

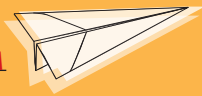
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2017

PITTMED



FOREVER YOUNGISH

IN SEARCH OF A UNIFIED THEORY OF AGING



FLY BABIES

I was a pediatric resident at Pitt from 1972–1975. During that time, our chair, Dr. Thomas K. Oliver, a neonatologist, organized a program to transport newborns who were born elsewhere and in distress to Magee-Womens Hospital and Children's Hospital via helicopter. We took off from and landed at Pitt stadium. After takeoff, we usually circled the Cathedral of Learning. People inside would clap and cheer as we flew by.

Several months ago, I had the good fortune to meet Dr. Paul Offit (Res '80)—like me, he graduated from the University of Maryland School of Medicine and completed a pediatric residency at Pitt. He made the comment that I must have gone up in helicopters a good number of times; he was correct. The experience was fantastic. We helped many infants survive.

It would be great to learn how many heli-

copter trips were made during these years. I'll never forget the experience.

John Nizioł (Res '75)
Clifton, N.J.

Editor's Note: *Can anyone help us come up with a number of flights for Dr. Nizioł?*

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

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MAKE TRACKS

'Cause you don't want to miss the latest Pitt Medcasts, like "Inside the World of OCD" and "How the Nose Knows."

bit.ly/pittmedcast

PITTMEDCAST



WILL I SEE YOU IN SEPTEMBER?

Come have a good time at Medical Alumni Weekend **September 15–16**, and remember:

We'll see you when the summer's through, with an opening ceremony at the Heinz History Center—and presentation of the Philip S. Hench Distinguished Alumnus Award to Theresa Guise, too.

maa.pitt.edu

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New York artist **JULIETTE BORDA** [cover, "Forever Youngish"] has been described as one of the defining illustrators of the twenty-first century. Borda refuses to put a label on her artistic style, saying it would be like describing someone's personality—it's too multifaceted. A seasoned artist, Borda says she never questions the inspiration that comes to her and often makes illustrations without first assessing their validity. She likes to experiment with bold colors and angular images. Her subtle but pointed imagery can be regularly found in the pages of the *New York Times*. It's also part of the collection at Pittsburgh's Carnegie Museum of Art.

As a reporter for the Associated Press in Los Angeles in the '90s, **NIKI KAPSAMBELIS** [*The Inheritance*] put in for a transfer to Pittsburgh after covering the O.J. Simpson trial. It's perhaps not surprising that Kapsambelis, who plays and coaches ice hockey, would become a die-hard Penguins fan living here. The move would eventually also lead her to the DeMoe family, several of whom carry the gene for early onset Alzheimer's. Initially assigned to write an article about them for Pitt, Kapsambelis was so captivated by the DeMoes that she dedicated the next few years chronicling their story in a book, *The Inheritance* (Simon and Schuster, 2017).

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2017
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7

DEPARTMENTS

OF NOTE 3

Good cells saved.
Seeing vision loss before it happens.
Skin protected from radiation therapy.

CLOSE-UP 7

They were in the neighborhood.

INVESTIGATIONS 8

A multipurpose biobutton.
How tumor growth goes into overdrive.
When you reminisce upon an fMRI.

ATTENDING 33

Students at the table.

ALUMNI NEWS 36

Haley: Dean of Jacksonville.
RIP Gordon-Burroughs, Needleman,
and Youngner.

LAST CALL 40

He got the lead out.

FOR REAL! 40 1/2

Eye dye.



40 1/2

COVER

Some people seem to age extremely well. Why?
(Cover: Juliette Borda © 2017.)



24

FEATURES

Forever Youngish

12

Can we get old without falling apart? Aging, the biggest risk factor for most chronic diseases, has always been dismissed as nonmodifiable. But maybe we can change how we age.

COVER STORY BY JENNY BLAIR

Untangling Darwin

18

Vaughn Cooper studies evolution in action. Now, he's beginning to think it may be possible to predict evolution.

BY ELAINE VITONE

Mutual Support

24

A support group at the Dorothy P. and Richard P. Simmons Center benefits doctors as much as it does patients.

BY GAVIN JENKINS

In Memory

28

Every week, someone calls Julia Kofler, offering a loved one's brain.

BY NANCY AVERETT

The Inheritance

30

Five out of the six DeMoe siblings, as well as their father and grandmother, had early onset Alzheimer's. This North Dakota family has helped Pitt's Chester Mathis and William Klunk begin to unmask the disease. A new book tells the family's story.

EXCERPT BY NIKI KAPSAMBELIS

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A

nything found to be true of *E. coli*
must also be true of elephants.

—Jacques Monod

A huge glow-in-the-dark replica of *Escherichia coli* will be on display in Manhattan's City Hall Park through the fall. It's part of an exhibition by Katja Novitskova showcasing life on this planet that appears otherworldly. The 3-D piece, at about twice my height, is not particularly beautiful. Nor is it likely to become a favorite among jaded New Yorkers. Still, like Novitskova, I appreciate—and in fact, I am in awe of—*E. coli*.

The microbe is used to notoriety. It's the germ that most people associate with food poisoning. Yet there are thousands of strains of the bacterium, many of which are critical citizens of our microbiome and important to our gut health. Biologists like it because it's easy to grow and to manipulate genetically, and its genome is now better understood than that of any other organism. The humble *E. coli* has played a vital role in biotechnology since the industry's genesis, and its usefulness continues to astonish me.

In the 1960s, enzymes were discovered in *E. coli* that cleave the DNA of attacking viruses at restricted sites (hence they were called "restriction enzymes"). It was soon apparent that when purified, these enzymes could be used to manipulate any DNA, and this advance in basic science (recombinant DNA) ultimately gave birth to the trillion-dollar biotechnology industry. For the discovery and characterization of restriction enzymes, the 1978 Nobel Prize was awarded to Arber, Nathans, and Smith. Also in 1978, Pitt alumnus Herb Boyer, in San Francisco, inserted a human insulin gene into *E. coli*, thereby producing large amounts of synthetic insulin. That approach laid the groundwork for many effective treatments for human disease and mega-companies such as Genentech. In 2012, UT Southwestern's James Chen, one of our Legacy Laureates, leaned on *E. coli* to identify a previously unknown pathway (cGAS-STING) that triggers an inflammatory and immune response when viral DNA is detected outside of the cell nucleus. This pathway appears to play a role in human tumor surveillance and autoimmunity, and it may help boost the effectiveness of vaccines.

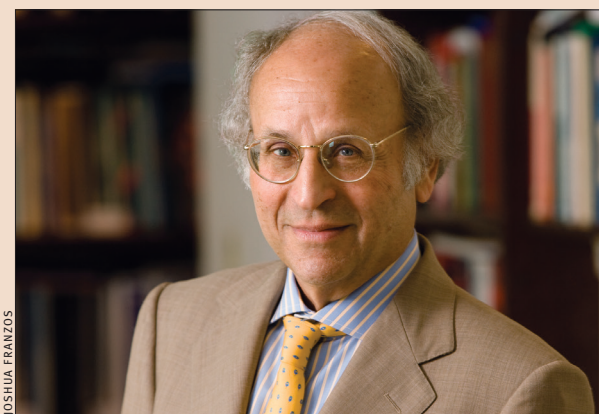
Another of *E. coli*'s ancient defense mechanisms—CRISPR-Cas9, further developed as a biotechnology tool by our 2016 Dickson Prize winner Jennifer Doudna—has created extraordinary scientific and ethical interest. CRISPR (clustered regularly interspersed short palindromic repeats) are sequences in our DNA that in bacteria were originally derived from invading viruses. Subsequently, any attacking viral DNA that matched those sequences in the bacterial genome was cleaved by a CRISPR-associated enzyme (Cas). Now scientists can apply that system, together with a "guide RNA," to target any gene that matches that RNA. Clearly, the technology can be used to edit genes that cause human disease—adding ones that are missing or disabling ones that cause a disease. And recently, labs in China and Oregon used this approach to alter the genes of very early human embryos in vitro. We will need to be vigilant in our ethics as we step into this precarious territory.

The idea that we have been able to carjack a seemingly simple bacterium's multiple defenses against invading viruses to gain profound insight into human biology, and even alter that biology, truly is, as I noted before, astonishing. What a testament to basic science investigation, which the National Science Foundation defines as research with no apparent application when it is begun!

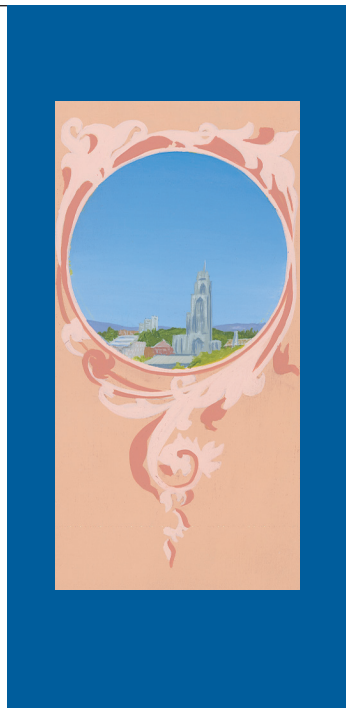
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JOSHUA FRANZOS



*Devoted to noteworthy happenings
at the medical school*

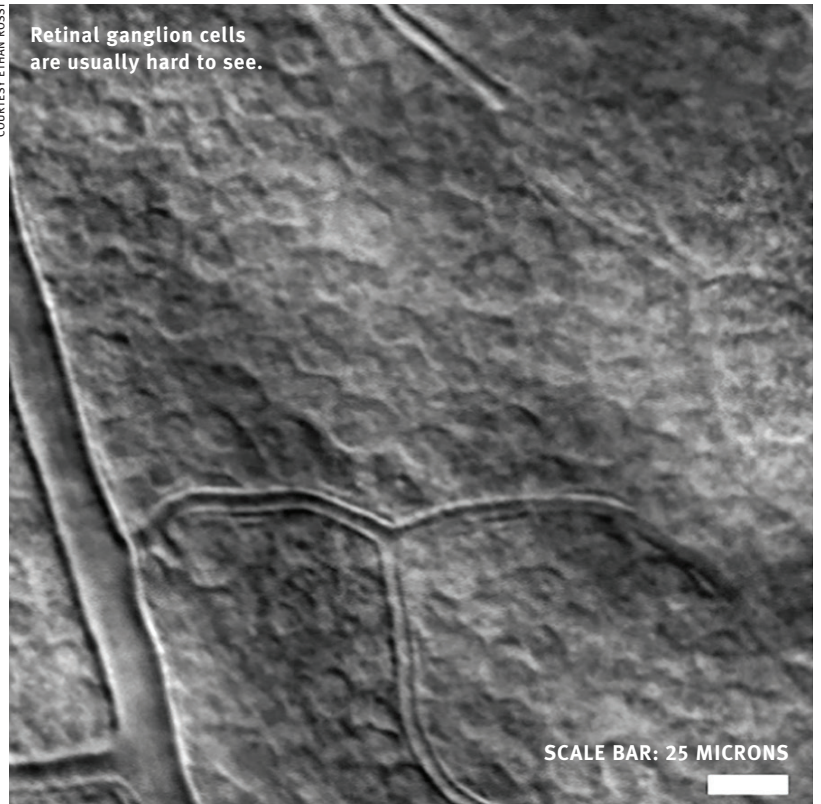
Saving Good Cells

Chemotherapy and radiation treatment can harm healthy cells in the struggle against cancerous ones. University of Pittsburgh researchers have found an alternative approach that may be used to target aggressive forms of cancer while avoiding harmful side effects.

