOOR (Women Neonates Diversity Opportunities Outreach Research), an organization that helps advance maternal and neonatal health worldwide. Through international partnerships with health care providers, it also provides training for emerging physicians. Mentoring young physicians—especially from underrepresented groups—has long been a priority for Larkins-Pettigrew, who was recently named the Edgar B. Jackson Jr., MD, Endowed Chair for Clinical Excellence and Diversity. To assuage health care inequities on a grand scale, she says, “We need to develop specialty physicians to stay in resource-poor countries.”



Larkins-Pettigrew

In **David Madoff's** (MD '95) years as an interventional radiologist, what has surprised him the most is how, as of late, cancer has become so multidisciplinary. (For example, specialists now come together to manage tumors affecting the liver, kidney, and lungs.) “In the past, radiology was largely limited to image interpretation. Nowadays, interventional radiologists often offer primary oncologic therapies that are minimally invasive, improving survival and quality of life, with low complication rates.” In September 2014, a book he co-edited, *Clinical Interventional Oncology*, received a “highly commended” citation from the the British Medical Association.

In 2008, **Clifton Callaway** (Emergency Medicine Resident '96), an MD/PhD and the Ronald D. Stewart Professor of Emergency Medicine Research at Pitt, and his colleagues in critical care medicine and surgery realized that, instead of competing for the same acute-care clinical trial participants, they just might do better by working together. So Callaway, along with **David Huang** (Critical Care Medicine Fellow '03), MD/MPH associate professor of critical care medicine and emergency medicine, and **Jason Sperry**, MD/PhD associate professor of surgery and critical care medicine, and a host of other Pitt colleagues joined forces in a new collective dubbed the Multidisciplinary Acute Care Research Organization, or MACRO. Its first director was Pitt's **Scott Gunn** (Critical Care Medicine Fellow '01), an MD associate professor of critical care medicine. Theirs was a big idea that's yielding big benefits, as detailed in a 2013 *Journal of Trauma and Acute Care Surgery* study. The team saw a 300 percent increase in patients enrolled in a three-year period. (For more on what Callaway has been up to, see our infographic on p. 12, “The Rush to the Hospital: Pitt People Paved the Way.”)

'00s

Matthew Hartman (MD '02) studied the second edition of *Clinical Radiology: The Essentials* as a Pitt med student. Now an assistant professor of radiology at Temple University, Hartman has come full circle, serving as a coeditor of the fourth edition. He thanked his Pitt mentor, **Carl Fuhrman** (MD '79), in the acknowledgments. And, he's quick to add, another alum, Pitt associate professor of radiology **Matthew Heller** (MD '01, Radiology Resident '06, Abdominal Imaging Fellow '07), cowrote a chapter.

The new edition includes references for docs in all fields, particularly in regard to their two most burning radiology-related questions, which Hartman identified in a study published in *Academic Radiology* in 2013: First, how to determine which imaging tests to order. Second, how to read a chest X-ray to ensure a tracheal tube has been put in correctly.

If you're wondering why Hartman's name sounds so familiar, it could be because you saw the name of his “superstar wife,” **Amy Hartman** (Microbiology PhD '03), in the newspaper. An expert in highly pathogenic viruses, she was a media go-to through much of the recent Ebola coverage in Pittsburgh, having studied the virus as a fellow at the Centers for Disease

Control and Prevention. Now, she studies Rift Valley fever at Pitt as assistant professor of infectious disease and microbiology in the Graduate School of Public Health and also serves as research manager of the Regional Biocontainment Laboratory at the Center for Vaccine Research.

In July, the journal *RadioGraphics* will publish a paper the Hartmans cowrote as a sort of microbiology 101 course for clinicians. “Most physicians don't

have a good sense of microbiology and infection control,” says Matt Hartman. The paper includes equipment-cleaning protocols, guidelines for protective gear, and other helpful hints for docs and techs as they cross paths with TB, MRSA, *Clostridium difficile* colitis, and other pathogens. Yet another Pitt med alum, **Melanie Fukui** (MD ’87, Radiology Resident ’91, Neuroradiology Fellow ’92), was a coauthor, as well.

Recently, Tripler Army Medical Center’s Colonel **Becket Mahnke** (Pediatric Cardiology Fellow ’03) was awarded the 2014 Thurman Award for Excellence in Telemedicine and Advanced Medical Technology from the comfort of his office chair in Hawaii. It was fitting that the American Telemedicine Association bestowed this honor during a video teleconference—working across several time zones, via various technologies, is SOP (standard operating procedure) for Mahnke. He serves as director of Pacific Asynchronous TeleHealth (PATH), a provider-to-provider teleconsultation platform used by military medical facilities throughout the Pacific Region. Mahnke continued to direct PATH during deployments to Iraq and Afghanistan.

—Robyn K. Coggins, Nick Moffitt, and Elaine Vitone

A FRIEND INDEED

Got the scoop on a fellow alum who’s doing something great? We’re all ears at medmag@pitt.edu.

MAA SAYS, “ICE, ICE, BABY.”

In 1897, Queen Victoria celebrated 60 years on the throne of England, and the party was so big, it got a name—the Diamond Jubilee. Since then, that flashy gemstone has become the traditional gift for a six-decade affair.

What’s that got to do with Pitt’s School of Medicine? Funny-show *Scope and Scalpel* will mark the big 6-0 with a special anniversary production. *Pitt Med: SPU* has an irreverent *Law & Order* vibe. Check out scopeandscalpel.org/videos to see a trailer for the upcoming act. And this year, the Class of ’55 will celebrate a whopping 60 years of camaraderie at the Medical Alumni Association’s Alumni Reunion Weekend, this May 15–18.

There are plenty of other gems to be found during the celebrations: Classes ending in 0 or 5 are invited to reunite during this extended weekend of laughs and memories (and maybe a few giveaways). The alumni weekend intentionally coincides with the School of Medicine’s graduation (Monday, May 18), so scholars young and not-so-young can party together.

Of particular intergenerational interest: the Champagne Breakfast, which will be Saturday, May 16 at 9 a.m. As usual, attendees will brunch with the dean, get a quick school update, and witness the Philip S. Hench Distinguished Alumnus Award ceremony. But this year’s breakfast comes with a new element—a student panel, which “will give the alumni an opportunity to ask questions about the students’ day-to-day activities, as well as the type of projects they have been a part of,” says Pat Carver, executive director of MAA.

So join your Pitt med brothers and sisters (and daughters and sons), and raise a glass to the next 60 years. May they be just as sparkling. —RKC

MEDICAL ALUMNI ASSOCIATION WWW.MAA.PITT.EDU

NICOLE SHIRILLA

UPHOLDS LIFE, AND DEATH

Outside a hospital in Port-au-Prince, Haiti, in 2008, several Pitt med students huddle around a priest. “Poverty degrades people’s humanity, and it doesn’t end when they die,” Father Rick Frechette warns. They see what he means when they enter a morgue where the bodies of deceased patients—whose families do not have the means to bury them—have been placed. Together they honor the dead with a burial service.

Among the med students is Nicole Shirilla (MD ’11), who arranged this trip after learning of the St. Luke Foundation for Haiti, an organization that provides education, medical care, employment opportunities, and humanitarian outreach to Haiti’s most underserved. After inviting six other classmates to volunteer with her during spring break, Shirilla approached professor of emergency medicine Susan Dunmire (MD ’85), then-executive director of the Medical Alumni Association, to inquire about financial assistance.

“They were incredibly responsive and supportive,” Shirilla says.

With MAA’s green light, the group observed day-to-day life in Cité Soleil, a



Nicole Shirilla (second from the right) and colleagues at St. Luke Hospital.

region near Port-au-Prince that, with 200,000 residents living without proper sanitation or infrastructure, is considered the largest slum in the Western Hemisphere. In Tabarre, Haiti, the students volunteered alongside Haitian doctors at St. Damien pediatric hospital, which successfully treats thousands of patients. At a nearby chapel, they paid tribute to those who died. This experience bolstered Shirilla’s desire to focus her life’s work on palliative care.