Developed by a team led by Jianhua Luo, director of the High Throughput Genome Center in the Department of Pathology, the approach takes advantage of the popular genome-editing technology called CRISPR-Cas9. This method can shrink tumors in mice as much as 30 percent by removing and replacing specific “fusion genes” that are often present in cancer cells. These fusion genes result from the merging of two separate genes and often code for abnormal proteins. Luo, whose lab has identified eight prostate cancer fusion genes, believes that the therapy only reduces tumor size rather than eliminating tumors completely. Why? Because each cancer has many fusion genes. Identifying and targeting these genes may be essential for cures. —*Rajiv Reddy*

COURTESY ETHAN ROSSI

Retinal ganglion cells
are usually hard to see.



SCALE BAR: 25 MICRONS

EYE-OPENING BREAKTHROUGH

Vision loss may be detectable before it happens, thanks to a breakthrough retinal imaging technique developed by Ethan Rossi, PhD assistant professor of ophthalmology at Pitt. Conventional technology used by eye doctors cannot detect the individual retinal ganglion cells (RGCs), which the brain relies on for visual information. With Rossi's new retinal imaging method, he hopes to catch changes to both the structure and size of the RGCs, allowing doctors to detect early signs of retinal disease long before nerve fibers begin to thin.

Rossi published his findings in the *Proceedings of the National Academy of Sciences* in December. “We have a lot of work to do to translate these new techniques into a clinical tool that we can use routinely on patients,” says Rossi. —*Kate Benz*

FOOTNOTE

Tolerant and welcoming. The staff and Pitt docs at Children's Hospital of Pittsburgh of UPMC and Western Psychiatric Institute and Clinic of UPMC can be described with these words. In March, the Human Rights Campaign Foundation named the institutions “Leaders in LGBTQ Healthcare Equality.” Children's and WPIC were recognized in the Healthcare Equality Index, a survey evaluating the inclusiveness of 590 facilities. Elizabeth Miller, chief of adolescent and young adult medicine at Pitt and Children's, says one reason for this acknowledgment is the willingness of key leaders to “learn and embrace change.”



Overheard: With Dr. G

Wondering how to build your child's character? Have him take out the garbage, says family physician **Deborah Gilboa** (MD '00), aka "Dr. G." A mother of four boys ages 9–15, Gilboa practices at the Squirrel Hill Health Center in Pittsburgh, and she has gained national acclaim as an author, *Good Morning America* contributor, parenting and youth development expert, award-winning educator, and keynote speaker. Gilboa, a former stage manager for the Second City theater, even offers improv programs to help families. During her recent appearances, she talks about how parents need to "step back so their kids can step up."

How does taking out the garbage build character?

It teaches kids that their contribution makes the family better. Not just by being. But by doing. It teaches that they're a necessary member of the family, that they are not too special to do things that are gross that benefit the whole home. To never have to do for themselves or for the household what is unpleasant leaves kids shocked and betrayed by the real world.

What do household chores tell us about the state of the world?

Kids should be unconditionally loved no matter what. But kids have moved to the center in pretty much every metric. Our society is going to grow a generation that expects to be constant receivers and doesn't understand their role as contributors.

How can parents step back so their kids can step up?

Two percent of the time, they need us to throw ourselves in front of them with our bodies, actions, and voices, because their lives are in danger, emotionally or physically. But 98 percent of the time, they need someone who's genuinely interested to see what they will do. And that is the hardest work of parenting: to not fix it for them. If your child is growing—physically, emotionally, spiritually, characterwise—you're doing your job. —Interview by Kate Benz

Faculty Snapshots

People who suffer from inflammatory bowel disease (IBD) are about twice as likely to suffer from anxiety or depression, according to Eva Szigethy, MD/PhD and clinical director of Pitt's Visceral Inflammation and Pain Center. And the link, Szigethy notes, is biological. Szigethy was featured in a December *Nature* article in which she noted that the somatic symptoms of depression, including fatigue, sleep disturbance, and lack of motivation, are associated with inflammation from IBD. The results of her randomized, controlled trials point to cognitive behavioral therapy as a promising treatment option for IBD patients with mental health problems. "What's really rewarding is, because of my work, now almost all pediatric clinics screen for depression [in IBD patients]," she says.



Szigethy

Pitt has received a contract from the U.S. Department of Defense that, throughout the next decade, could fund up to \$90 million for research to improve civilian and military trauma care. The contract's initial \$10.8 million grant will create a nationwide network of trauma centers that collect data from prehospital care through recovery after discharge. This network is known as the Linking Investigations in Trauma and Emergency Services (LITES) Network. Jason Sperry, MD/MPH professor of surgery and critical care medicine, and Francis Guyette, MD/MPH associate professor of emergency medicine, are leading the effort. Their team includes Barbara Early, RN program administrator, Stephen Wisniewski, PhD professor of epidemiology, and David Okonkwo, MD/PhD professor of neurological surgery.



Sperry



Guyette

Earlier this year, Jeremy Berg was elected as an American Academy of Arts and Sciences fellow.

Berg is Pitt's associate senior vice chancellor for science strategy and planning, health sciences, and a PhD professor of computational and systems biology. And last year, he was appointed as the editor in chief of the *Science* family of journals. Academy fellows are expected to represent the current state of their respective fields, propose studies, and shape policy.



Berg

William Wagner, PhD director of Pitt's McGowan Institute for Regenerative Medicine, was inducted as a fellow into the National Academy of Inventors this spring. Wagner lays claim to 19 patents and more than 40 invention disclosures. Among those: a series of new biodegradable, elastic polymers with potential applications in cardiovascular medicine. Wagner also is a cofounder of Neograft Technologies, which is developing new treatment options for coronary artery bypass surgery. —RR



Wagner

A Commentary on Life

Ralph Kniseley (MD '43), who died on March 1, painted and sculpted for much of his life. Forty-five of his pieces, ranging from abstract nature scenes to catenary curves, hang on the walls of Pitt's Falk Library of the Health Sciences. "Some of his paintings were a response to the human condition. They were a commentary on life," says Kniseley's son, Greg Kniseley, who fondly remembers his father painting next to him as Greg did his homework. Kniseley had five children. He did a residency at the Mayo Clinic and served in the U.S. Army from 1946–1948. He was instrumental in developing the nuclear medicine specialty at the Oak Ridge Associated Universities and directed the Life Sciences Division of the International Atomic Energy Agency in Vienna for two years. He then worked as a primary care physician for 20 years.

As a painter, among his favorite subjects was the string quartet; two in that series are shown right. —RR



Skin in the Game

Each year, more than a million cancer patients in the United States receive radiation therapy. Many develop painful burns. Their skin peels or blisters. For some, this leads to infections or skin so damaged that treatment must be delayed or stopped completely. Others are left with permanent scars.

A team of University of Pittsburgh researchers may have found a solution: a topical therapy targeting the mitochondria in skin cells. Mitochondria perform cell respiration, and it seems that protecting them prevents inflammation and cell death. The therapy may mitigate the side effects and the long-term effects of radiation.

The team consists of Louis Faló, MD/PhD and chair of dermatology; Peter Wipf, PhD and Distinguished University Professor of Chemistry; and Joel Greenberger, MD and chair of radiation oncology. Their paper, in the *Journal of Investigative Dermatology*, reported the treatment was effective in both animal models and humans. They hope to begin clinical trials soon and to eventually expand their research to include treating sun-damaged and aging skin. —Elizabeth Hoover

FOOTNOTE

March Madness champions—that has a nice ring to it. This spring, scientists from Pitt won the first *STAT* Madness tournament. Thirty-two discoveries from universities across the country competed. After nearly 60,000 online votes, Pitt won for its study that gave Nathan Copeland, who'd lost sensation in his limbs when paralyzed in an accident, the ability to feel touches to a prosthetic arm (a limb he can move with his mind, btw). The study was led by Pitt's Robert Gaunt, Jennifer Collinger, and Michael Boninger; it was based on neurobiology insights of Pitt's Andrew Schwartz. The championship team included bioengineers, scientists, and neurosurgeons. *Swish.*



AND ACCESSIBILITY FOR ALL

When you see a guy breeze into a park riding a skateboard with crutches under his arms, you're gonna do a double take. And that's what onlookers did this spring when performance artist Bill Shannon (shown above) rolled into Schenley Plaza to kick off the third annual Ramp Crawl hosted by Oakland for All: Beyond Accessible, of which Pitt is a partner. The group aims to raise awareness about accessibility issues and make Oakland a model user-friendly community. Diagnosed with the joint disorder Perthes disease at 5, Shannon, a Pittsburgh native, has gained critical acclaim for street art that challenges what the word "freedom" really means. "All struggles for universal equality and access are linked," he says. —KB



Top Physician-Scientists

Many of the country's top physician-scientists met in Chicago in April at a joint meeting of two elite societies: the American Society for Clinical Investigation (ASCI) and the Association of American Physicians (AAP). Pitt was well represented—in addition to the dozens of Pitt physicians already honored with membership in the organizations, six more Pitt faculty members joined these clubs this year.

ASCI's 2017 honorees include **Thomas Gleason**, the UPMC Pellegrini Professor and chief of cardiac surgery; **Douglas White**, the UPMC Endowed Professor of Ethics in Critical Care Medicine; and **Ivona Vasile-Pandrea**, an MD/PhD professor of pathology.