The 2010 earthquake magnified the area’s need, and Shirilla has maintained her connection to St. Luke, returning to Haiti when possible. Alongside the pediatric facility, a makeshift general hospital was erected; Shirilla has volunteered in its emergency department.

Now, as a hospice fellow at the University of California, Irvine, Shirilla remains committed to upholding the dignity of all, particularly those suffering from terminal illness or approaching the end of their lives. She often recalls those moments of honoring the dead in Haiti: “Your work doesn’t end when you can’t cure someone.” —Liberty Ferda



Playbill from *Scope and Scalpel's* 1955 PMS IV.

CAROL M. ANDERSON

NOV. 1, 1939–NOV. 20, 2014



Anderson



Schultz



Szulman



Turner

University of Pittsburgh professor emerita of psychiatry and social work Carol Anderson, a PhD, “was incredibly innovative and far-sighted—she turned the treatment of schizophrenia completely on its head,” says Armando Rotondi, PhD associate professor of critical care medicine and health policy and management at Pitt.

Anderson, coauthor of *Schizophrenia and the Family: A Practitioner’s Guide to Psychoeducation and Management*, widely viewed as a seminal publication in the field, died in November.

After earning her PhD in interpersonal communication at Pitt, Anderson joined the Yale University School of Medicine faculty in 1968 and then returned to Pittsburgh in 1973, as part of Thomas Detre’s team of researchers and clinicians at the School of Medicine and the Western Psychiatric Institute and Clinic.

At WPIC, Anderson established a psychoeducational program for patients with schizophrenia and their families (teaching them how to best deal with the disorder), which became a national model for treatment. Anderson “was a pioneer” in this area, says Gretchen Haas, a PhD and Pitt associate professor of psychiatry and psychology.

“Her approach to treatment was radical and had far-reaching effects on mental health care,” says Rotondi. —Lori Ferguson

STANLEY G. SCHULTZ

OCT. 26, 1931–OCT. 23, 2014

Stanley Schultz, an MD, was renowned both as an outstanding scientist and skilled educator.

A former dean of the University of Texas Medical School at Houston, Schultz was a critical figure in advancing the understanding of epithelial ion transport. His early work demonstrated, for the first time, sodium-coupled sugar and amino acid absorption by the small intestine and underpins the science of oral rehydration therapy (ORT), a process cited by the World Health Organization as second only to vaccination as a lifesaving intervention.

Schultz joined the Department of Physiology at the University of Pittsburgh in 1967 where he earned several Golden Apple awards. “I learned how to teach from Stan,” says John H. “Jack” Byrne, a PhD and the chair of neurobiology and anatomy at UTHHealth.

“He was a master of pedagogy.”

“Stan had the unique ability to explain difficult concepts by use of examples and humor,” notes Raymond Frizzell, a PhD professor of cell biology and director of the Cystic Fibrosis Research Center at Children’s Hospital of Pittsburgh of UPMC. (Schultz once likened the way a pair of charged molecules moves through a membrane channel to establish a diffusion potential to a poor swimmer being attached to an Olympic swimmer via a rubber band.) “He was a mentor to us all,” says Frizzell. —LF

ARON E. SZULMAN

MAY 3, 1920–NOV. 22, 2014

Aron E. “Bob” Szulman, MD professor emeritus of pathology, conducted groundbreaking work on rare uterine masses known as hydatidiform molar preg-

nancy and choriocarcinoma, notes Pitt pathology chair George Michalopoulos (an MD/PhD who is the Maud L. Menten Professor of Pathology). “He nurtured and trained a lot of people on the role of chromosomes in embryonic development and maternal fetal medicine. And he was one of the nicest people I’ve ever met.”

Szulman, who joined Pitt in 1964 and became full professor in 1981, was a popular lecturer, speaking frequently at symposia internationally. His contributions were recognized upon his retirement with the establishment of an annual scientific lectureship at Pitt.

Szulman “had an amazing sense of humor and a great intellectual curiosity, both of which he maintained until the end of his life,” observes Urvashi Surti, a PhD and director of the Pittsburgh Cytogenetics Laboratory. “Even in his final days, he was very interested in discussing my latest research.”