And this year, the AAP elected to its membership **Derek Angus**, Distinguished Professor and Mitchell P. Fink Professor of Critical Care Medicine; **Charles Reynolds III**, UPMC Endowed Professor in Geriatric Psychiatry; and **Mark Shlomchik**, an MD/PhD and the UPMC Endowed Professor of Immunology. All are recognized for bringing laboratory innovations into the clinic.

—Kylie Wolfe and Erica Lloyd



THEY WERE IN THE NEIGHBORHOOD

On an overcast spring day in 2013, then 11-year-old Luke Maeding went to see his doctor, Pitt professor of pediatrics Geoffrey Kurland, when Batman showed up.

The caped crusader, along with Superman, Spider-Man, and Captain America, was rappelling off the facade of Children's Hospital of Pittsburgh of UPMC. Kids rushed to the windows, greeting the superheroes with cheers and fist bumps against the glass. Then these supers—from Allegheny Window Cleaning—got to work with squeegees and buckets.

The costumed cleaners come twice a year: in the spring and around Halloween. The tradition began in 2012, when Elizabeth Munsch, director of facilities at Children's, saw a picture of a window washer dressed as Spider-Man in a London newspaper. Coincidentally, Michelle Matuizek, office manager of Allegheny Window, saw the same story. Together, they decided to try it at Children's and started a trend. Many children's hospitals in America

have followed suit after seeing coverage of the event in Pittsburgh, says Munsch.

"The children just go nuts," she says. "It helps them forget why they are here."

It's a special day for the window cleaners. They are accustomed to hastily closed blinds, not smiles and waves. "You can tell you made their day a little bit better," says Mark Errico, who was Captain America this year.

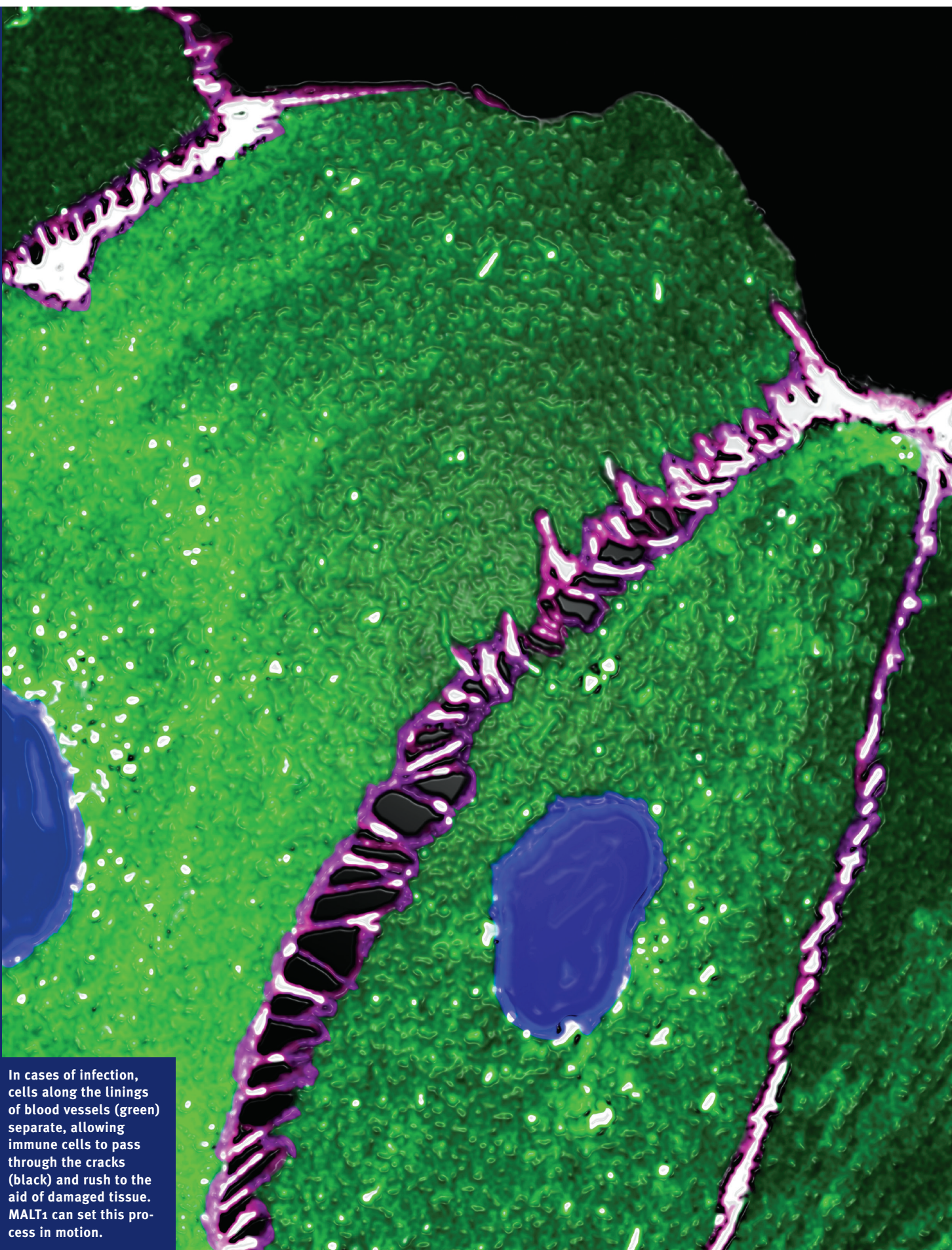
"And my day is better too, absolutely."

Kurland, who is medical director of pediatric lung transplantation at Children's, says patients like Luke (see inset above) are the real heroes: "They are the ones withstanding the treatments, medications, and surgeries." —Elizabeth Hoover

—Photography courtesy Children's Hospital of Pittsburgh of UPMC



Maeding and Batman



In cases of infection, cells along the linings of blood vessels (green) separate, allowing immune cells to pass through the cracks (black) and rush to the aid of damaged tissue. MALT1 can set this process in motion.

PROTEASE AND SWITCH

A MULTIPURPOSE BIOMED BUTTON

BY JILL NEIMARK

When scientists first isolated the protein MALT1 in 1999, they discovered it was a culprit in B-cell lymphoma. Then, a decade later, other researchers found it was also a protease—a crucial kind of enzyme that busts bonds and breaks proteins down into smaller pieces. And in recent years, the plot has continued to thicken. MALT1, as it turns out, is a kind of multipurpose molecular switch in a range of cell types: certain immune cells, smooth muscle cells, and barrier cells that line blood vessels, to name a few. It performs different functions depending on its location.

MALT1 is now the focus of a wide range of studies with the potential to help treat everything from lymphoma to coronary artery disease to sepsis and acute allergic/hypersensitivity reactions, explain Linda McAllister-Lucas, an MD/PhD associate professor of pediatrics at the University of Pittsburgh and chief of the Division of Pediatric Hematology/Oncology at Children's Hospital of Pittsburgh of UPMC, and her coprincipal investigator Peter Lucas, MD/PhD associate professor of pathology and pediatrics at Pitt.

"Pharmaceutical [companies] are very interested in the fact that MALT1 is a protease," says McAllister-Lucas. "We already have drugs that target proteases. There are many examples in medicine. The most famous is probably the cocktail of protease inhibitors that treat HIV."

Lucas adds that in 2012 a team in Germany discovered that common antipsychotics called

phenothiazines inhibit MALT1. "Nobody even knew this was something these compounds did, and now we might repurpose them in new and exciting ways."

In September, the Lucas/McAllister Lab published in *Cell Reports* another surprising role for MALT1.

The team found that in models of inflammation, MALT1 can set in motion a series of molecular actions that help cells along the lining of blood vessels to separate, becoming temporarily leaky. This allows immune cells to leave blood vessels and move rapidly into damaged tissue, which results in swelling, or edema. This is one way the body attempts to protect itself during trauma, as well as infection.

Too much edema, however, can be deadly. Case in point: sepsis-related acute lung injury, where infection leads to potentially fatal pulmonary edema.

The team used an animal model of inflammation, comparing controls in this setting to mice that were genetically deficient in MALT1 protease activity. They found that these deficient mice were protected from potentially dangerous vascular leak and fluid accumulation. McAllister-Lucas says this study is a proof of principle that MALT1 protease activity could be a new target in treating pulmonary edema. In new work, which has been submitted to a journal for consideration, the team has identified a protein that binds to MALT1 and inhibits it.

"We're very excited about this," she says.

McAllister-Lucas explains that in an acute

setting, MALT1 protease inhibitors might reduce acute respiratory distress syndrome (ARDS) by helping dampen endothelial leakiness.

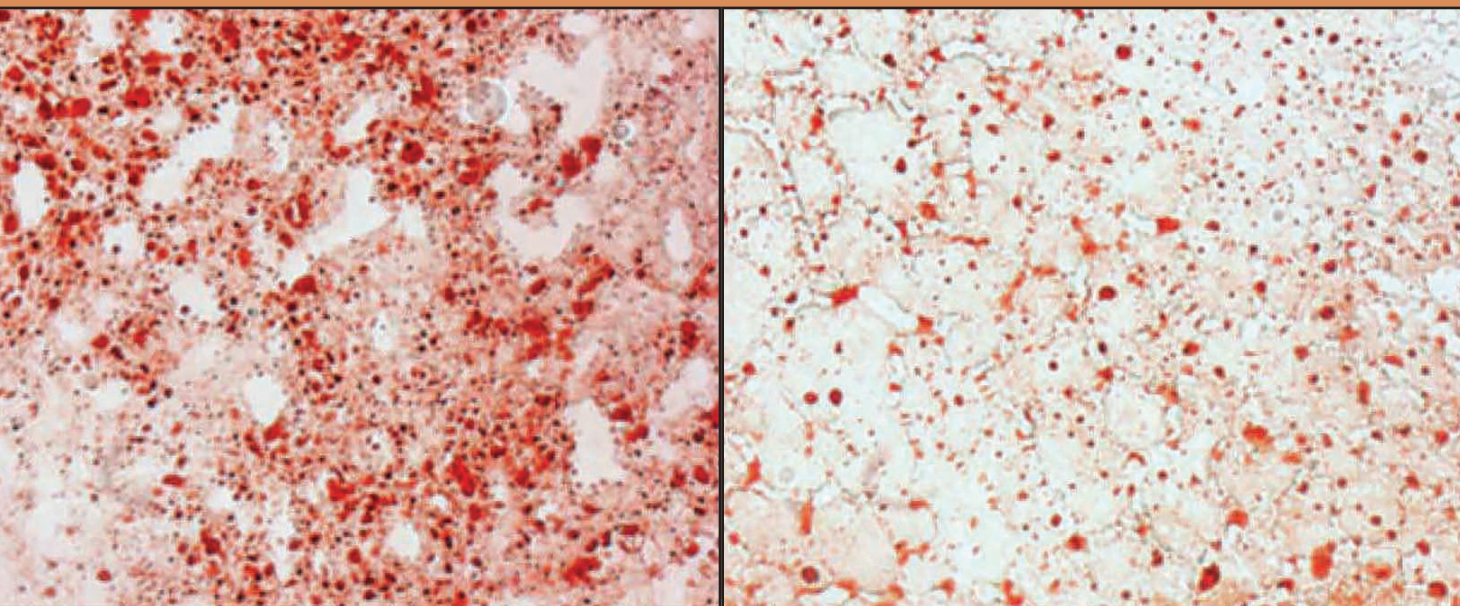
And in a chronic setting, MALT1 inhibitors might be effective in reducing the inflammation in the lining of the blood vessel in atherosclerotic disease. You see, active inflammation is a critical feature that distinguishes unstable atherosclerotic plaque—which is susceptible to rupture—from stable plaque, so MALT1 inhibition might be able to reduce the risk of acute coronary events in advanced atherosclerosis.

Someday, McAllister-Lucas says, MALT1 research may have an even bigger impact.

Though excess MALT1 activity can induce lymphoma, it is also absolutely essential for the function of both B and T immune cells, she explains. MALT1 is activated whenever a B or T cell responds to an antigen; it also is essential for the activity of natural killer cells and other types of immune cells.

"So whenever your immune system wants to fight off an infection, MALT1 is activated," she says. "But too much [activation] causes excessive proliferation that allows cells to survive when they shouldn't, and this can lead to cancer."

It turns out MALT1 may be involved in more cancers besides lymphoma, where it was originally discovered. A paper along these lines is in the works, McAllister-Lucas says. "It appears that MALT1 may change the behavior of certain cancer cells and make them more capable of invading and spreading." ■



In a model of liver cancer, Prochownik compared tumors from control mice (left) with tumors from mice lacking *Myc* (right). Controls served up far more lipids (red), among other building blocks that are essential for cancer's runaway growth.

MYC FIX

A SLICK TRICK TO
NIX CANCER

BY ALLA KATSNELSON

At a seminar some three years ago, Edward Prochownik encountered a close acquaintance—not a colleague, but a protein. In the talk, the speaker was describing a new mouse model of hepatoblastoma, the most common type of liver cancer in children, and how his team had identified the genes with particularly cranked-up expression in the tumors. The most off-the-charts gene was *Myc*, which the University of Pittsburgh's Prochownik, MD/PhD professor of microbiology and molecular genetics and Paul C. Gaffney Professor of Pediatrics, had been studying for years.

Prochownik and the seminar speaker, Satdarshan (Paul) Singh Monga, a professor in experimental pathology at Pitt, decided to team up.

Myc holds an important middle-management position in the gene world; *Myc* is present pretty much throughout the body, and its job is to regulate the transcription of thousands of other genes. But it is also commonly overexpressed in tumors. Many tumor types carry a version of *Myc* that is always switched “on.” This persistent expression, in turn, jams several of *Myc*'s downstream genes into their “on” positions, as well, and cancer can result. At least half of all cancers overexpress *Myc* in some way, Prochownik says.

Prochownik's team at Children's Hospital of Pittsburgh of UPMC has long explored *Myc*'s

role in cancer, but more recently it has been studying the gene's involvement in normal liver development, as well as liver regeneration; the liver is the only organ in the body that can regenerate itself on a grand scale, starting with as little as one-third of its original mass intact.

In animal studies, it's long been known, removing half of the liver almost instantly causes *Myc* to ramp up its expression as the remaining half switches into regeneration mode. This suggested that *Myc* played a role in the process. But in a recent study, Prochownik's lab deleted the gene solely from the liver—and regeneration occurred anyway, at a completely normal rate. “We showed beyond a shadow of a doubt that *Myc* is absolutely not required for normal liver regeneration,” he says. This finding led Prochownik to think that *Myc*'s role in generating tumors is not as obvious as he had originally thought.

When his and Monga's labs tested *Myc*'s role in hepatoblastoma tumors, they found that without *Myc*, tumors do develop, but they grow at a markedly slower rate, increasing the animal's life span five-fold. “So we realized the role of *Myc* in normal regeneration and in tumorigenesis is very, very different,” he says. The researchers published their findings in the *Journal of Biological Chemistry* last fall.

If you think about it, there's a certain parallel between normal tissue regeneration

and cancer: both involve tissue growth. In the case of cancer, however, that tissue growth is on overdrive. A tumor cell divides every day, which means that every day it needs supplies—amino acids for proteins, nucleotides for DNA and RNA, lipids for membranes, and so on.

Prochownik and his colleagues speculate that *Myc* upregulates the metabolic processes that are needed for this uncontrolled growth. “We showed that all these processes—protein synthesis, glycolysis, the synthesis of all these different building blocks—were suppressed significantly in tumors that didn't have any *Myc*,” he says. “We think that's the role of *Myc* in these tissues—to really provide that extra metabolic boost that's needed for sustaining tumor growth.”

The fact that it is not required for normal, noncancerous tissue growth means that interfering with *Myc* might be a way to target tumor growth. Such a therapy might not work with hepatoblastoma, where tumors do still grow even without *Myc* in the mix (albeit more slowly), but other cancers are much more dependent on the gene.

The researchers are now trying to better understand how exactly *Myc* subtly regulates metabolism. They are also fiddling with the cell's energy-generation mechanisms in order to interfere with *Myc*. Such a means of metabolically “starving the tumor,” as Prochownik calls it, could be a slick new trick. ■

PIXIE DUST

THINK HAPPY THOUGHTS . . .
IN A SCANNER, TO TRAIN
YOUR AMYGDALA
BY ELAINE VITONE

If you ask people with depression to reflect on their experiences, they tend to gloss over the good stuff. “It’s: *Yeah, I went and had a great dinner with my kid . . . but then we went home and got in a fight the next week.* Positive memories are ignored or discounted,” says Kymberly Young, assistant professor of psychiatry at Pitt.

As a postdoc at the Laureate Institute for Brain Research in Tulsa, Okla., Young uncovered a surprising new insight into this disorder. At the time, Young was conducting imaging studies of the amygdala, a brain region that has historically been seen as a seat of fear and other negative emotions—but as it turns out, it’s more than that. The amygdala responds to anything that’s important to you, either in your environment or in your thoughts, Young explains. “It’s actually a salience detector.”

Young observed the brain activity of patients with depression as they reflected on their memories, and she saw a pattern: The amygdala’s activity was unusually high as patients thought about negative memories, and unusually low through the good stuff. And interestingly, as these volunteers emerged from the scanner, many reported the same curious phenomenon: When they were instructed to focus on their memories, both good and bad, they got a little rush from it. Which gave Young an idea.

Young teamed up with Jerzy Bodurka, a physicist and chief technology officer at Laureate Institute who was developing a new application for brain imaging technologies, called neurofeedback. Like biofeedback, it uses real-time physiological activity data to enable conscious control over unconscious processes. The pair wondered if, just like a person can

learn to control her heart rate by focusing on her own EKG strip in real time, someone with depression could use fMRI imaging to control his amygdala activity at will.

Heartened by the results of a small pilot study, the team then validated their findings in a follow-up study, the results of which came out in the *American Journal of Psychiatry* this April. The study showed that after just two sessions, participants’ depression scores dropped by half. And one week out, one-third of the patients no longer met the criteria for depression at all.

Here’s how neurofeedback works: The volunteer climbs into the scanner and is asked to think about three positive memories. Meanwhile, the patient looks at the thermometer on a screen—the “temperature” represents the amygdala’s level of activity. The patient aims to raise the temperature to a given target. The researchers then raise the target incrementally, as amygdala activity increases.

For people often caught in a negative-feedback loop, this experimental treatment creates a positive one. They go into the scanner with three positive memories—they come out with somewhere between seven and 12. “It leads to a cascading effect,” Young says.

When Young first started this work, she got some snide comments. “The most common was, *Well, Peter Pan—he says, ‘Think*

happy thoughts, and then you’ll fly,” she says. But Young has learned to embrace the metaphor. If the Darling children of Sir James Matthew Barrie’s novel were to heed that advice and step out of a window, they couldn’t fly—unless they had pixie dust onboard.

“I’m considering amygdala activity the pixie dust,” Young says. “It allows you to use the positive memories in a way that is helpful and useful,” rather than continuing to discount them. Because it’s not as simple as thinking happy thoughts, she says. Unfortunately, the more people tell depressed patients simply to “think positive,” the worse it makes them feel. “The research has shown that,” Young notes. Amygdala activity may be the magic ingredient that’s missing.

In the future, Young, who is funded by the National Institute of Mental Health and the Brain and Behavior Research Foundation, hopes to help make neurofeedback more widely available. She also plans to work with therapists to share what she’s learned. Cognitive behavioral therapy could be enhanced by these insights, she believes.

Her study volunteers immediately warm to the idea, she says. “They’re not taking a drug, they’re not talking to a stranger about their mother. [The technique] is informed by neuroscience; it’s a train-your-brain intervention—and they enjoy it.” ■





AGING AS A MODIFIABLE RISK FACTOR

BY JENNY BLAIR

FOREVER YOUNGISH

Johanna Quaas is a gymnast. In recent videos, she does somersaults, headstands, and lithe leaps and turns. With arms bearing her entire weight on the parallel bars, she holds her body horizontally or upside-down, pausing for long, graceful moments before lowering herself again. It's more than impressive—it's astounding. Quaas was born in 1925.

Though she's in her 90s, Quaas would put most young people to shame with her athleticism. Biological pathways we're just beginning to understand give some people extraordinary resilience to aging, while leading others to become worn down in their 50s. Researchers at the University of Pittsburgh Aging Institute are working to unlock the genetic and metabolic secrets inside people like Quaas—and duplicate them with practical therapies.