The pathologist was a member of the World Health Organization Scientific Group and a fellow of the UK’s Royal College of Pathologists. —LF

MORRIS E. TURNER

OCT. 2, 1948–JUNE 30, 2014

Morris Turner (MD ’73, Res ’76) hit his 60s before his chair in Pitt’s Department of Obstetrics, Gynecology, and Reproductive Sciences, W. Allen Hogge, an MD, told him he needed to slow down. Turner was still on call every fourth night, providing services to women who otherwise might not have had access to care.

I can’t slow down, he told Hogge, who recently retired as chair. Turner was too concerned about making sure the women of Pittsburgh got the care they needed. As a med student, Turner saw the devastating effects of back-alley abortions, and, when he opened his East Liberty practice in 1976, he became one of the few abortion providers in the city. He and his partner later planted clinics throughout the county.

Turner served as president of the medical staff at Magee-Womens Hospital of UPMC, chief of gynecological services at UPMC McKeesport, and medical director for both Adagio Health and Allegheny Reproductive Health Center, as well as a member of the Allegheny County Medical Society’s Board of Directors. At Pitt med, he was an active student mentor and member of the Admissions Committee. —Amy Whipple

IN MEMORIAM

’50s

WILLIAM HARRISON PITTS
MD ’51
OCT. 26, 2014

OTTO F. SWEGAL
MD ’52
DEC. 5, 2013

JOHN R. QUINN
MD ’53
OCT. 21, 2014

FENTON M. MITCHELL
MD ’57
OCT. 15, 2014

EDWARD WILLIAM HEINLE JR.
MD ’58, RES ’63, FEL ’65
AUG. 30, 2014

’60s

ROBERT R. CASSELLA
MD ’60
DEC. 1, 2014

RICHARD MINNEAR
MD ’61
OCT. 6, 2014

PAUL HARKINS
MD ’62
OCT. 28, 2014

LEROY S. INDORATO
MD ’67
OCT. 26, 2014

’80s

MICHAEL D. PATTERSON SR.
MD ’80
NOV. 26, 2014

DAVID L. WEINSWEIG
MD ’85
SEPT. 13, 2014

BRIAN J. CAPUTO
MD ’89
NOV. 9, 2014

’00s

NICOLE M. KOTCHEY
MS ’07
NOV. 12, 2014

FACULTY

ALBERT STRATTON
NOV. 21, 2014

SURGEON HERBERT ZEH RETHINKS PANCREATIC CANCER

BY SHARON TREGASKIS

Surgical oncologist Herbert Zeh (MD '94) says he isn't a runner. And yet he signed up for the Pittsburgh, New York, and Dublin marathons. "It seemed like an interesting challenge," says the Pitt associate professor of surgery, who completed every step of the 26.2 mile routes in New York and Pittsburgh. (And the Dublin finish line? "The pint of Guinness seemed more important," he quips.)



And as a third-year medical student, Zeh signed up for a post in the laboratory of the University of Pittsburgh's Michael Lotze, investigating the role of the immune system in cancer. The collaboration was so productive, Zeh took a year off from his coursework to author seven papers on their findings.

So don't let that quip about the Guinness distract you—Zeh is tenacious. Consider his chosen field. He is chief of UPMC's Gastrointestinal Surgical Oncology Division and codirector of the UPMC Pancreatic Cancer Program.

Typically identified late in its progression, pancreatic cancer kills 75 percent of patients in the first year after diagnosis. "Pancreas cancer was the highest mountain out there," says Zeh, who also directs clinical research for UPCI's Division of Surgical Oncology.

Prospects for survival are better for those who undergo the Whipple, a complex surgical procedure with an ominous reputation among surgeons and patients alike. During the operation, surgeons remove the head of the pancreas, the gallbladder, and portions of the small intestine, bile duct, and sometimes the stomach.

Then they replumb the whole system to excise pancreatic tumors and their blood sup-

ply while preserving gastrointestinal function.