This summer, the Institute welcomes new director Toren Finkel, who will lead a basic and translational research effort on aging that is unprecedented at Pitt.

Pitt researchers
want to slow the rate
at which we age.

ILLUSTRATION | JULIETTE BORDA

"Aging is the biggest risk factor for every [chronic] disease that we have to deal with, but it's always been dismissed as nonmodifiable," says Finkel, who comes to Pitt from the National Heart, Lung, and Blood Institute.

"It's becoming possible to think about intervening in the rate of aging, pharmacologically. You could really slow the rate that you age, and thereby, slow the rate that you develop all of these diseases. That's incredibly exciting."

As we age, a lot of things tend to go wrong in our bodies. Our cells' housekeepers fail to show up. Our energy sensors sense wrong. Our nondividing cells sit there and cause trouble. The telomeres—caps on the ends of DNA—wear down. Genes get switched on and off at the wrong times. The bacterial population in the body can veer away from a healthy mix.

What scientists are beginning to realize is that these processes are often connected, that they can show up as many different diseases that have a lot in common, and that certain points along these pathways offer promising drug targets. In other words, the common chronic diseases of aging—including neurodegeneration, cancer, and heart disease—are linked.

Pitt and UPMC officials believe a holistic research effort that unites researchers from a variety of fields under a leader who's willing to totally rethink aging could yield enormous benefits.

"Toren Finkel is a fantastic researcher and wonderful human being who's going to fit into our culture extremely well," says Steven Shapiro, the executive vice president and chief medical and scientific officer of UPMC. "He has not only a great understanding of basic science, but an urgency to translate this into clinical programs and help patients. He spent the first half of his career defining these pathways. Now he wants to do something to help people."

With the renowned Charles Reynolds, UPMC Endowed Professor of Geriatric Psychiatry, at the helm for many years, the Institute already offers top-notch clinical care for Western Pennsylvania elders and caregivers. It educates professionals and laypeople in geriatrics. And it has conducted important

clinical research while building its basic science portfolio.

Finkel will expand the Institute's investigations in geroscience, the study of the relationship between aging and disease. That's not to be confused with gerontology, the study of aging, or with geriatrics, the branch of medicine dealing with treating disease in elders.

Geroscience aims to discover, test, and develop drugs and lifestyle changes that could lengthen not only life span, but also health span—the period of life during which a person remains free from serious illness.

An interesting thing about people who survive nearly a century or longer is that they tend to remain in good health for most of their lives. Life span and health span are, somehow, tightly linked.

Finding drugs that alter aging pathways enough to lengthen health span could fundamentally alter the practice of Western medicine, which now emphasizes the diagnosis and treatment of disease.

"Your DNA is repaired. Your mitochondria are strong. You avoid developing that cancer in the first place, you avoid developing that lung fibrosis, you avoid developing that coronary disease," says Mark Gladwin, who holds the Jack D. Myers Chair of Medicine and helped recruit Finkel to Pitt.

"We're not trying to make people live beyond 120," he adds. "But wouldn't it be great if you could live a strong, healthy life until you're 95 to 120 and die peacefully in your sleep? Wouldn't that be the dream we'd all have?" No one dies purely of "old age," but a sudden deadly stroke or fall might be an enviable exit.

In the United States today, there are 46 million people age 65 or older, a number expected to double to 98 million by 2060—nearly a quarter of the country's population. By 2030, about 2.3 million older U.S. residents will require skilled nursing care, a 75 percent increase from 2010. This isn't just happening in this country. Sometime before 2020, the number of people on the planet age 65 and older will surpass the number of children under age 5, a first in human history.

Caring for these folks can be difficult. More than 90 percent of elderly people today have at least one chronic health problem,

and three-quarters have at least two. Such diseases consume three-quarters of U.S. health care dollars. A 2013 study published in *Health Affairs* concluded that delaying aging's complications by just 2.2 years would lead to a savings of \$7.1 trillion throughout 50 years.

Industry has caught on to the promise of anti-aging drugs. A small study by the drug company Novartis made headlines in late 2014 when it found that giving a drug called rapamycin to elderly people boosted their response to the flu vaccine. (We'll come back to rapamycin in a bit.) Google's life-sciences company Calico partnered in 2014 with pharma giant AbbVie to run clinical trials on anti-aging compounds.

"[Geroscience] really started to gain traction in the last five years. There's a lot of interest in trying to look at common themes across the system so that we can be able to treat aging more systemically and less from a disease-specific approach," says Fabrisia Ambrosio, an associate professor of physical medicine and rehabilitation who has helped nurture basic aging research at the Aging Institute for the past several years. "Why is it that over time our cells seem to default toward this more dysfunctional nature? And what can we do to counteract it?"

Finkel and his colleagues are determined to find out. The chief strategy: to identify and test small molecules in house, then pass them along to the Institute's translational and clinical scientists for human trials and eventual commercialization.

The son of a NASA physicist, Finkel majored in physics. But thanks to an inspiring professor, the biology bug bit him. As an MD/PhD, Finkel tried his hand at molecular biology bench research, mentored by physicist-turned-biologist Wally Gilbert, shortly before Gilbert jointly won the 1980 Nobel Prize in Chemistry. After completing his training as a cardiologist, Finkel joined the National Institutes of Health, where he remained for 24 years until his jump to Pitt this year.

Finkel first made his name in 1995 with a paper in *Science* describing his lab's discovery that reactive oxygen species (ROS)

within the cell, specifically hydrogen peroxide, are actually important in cell communications. This was a surprise. For decades, these molecules were thought to be purely destructive, to be gotten rid of, pronto, with antioxidant foods and pills. Yet clinical studies found that antioxidant foods and pills didn't bring the hoped-for benefits.

"Our work provided an explanation for why it may not be so good for you to just completely scavenge off oxidants," Finkel says. The paper has been cited more than 2,000 times. It touched off a new field called redox signaling.

At that time, Finkel didn't consider himself an aging expert. Then *Nature* asked

One crucial kind of cellular housekeeping is called autophagy—literally, self-eating. It's a process in which cells break down and reuse their own damaged or aged components in response to stress. Autophagy recovers energy and resources while clearing away useless organelles, membranes, and protein. As autophagy slows with age, though, debris can accumulate, and evidence suggests that cancer, impaired immunity, and neurodegenerative disease can result. Aging Institute researchers would like to find a drug to rev up widespread autophagy or mitophagy.

Finkel is studying the latter, a type of autophagy in which mitochondria are the objects recycled. The descendants of ancient

met humans who are privately experimenting with this approach.

"I went to a lot of meetings recently, and all the big shot scientists—everybody I know—is on this calorie-restriction diet," he says. (Finkel is not one of them—"I love eating too much," he says.)

"Of course we all want to live a happy life," Chen says. "You tell me I cannot eat cheeseburgers, I can only eat one meal a day—that's kind of hard. That's why we're trying to see whether we can come up with a therapy approach, maybe a pill or small compound inhibitors ... that can still achieve the same goal here. That's the ultimate dream—to find a way to activate autophagy without doing the

"Aging is the biggest risk factor for every [chronic] disease that we have to deal with, but it's always been dismissed as nonmodifiable. It's becoming possible to think about intervening in the rate of aging, pharmacologically. You could really slow the rate that you age, and thereby, slow the rate that you develop all of these diseases. That's incredibly exciting."

him to write a review of aging research to appear in 2003. The editors knew he was an outsider. Finkel believes that by selecting him, they were tacitly acknowledging cracks in the foundation of the oxidation-causes-aging theory (cracks that Finkel's own work had helped put there).

As Finkel prepared to write the review by reading scientific literature on aging, he recalls, he was "blown away" by some of the discoveries in the field.

"This central question was so fundamentally important, and so poorly understood, that I was hooked on the topic," he says.

Finkel soon steered his lab toward questions of aging in mammals. Through time, he has helped to illuminate some pathways down which aging proceeds, and some promising ways to intervene.

In any complex system, be it a spaceship or a cell, maintenance is a must. Cells constantly recycle broken parts and repair damaged DNA to stay fully functional.

symbiotic bacteria, these cylindrical organelles are the cell's power plants, and they're also important in cell signaling, metabolism, and trafficking. Mitophagy helps cells regulate energy production and protects cells from defective mitochondria, which can more or less poison their surroundings.

The Finkel lab has demonstrated that, in the area of a mouse's brain that encodes learning and memory, mitophagy slows dramatically with age.

"We think that may be important for why memory and learning decline as we age—you're not able to turn over [and] get rid of the damaged mitochondria," Finkel says.

There is an unpleasant but effective way to activate autophagy: a near-starvation diet. Cells normally scavenge their own damaged components for energy; if they sense starvation, they go on a scavenging frenzy. Calorie-restricted diets are known to dramatically increase life span in yeast, fruit flies, nematodes, and mice.

Beibei Bill Chen, an assistant professor of medicine and a drug discovery expert, has

calorie-restriction diet."

Chen, who is also director of the Small Molecule Therapeutics Center, is well equipped to help with the search. The center includes libraries of molecules that can be tested by the thousands—first virtually, via supercomputer, then with real-life assays—for various functions, like stimulating autophagy. He has already found one compound that boosts mitochondrial function and another that induces autophagy, and he's working to commercialize them.

Another aspect of cellular housekeeping is DNA repair. This, too, is a constant necessity. DNA is always under assault from one thing or another, be it oxidative stress, replication errors, botched corrections, tobacco and alcohol, air pollution, or infections. Mutated DNA can lead to cancer or simply malfunctioning cells. Fortunately, we have enzymes that read and repair our DNA. Stronger DNA repair systems could mean better resistance to age-related complications in general, so they're something we'd like to learn to shore up as well. (As long as they don't promote

cancer—cancer cells themselves are famously good at DNA repair.)

Pitt has one of the strongest groups in the world dedicated to understanding DNA repair and genome stability. This summer, Aditi Gurkar from the Scripps Research Institute in Florida will join Pitt as an assistant professor of medicine. She studies how DNA damage leads to aging.

“Until now, we have not found anything that can keep our DNA completely safe. That’s almost impossible—in fact, it’s not good for us,” Gurkar says, pointing out that DNA mutation allows for adaptation and evolution. “What is then important is: how do we react to the damage that is already there?”

Gurkar’s research focuses on the fact that repairing DNA damage costs the cell a lot of energy, which is supplied by mitochondria. Under normal circumstances, mitochondria

so stimulating that might help. But there are other molecules involved in detecting and preventing misfolding that we might be able to work with, too.

“Improving the body’s repair processes, either at the nucleus with DNA or [outside the nucleus], are really hot areas in aging biology,” Finkel says. He’ll be recruiting some proteostasis experts to fill out the Aging Institute’s perspective.

In 2013, Finkel’s lab knocked a mouse gene down to a quarter of its normal activity. The result: mice that lived 20 percent longer. That’s the equivalent of a 75-year-old life span stretching to 90 years. The gene encodes a protein called mTOR, part of a complex called mTORC1, for “mechanistic target of rapamycin.” The protein is a kinase that controls the activity of

tive immune system.)

The mTOR protein is part of a piece of cellular machinery called the AMPK pathway, whose job is to sense low energy levels in the cell. The pathway appears to protect cells from aging, perhaps because mTOR inhibition is one of its effects. Fasting activates this pathway, as does exercise, which evidence suggests keeps us young. Another group of molecules involved in energy sensing and life span are the sirtuins, which help the cell figure out how many mitochondria it needs.

There’s a familiar drug that acts on AMPK: metformin, an old standby for treating type 2 diabetes. Researchers have noticed that people who take metformin have lower rates of cancer and longer life spans—results that can’t be accounted for by metformin’s effect on blood sugar. It

“We’re not trying to make people live beyond 120. But wouldn’t it be great if you could live a strong, healthy life until you’re 95 to 120 and die peacefully in your sleep? Wouldn’t that be the dream we’d all have?”

are recycled as needed (mitophagy!), with a process that keeps destructive ROS at a safely low level. But when DNA requires constant repairs, there is an ongoing demand for the intracellular energy-transfer molecule ATP, and the cell halts its ordinary recycling of mitochondria to save energy. In the process, more ROS are created, an increase that can lead to age-related disease.

It is perhaps not surprising that the many processes that control the creation, folding, and destruction of proteins (an aspect of cellular housekeeping known as proteostasis) can go wrong. Protein folding alone is an immensely complex process that challenges the powers of supercomputers to model. Proteins tend to misfold more with age, and age-related diseases like Alzheimer’s and Parkinson’s involve the buildup of clumps of nonfunctional proteins. It’s the job of autophagy to recycle those botched proteins,

perhaps 800 other proteins, and it’s a star player in the world of aging.

In yeast, worms, flies, and mice, what inhibits mTOR lengthens life. Inhibiting mTOR blocks cellular proliferation (which effectively also blocks cancer growth), activates cell-cycle arrest, improves the growth of new mitochondria, and improves insulin sensitivity. Giving a genetically normal mouse the drug rapamycin inhibits mTOR and boosts the animal’s life span by 10 percent.

Perhaps it’s not surprising that rapamycin, originally used as an antifungal, is also an immunosuppressant and a cancer suppressor. Drugs like it are studied and used for a wide variety of indications—its derivative sirolimus, for example, is used in drug-eluting coronary stents, as well as to prevent rejection of transplanted kidneys. (Note how distinctions blur, at this level of cellular function, among heart disease, cancer, and an overac-

turns out the drug gears down mTOR via an upstream effect on AMPK. Pitt leaders are planning an internally funded human trial of metformin in post-op and critical care patients. They’re also working out a way to surveil other familiar drugs, in case more of them have anti-aging properties scientists have overlooked.

Senescent cells are those that have stopped replicating. As with damaged mitochondria, as they accumulate, they become a toxic, inflammatory nuisance to their neighbors. The immune system takes them out, but assisting with that process by preventing senescence or selectively destroying senescent cells with so-called senolytic drugs could help slow down aging.

Gurkar has worked on this problem, too. In 2015, she was part of a group that



Led by Toren Finkel, Pitt's Aging Institute will focus on geroscience, which points a finger at aging itself as the cause of many chronic diseases.

demonstrated health span got longer in mice after treatment with senolytics. One drug they tried was quercetin, a plant pigment found in olive oil and blackberries and suspected of having a number of healthful effects in humans, including lowering blood pressure and potentially reducing cancer risk. (Olive oil could be one reason the Greek island of Ikaria is home to so many nonagenarians. It's been nicknamed "the island where people forget to die.")

So, with all these pathways, with all their linkages to one another, to cancer, to inflammation, to other chronic diseases, how close are we to untangling aging and slowing it down with a couple of pills?

"It's a thing that all of us have and will get—aging. It's probably the most fundamental thing," says Finkel. But it's poorly under-

stood in terms of: What are the unifying drivers of aging, the basic molecular mechanisms that everybody can agree on?"

There's no unifying theory of aging yet—just a set of tantalizing associations.

"There is an association of free radical damage," Finkel says, "but it's not clear that that's causative. There is this idea of sterile inflammation [i.e., inflammation without bacteria, as happens in gout or atherosclerosis] that occurs in elderly people; but again it's not clear if that's cause or consequences. Is there DNA damage as we age? Yes. Is it driving aging, or is it accompanying aging? If you block DNA damage, would you block aging? Or would you just block one aspect of aging? People really don't know. There [are] a lot of candidates, but there's no clear winner at this point," he says.

"They certainly have all been linked to

aging. They're certainly all in play. Certainly you can get something that looks like aging by perturbing all of those things," Finkel says. "But the question is, *What really is the most important? And what really drives the others?*"

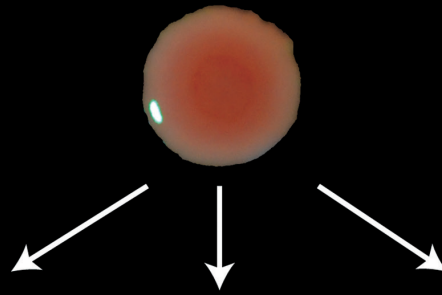
Finkel wouldn't be here if he weren't optimistic.

"Twenty-five years ago, nothing was really known about the basic mechanisms. Now, quite a bit is known. There are still a lot of gaps, but I think there are rational targets out there that make sense. Pitt [is] very good at clinical translation, and I think that is where the field is moving," he adds. "It's going to be a great place to figure out, *Can we really slow the rate of human aging?* It's a great unknown, but a great target to go after."

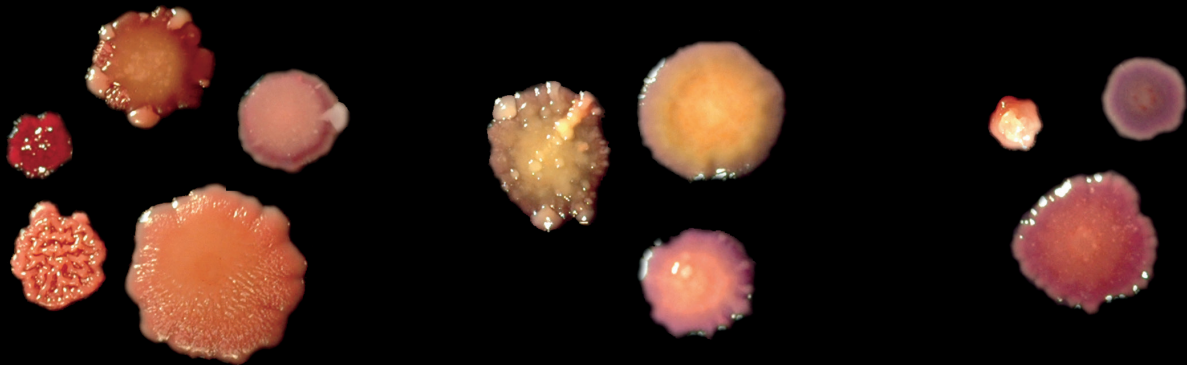
It's a heck of a challenge.

"Oh, yeah," Finkel, age 59, replies. "I'm young." ■

ANCESTOR



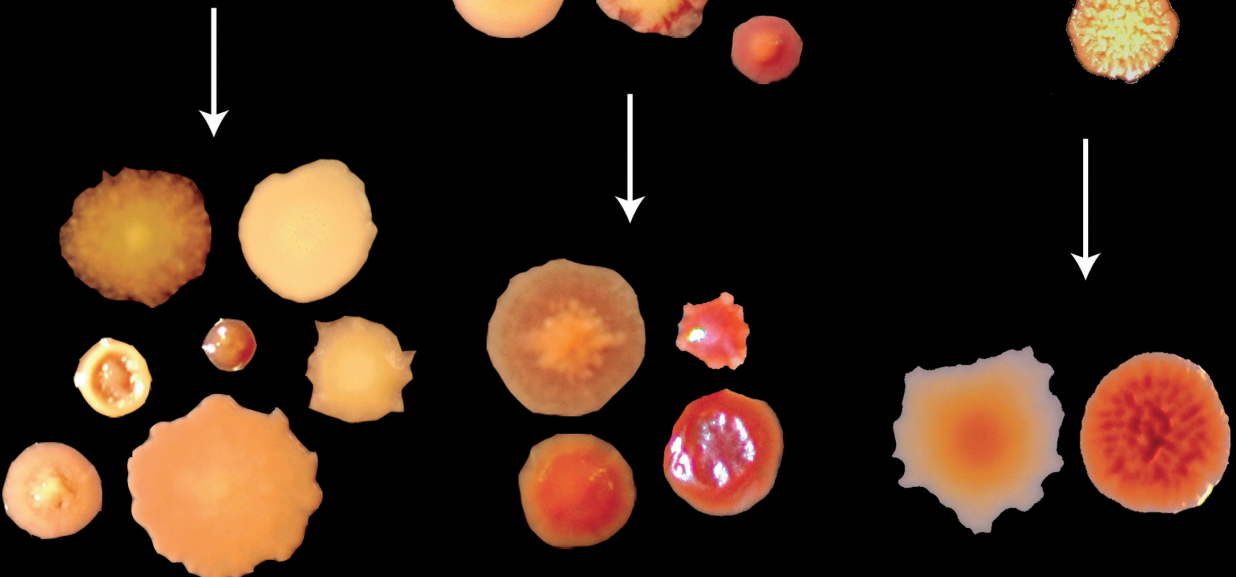
17 DAYS
110 GENERATIONS



45 DAYS
300 GENERATIONS



90 DAYS
600 GENERATIONS



EVOLUTION CAUGHT IN THE ACT

BY ELAINE VITONE

UNTANGLING DARWIN

On a recent summer afternoon, in a Bridgeside Point laboratory overlooking the Monongahela River, the University of Pittsburgh's Vaughn Cooper and his team are coaxing bacteria to do in captivity what they've always done so artfully in the wild, as have humans and every other life form.