Despite significant advances in the past 40 years, about 40 percent of patients experience significant postsurgical complications. Zeh mastered the procedure as a senior resident and fellow at Johns Hopkins Hospital, training at the elbow of John Cameron. "When Cameron started in the '70s, patient mortality was 30 percent from the Whipple," says Zeh. "By the time I graduated, only 1 to 3 percent of our patients died from the surgery. But we hadn't made any progress on survival from the pancreatic cancer. Even if we did a successful surgery, 90 percent of the time, the cancer would come back."

In 2002, Zeh joined the Pitt faculty and set about developing a robotic surgical program to further minimize the trauma and blood loss of the conventional Whipple and speed recovery. Recently, he partnered with assistant professors of surgery Melissa Hogg (Fel '13) and Amer Zureikat (Fel '10), to develop a surgical training program using the robotic techniques. "This approach gets more patients on to chemo, helps them return to health and work quicker, and they don't have as much pain," says Zeh. "The bottom line is that a complex operation like the Whipple can't be done safely with the current [nonrobotic] laparoscopic technology," because of the extremely fine dexterity required, he says.

Back at Pitt, Zeh also reconnected with

Lotze, MD professor of surgery, immunology, and bioengineering and vice chair for research in the Department of Surgery, who had overseen Zeh's foray into research as a med student. In 2003, they started work on a study that would be published in 2005 by the *Journal of Immunotherapy*, "Addicted to Death."

"We suggested that cancer cells had learned to die in the wrong way, and [that] what we see as cancer is a consequence of their dying—a terrible, awful, crying out loud, blood-in-the streets kind of death," says Lotze. "Virtually everything we imagined has come true."

The two have since coauthored 56 papers, many on aspects of what is known as autophagy, a process that recycles damaged cellular components and returns a cell to useful service and, in cancer, appears to fuel a malignant cell's survival.

In a series of ongoing investigations, Zeh, Lotze, and Daolin Tang, a PhD assistant professor of surgery, are testing tactics to interrupt autophagy in pancreatic cancer and elucidate the molecular mechanisms by which the cellular repair process runs off course. Promising data from clinical trials of a drug that halts autophagy in pancreatic cancer patients suggest the trio is on the right track. "Over the last two years, we're starting to see changes that make me think we might get the rock up the hill," says Zeh. "And I'm crazy enough to think the gods won't push it back down." ■



COURTESY ZEH

Zeh performing a robotic Whipple at UPMC Presbyterian, one of only a handful of hospitals in the United States to offer the procedure.



THE MOST KISSED FACE

It is said that at the end of the 19th century, a mysterious young woman drowned in Paris in the Seine. Though her body was put on display, as was the custom then, no one could identify her.

Yet her presence attracted many gawkers and much romantic speculation. People suggested she threw herself in the river because of a broken heart. The story goes that the morgue director was so enamored with her visage that he had a mold of her face made. Eventually, copies of this death mask would be sold by the millions throughout Europe. It was transfixing. The girl's expression was, all at once, innocent, beguiling, and knowing. And oddly peaceful.

L'inconnue de la Seine, or the Unknown Woman of the Seine, has inspired poets and novelists alike.

Yet forensics experts have wondered aloud if it is possible that the mask could have been made from a drowning victim—such corpses tend to have bloated, or worse, skin.

Ironically, the “death mask” would go on to save many lives.

In 1960, after Pitt's Peter Safar co-developed cardiopulmonary resuscitation (CPR), he called Norwegian toy maker Asmund Laerdal. Would he be willing to create a mannequin on which people could practice CPR? Laerdal, as it turned out, had just saved his 2-year-old son from drowning. He consented and suggested the mannequin bear the face of the unknown drowned girl; his family had one of the masks.

The girl now has a name—Resusci Anne. And each year, more than 12 million CPR trainees attempt to breathe life into her.

—Jamar Thrasher and Erica Lloyd

—Photo from Wikimedia Commons

CALENDAR

FOR ALUMNI & FRIENDS

HEALTH SCIENCES

ALUMNI RECEPTIONS FLORIDA

MARCH 11

Winter Academy Palm Beach

MARCH 13

Winter Academy Naples

FOR INFORMATION:

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MEDICAL ALUMNI ASSOCIATION REUNION WEEKEND

MAY 15-18

Reunion Classes:

1955, 1960, 1965, 1970

1975, 1980, 1985, 1990

1995, 2000, 2005

MAY 15, 11 a.m.