We evolve.

It's a never-ending story: This environment selects for this trait, that for another trait, and so on, in a highly complex network of falling dominoes. Evolutionary biologists like Cooper have been working to retrace this network—the life story of life itself—for the past 150 years.

Cooper's experiment is a little different from his progenitors', though.

Instead of hypothesizing about evolution after the fact, his team is watching it happen. He figured out how to catch it in the act about a decade ago. And it's actually “ridiculously simple,” he says.

In studying evolution in action, Vaughn Cooper has seen patterns emerge. As biofilming bacteria attach to surfaces and set up shop, they mutate by multitudes. This is not a “winner-take-all” operation; rather, the bacteria seem to evolve together to fill complementary metabolic niches. **LEFT:** Here, a single *Pseudomonas aeruginosa* ancestor yields “a zoo.” In a matter of months, the colony becomes an interdependent community.

The experiment goes like this: Stick some bacteria in a test tube with a plastic bead, give the cells some nutrients to nosh on and a nice warm spot in an incubator, and leave them be for 24 hours. Overnight, these tiny pioneers make a happy home of their 7 millimeter-wide world—just as they would on, say, a hospital handrail, or a catheter, or the lung of a patient in the ICU. Then, the bacteria asexually beget a whole mess of babies, many wee teams of clones and mutants amassing in a motley crew.

Of course, which ones among them survive to make their own broods is up to chance, at least in part. And as chance would have it for this particular bacterial family, the lab introduces a do-or-die ultimatum.

Each day, the researchers replace the nutrients, add a second bead, and let the test tube simmer for 24 hours. Then they swap out the older bead for a brand new one. The old bead's breeds are dead, as far as the experiment is concerned. (Well, retired to the freezer, anyway—more on them later.) In this daily test of fitness, survival favors the bacteria that are best

evolution in action, he says. To his amazement, Cooper has seen patterns appear in evolution, leading him to believe what was once unthinkable: that we may be able to *predict* evolution, at least in certain contexts.

Such an ability would have real medical value. Evolutionary biology is at the center of some of the most vexing public health challenges of our time.

In cancer, tissue gives rise to mutations—naturally, inevitably, and continuously—until one day, spurred by some challenge, or selective pressure, certain cells escape the normal checks and balances of our biology.

Caught between do and die, they *do*.

In antibiotic resistance, bacteria face evolution in a hospital patient's body, a cruel selective-pressure cooker of drug after murderous drug and an immune response at the boiling point. So the bacteria fight fire with fire, armies of mutants redoubling and re-emerging, emboldened. If just one cell out of a million survives, it's a chance to win.

And they *do*.

chemist Rosalind Franklin). With her help, the team can tell exactly what mutations appear, and when. They can track entire bacterial family trees and study biofilms down to the level of individual organisms.

Cooper says he's living in the best time ever to study evolutionary biology and microbiology.

His studies focus on these evolving organisms not only in test tubes and animals, but also in samples from UPMC patient volunteers. Across these bacterial habitats, he's found common themes:

Bacterial communities quickly become diverse, and they stay diverse. A lot of diversification is driven by relatively small numbers of genes, no matter how many times Cooper's team repeats the experiment. And, when biofilming bacteria reinvent themselves to adapt to new territory, the adaptation they prioritize above all else is sticking, regardless of whether they land on a surface or inside a living, breathing host. "It doesn't matter what they stick to, very much," he says.

History is repeating itself again and again with a predictability he finds "stunning."

Evolution has always been taught as a retrospective science, says Cooper.

"But now, we can almost look at it from the perspective of an engineer."

at pressing on to new frontiers.

The bacteria Cooper primarily studies, *Burkholderia cepacia* and *Pseudomonas aeruginosa*, are infamous frontiersmen. They're able to claim new territory with the help of what are known as biofilms.

Put simply, a biofilm is a microbial growth on a surface, usually encased in "slime," Cooper explains. The goo not only gives bacteria sticking power, but it also makes these cells up to 1,000 times tougher to kill. "They are physically protected," says the PhD and Pitt associate professor of microbiology and molecular genetics. "And once the cells start to accumulate in these biofilms, they start to grow more slowly—and it's a lot harder to kill slow-growing cells." For bacteria in no particular metabolic hurry anyway, a drug that inhibits what feeds them is like water off a duck's back. "This is the same reason it's hard to kill slow-growing solid tumors," Cooper notes.

There's a lot to be gained from studying

Most bacteria live on surfaces, in biofilms, but historically, that has been a tough setting to study. Simply sticking some scum in a tank full of swirling warm liquid and letting nature take its course is kinda like sending the bacteria off to Vegas, Cooper says. "What happens there stays there. You can't go into that environment and figure out the forces that led to those changes.

"But our system, because it has this daily cycle of renewal, allows you to define those forces as they happen. Because the whole population has to disperse and recolonize."

Not only that, but each time a bead comes out of a test tube, it goes to the freezer to join thousands of other ancestors, their icy afterlife amounting to an exquisitely detailed fossil record.

On a counter in the lab, catercorner from the incubator, is a machine that looks a bit like a gigantic microwave—a genetic sequencer the researchers affectionately named Roz (for

Gavin Sherlock, a Stanford geneticist who studies evolution in yeast, notes that evolution is largely driven by randomness, thus we can never predict its future with perfect clarity.

But we *can* project probabilities, he says (as scientists now do in determining which flu vaccine to create each year). And, in cases of extreme selective pressure—like that of antibiotics on bacteria—there are only so many mutations that will be viable. Then, the probabilities get much higher.

Cooper acknowledges that there's work to do yet before the consistency, and thus predictability, of evolutionary patterns is clear. But he's hopeful—and he says he's not alone. "We've had a few [international] meetings where we've talked about predicting evolution. And that really is . . . *gosh*. That's a game changer."

Evolution has always been taught as a retrospective science, says Cooper. "But now, we can almost look at it from the perspective of an engineer."

The Hawaiian bobtail squid harbors a bioluminescent bacterium. Because the squid's light organ is composed of mucosa, new insight regarding how the bacterium probably adapted to its host could help illuminate our understanding of chronic infection in humans.

Cooper, a lean 44-year-old from Massachusetts, completed his 20th Ironman triathlon a few years ago before his knees “mostly” retired him from the sport. “I still love to swim-bike-run, though,” he says. He’s also an avid naturalist—he taught himself to fish at age 5. These days, he mostly casts in trout streams near his home in the North Hills and in various area ponds and lakes for bass—always with his kids (Soren, 10, and Harlan, 7).

As an undergrad at Amherst College, Cooper had designs on an honors program thesis on river ecology and the dynamics that shape selective pressure therein. Cooper recalls his adviser, an evolutionary biologist named Paul Ewald, telling him, *Yeah, Vaughn, that’s great, but you’re never going to get that done as an undergraduate—or a PhD candidate, for that matter. How about we try some experiments that are a bit more feasible?* Cooper then enlisted in Ewald’s study of a particular virus that was decimating a regional species of moths. That experience reeled in Cooper, so to speak. He has been studying the evolution of pathogens ever since.

In grad school he worked in the lab of virus-evolution luminary Richard Lenski of Michigan State University. It was the presequencing era, and yet the lab discovered (“by a combination of luck and a lot of sweat,” Cooper says) some of the first mutations that drove adaptation in *E. coli*.

Along the way, Cooper was waking up to the fact that most microbes don’t live in well-mixed cultures. When he got his own lab at the University of New Hampshire, he developed his bead model, which made the covers of *ISME* (from the International Society for Microbial Ecology) in 2011 and the *Journal of Bacteriology* this October.

Collaborations with his New England colleagues continue. Just this April, *eLife* published Cooper and Cheryl Whistler’s study of a dazzling little luminescent sea-beast known as the Hawaiian bobtail squid. “This is an amazing creature,” Cooper swoons. “It cultivates bacteria to produce light for it. ... [Then, the animal]

doesn’t cast a shadow, so it’s harder for predators to detect it.”

The squid and its mutualistic symbionts, *Vibrio fischeri*, are darlings of science literature for a host of reasons (forgive the pun). But one mystery is how the bacteria adapt to this symbiosis. So basically, the team simulated it. They took a close cousin of the bacterium and paired it with the squid. (Native strains of *Vibrio fischeri* themselves wouldn’t do—they’ve already evolved to inhabit this host.)

As the cousin adapted to the fix-up, Cooper sequenced the bacterial DNA and found the mutation that made the marriage possible. “I think it’s one of the best things we’ve ever been a part of,” Cooper says.

His gushing isn’t just his naturalist’s tendencies talking. He explains that little is known about bacteria/host interactions at all, let alone on mucosal surfaces like the squid’s light organ—or our own noses, lungs, and guts. He calls the paper a sign of things to come. The lab is deeply involved in deciphering how bacteria establish chronic infections.

Working with Jennifer Bomberger, a PhD assistant professor of microbiology and molecular genetics at Pitt, Cooper’s lab is beginning to study the evolution of pathogens in the airways of people with cystic fibrosis. It’s long been known that once these patients catch certain viruses, chronic biofilming bacterial

infection tends to follow. By studying cultured cells from the airways of these patients, Bomberger may have uncovered the reason why. Respiratory syncytial virus appears to cause these epithelial cells to jettison their stores of iron—which the bacteria gladly eat up. Iron is biofilm fuel.

Recently, thanks to a \$25,000 seed grant from Pitt’s Clinical and Translational Science Institute (CTSI), Bomberger teamed up with Stella Lee—MD assistant professor of otolaryngology at Pitt and director of the Division of Sino-nasal Disorders and Allergy at UPMC—for a pilot study on how well this hypothesis holds up in humans. Its success led to further funding from Gilead, a biopharmaceutical company, to begin recruiting a larger group of patient volunteers this summer.

Pseudomonas is not the kind of bacterium that particularly likes living in the lungs. It prefers much more moisture, gravitating to enclaves like the puddles you pass on the street. In a pinch, it might colonize your nose. “The thought in the field has been that it adapts in the sinuses, and then some event happens that allows it to move to the lung,” Bomberger says.

That event may well be viral infection, and the bacteria’s adaptation to it. By studying sinus and sputum samples collected from Lee’s surgical patients over time, Cooper and Bomberger hope to find out.