Graduation Luncheon

Alumni Hall, J.W. Connolly Ballroom

MAY 15, 5 p.m.

Grand Opening Reception

Pittsburgh Athletic Association

MAY 15, 6:30 p.m.

An Evening at the Symphony

Heinz Hall for the Performing Arts

"The Sound of a Modern Symphony"

MAY 15, 7 p.m.

Scope and Scalpel

Central Catholic High School, McGonigle Theater

MAY 16, 9 a.m.

Breakfast with the Dean and

Today's Medical Student

Scaife Hall, 11th Floor Conference Center

MAY 16, 6 p.m.

Reunion Gala: Dinner and Dance

Twentieth Century Club

MAY 17, 2 p.m.

Scope and Scalpel

60th Reunion Celebration

Central Catholic High School, McGonigle Theater

MAY 18, 11:30 a.m.

Farewell Alumni Reunion Brunch

Wyndham Pittsburgh University Center

MAY 18, 4 p.m.

Class of 2015 Graduation Ceremony

Soldiers & Sailors Memorial Hall & Museum

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MACE FROLOW/BETTY IMAGES



Organ magic



FOR REAL! TWEEN SCIENCE

Right now, about 84,000 people in the United States are waiting and hoping for new livers, hearts, and other essential organs to save their lives. Unfortunately, their hopes for a better future rely on tragedy for others—organs are donated by people who have agreed to share theirs when they die. But even when organs become available, they need to be good matches in blood type, size, and other factors in order for the operation to succeed. This is why many patients wait years for new organs; it's a problem with no easy solution.

But what if doctors could instead make new organs for people as needed? It sounds like something you might expect to find in the infirmary at Hogwarts, but scientists are actually inventing ways to "print" organs. Researchers can scan the patient to determine the size and shape of the failing organ, and then use a 3-D printer loaded with collagen (a structural protein that gives shape to otherwise amorphous blobs of cells) instead of ink, to create a custom-made organ scaffold. Doctors can then "plant" cells from the patient—often from bone marrow—onto the scaffold and let them multiply.

Researchers don't yet know how to print fully functioning organs like a lung, which is made up of several different types of cells and requires complicated networks of blood vessels to work properly. (So hold on to your broomsticks, Quidditch enthusiasts.) Yet they are making progress. Some have grown skin and other tissues from tailor-made scaffolds to treat patients for burns, birth defects, and injuries. (Pitt's Rocky Tuan has grown living cartilage.) Some are starting to use 3-D printed scaffolds as guides in surgery. And others have conjured up 3-D generated models to better understand molecular structures and how the body works its magic. —Jennifer Lienau Thompson

For more on bio-conjuring gadgetry: See this TED talk tinyurl.com/664neeu and this *New Yorker* story, tinyurl.com/opq3stj

For more kids' stuff: www.howscienceworks.pitt.edu

The Scope and Scalpel Society Presents . . .

SCAR TREK

A
MUSICAL FLIGHT
OF IDEAS

Free

May 23rd
and 24th
1975
8:00 p.m.

Taylor Allderdice
High School
Auditorium
2409 Shady Avenue

“DAMMIT, JIM. I’M AN ALUM!”

So it’s been a few trips around the sun since the Class of ’75’s production of *Scar Trek*. Fortunately, catching up with the crew at Medical Alumni Association Weekend this May 15–18 is as good as traveling back in time—but without those beehive-mussing warp speeds. While you’re aboard, don’t miss brunch with the captain (er, dean) and the highly illogical antics of Scope and Scalpel, celebrating 60 long and prosperous years. Phasers on pun!

The full reunion schedule appears on the other side of this cover.

Reunion Classes:

1955, 1960, 1965, 1970

1975, 1980, 1985, 1990

1995, 2000, 2005

For more information, contact Pat Carver at
412-648-9741, cpat@pitt.edu