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In an increasingly more mainstream view of human disease, our vulnerabilities are thought to stem from some trade-off our ancestors' DNA made to stay afloat. Did, say, your forefathers dodge malaria? Maybe you'll wind up with sickle cell disease. Did your Old Country kin survive plague? Perhaps your autoimmune disease is the price your family paid.

But it's still a win, because you're *here*. If you make it long enough to reach reproductive age, that's really all evolution cares about. "Selection doesn't optimize, right?" Cooper says. "It just sort of acts on the lowest-hanging fruit."

The same goes for bacteria, explains Yohei Doi, an MD/PhD, associate professor of medicine, director of Pitt's Center for Innovative Antimicrobial Therapy, and Cooper collaborator. But if you put bacteria in the environment of a hospitalized patient, suddenly it's "evolution on steroids." The bacteria are forced into mutating mucho, and fast, and those rapid-fire changes can't be pleasant. This leads Doi to believe that the so-called "superbugs" we read about in the headlines probably aren't built to last after all. "It's so totally unnatural for them," he says.

In 2008 or so, Doi, who was a Pitt fellow at the time, saw a worldwide spike in super-

damage they do to host cells, and so on. And they are finding that, as the bacteria bend over backward to cope, new vulnerabilities do indeed bubble up. Doi is hoping to eventually capitalize on these shortcomings in the clinic. Say, for example, Mutant A warps its structure so antibiotics can't bind to it. Are there weaknesses in the walls? Say Mutant B produces an enzyme that eats up the antibiotic *du jour* like acid. Can that enzyme be blocked?

In some cases, the solution may be much simpler, says Doi. Sometimes, the bacteria mutate to survive an antibiotic, but then when the coast is clear, they mutate back. Which means that antibiotic can be used again.

In this new Big Data era, getting data is the easy part, says Doi. The rub is distilling it all down to a manageable number of targets to work on in-depth. "That's where there's a chasm. And [Cooper] is one of the people who bridges that."

Since landing at Pitt in 2015, Cooper's lab has published several papers with Doi, as well as others at Pitt. This productivity suggests a bright future for the emerging field of evolutionary medicine.

In February, Cooper and Pitt associate professor of medicine Cornelius Clancy published in *Clinical Infectious Diseases* a

cleared the infection within days and recovered.

Throughout the course of her infection, the medical team had the forethought to collect samples. They later invited Cooper to analyze the samples to learn why the pathogen had persisted for so long. After sequencing the genomes of 22 variants, Cooper found the bacteria had mutated to create "a Faustian bargain for that bacterial population," he says. The bacterial cells had adapted to this depleted immune status. And then, once the immune system was back online, *adios*.

But the bacteria's story didn't play out as you might expect, with mutant begetting warped and mangled mutant over and over again. "It turns out there was one mutation. That's it. That means that the path to pan-resistance is very short for that organism." The reason for this outlier is that infection in immunocompromised people is its own separate, terribly formidable animal. (Cooper is working to further understand its underpinnings.)

In another way forward with broad implications for human health, Cooper is chasing down a goal shared by just about every other branch of biomedical research: precision medicine.

As microbial evolution keeps playing out predictably right before his eyes, he has high hopes (albeit with a healthy dose of skepticism).

They are finding that, as the bacteria bend over backward to cope, new vulnerabilities do indeed bubble up. Doi is hoping to eventually capitalize on these shortcomings in the clinic.

resistant strains hit home. Working with his mentor, David Paterson, he began collecting samples from patients at multiple time points. (He directs a hat-tip to UPMC's clinical microbiology lab, directed by Pitt associate professor of pathology A. William Pasculle, for so proactively rounding up specimens with each new outbreak.) Today, Pitt/UPMC has one of the largest collections of longitudinal strains of *Acinetobacter baumannii* in the country.

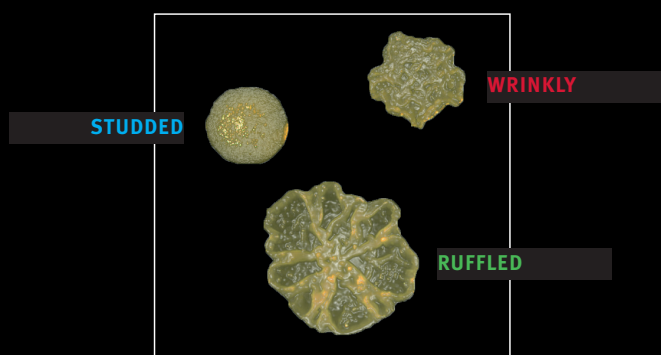
In six months, a dozen strains can evolve in a single hospitalized patient, says Doi. He's working with Cooper to learn what traits distinguish them: fitness levels, rates of growth,

study pinpointing the mutations that enabled *P. aeruginosa* to gain resistance to a class of go-to antibiotics known as beta-lactamase inhibitor compounds.

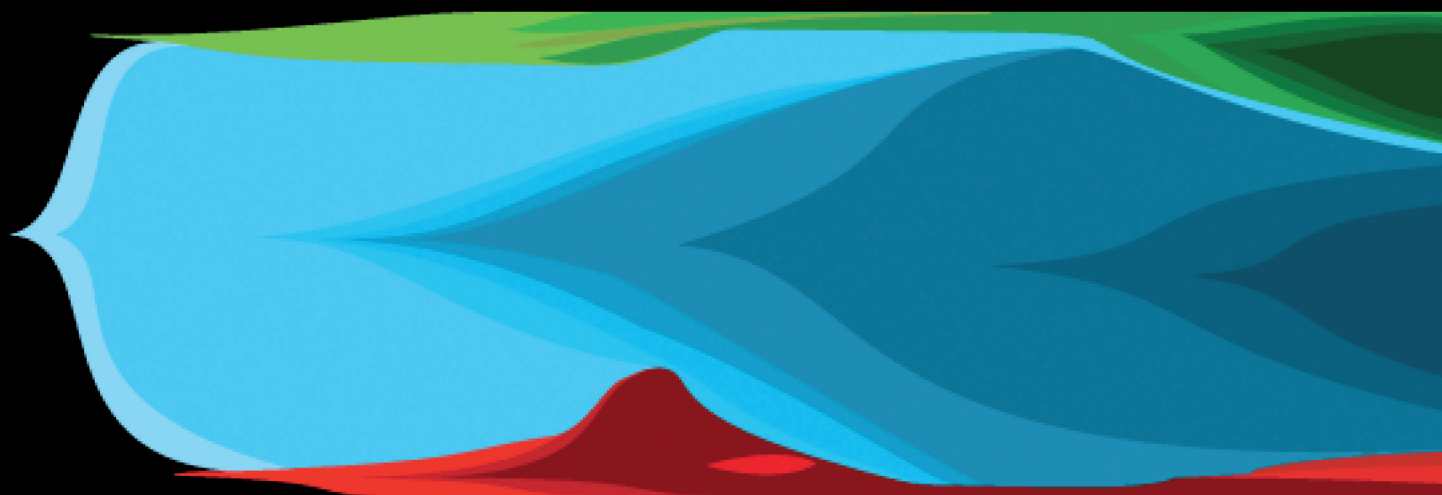
The month before that, *mBio* published the Cooper lab's study of a pediatric leukemia patient case at St. Jude Children's Research Hospital. The infant, whose immune system had been completely wiped out by her chemo, unfortunately caught an *Enterococcus faecium* infection in spite of the hospital's best efforts. The bacterium resisted every drug they threw at it—until, that is, the girl's medical team infused her with certain cells that essentially amounted to an immune-system reboot. She

Perhaps in some cases, we will know at the onset which kinds of antibiotics are worth prescribing to a patient, and which ones are a dead end. And we will know this based on genetic sequencing—an approach that, thanks to Roz and her ilk, is quite fast compared to the days or even weeks a lab culture can take. Just give Roz a sputum sample, and within hours you're in business.

In fact, it has been done before. In March, a colleague of Cooper's in Oxford predicted a resistant strain of tuberculosis (TB). "We know enough about what allows TB to resist various drugs that the sequence will tell you the answer," Cooper says.



In this data visualization, frequencies of mutations are represented through time. From a single clone, three main ecotypes of biofilming bacteria evolve over hundreds of generations: “wrinkly” (red), “studded” (blue), and “ruffled” (green). Note the bump in the red, followed by the blue ribbon’s shift to a darker shade. The mutations of both breeds, which helped the cells acquire needed iron, happened in the same sequence of DNA. “It’s sort of tit for tat—coevolution over a limited resource,” Cooper says. “But they all persisted.”



In a bacterial homestead, a world where every single day is a new test of do or die, you might expect a wild west—an every bug for itself kind of rough and tumble.

But surprisingly, as Cooper’s lab was the first to report, that’s not the case.

When biofilming bacteria are ready to yield young’uns, they send out single-celled swimmers to stake new claims and plant new seeds. As they land, they glom onto something—like a bead from Cooper’s experiments—and start pumping out polysaccharides, extracellular DNA, and a protein glue to hold it all together. Cooper hypothesizes that, in time, the goo surrounding this first wave of migrants takes shape, forming a distinct structure he calls a “wrinkly.”

Two other kinds of characters show up and put down stakes in a similar fashion. The ones called “ruffled,” for their lovely rosettes, fill in the gaps, sticking partly onto the plastic and partly onto their wrinkly brethren. The spurred specimens, which Cooper calls “studded,” line the top.

Much like how Pittsburgh’s topography has preserved its cultural communities over time (Polish, African American, Jewish, pick your hillside), in biofilms, bacterial societyfolk form physical niches and cultivate group identities. Nested in their neighborhoods, they adapt and evolve, and adapt and evolve again. But instead of being cutthroat in their ways—with winners,

losers, and cheats—these three groups (and ever-growing numbers of subgroups therein) evolve *together*.

“The [studded biofilm] that’s on the outside is tending to feed the guys it’s sticking to,” says Cooper. “That’s a food web, right? That’s the producer-consumer relationship. . . . Very, very simple experiment producing these really complex phenomena that we see in nature. And it only takes a few months.”

This is the story of life, in miniature: a single cell evolving into what Darwin famously called the “tangled bank” of complex, varied, and interdependent species. And it’s all told in a replicable and measurable way. A few years ago, NASA took note and awarded the lab a spot in the NASA Astrobiology Institute, a research collective with the goal of uncovering the origins of multicellular life.

In 2014, Cooper used his super simple bead experiment to launch what he says is the most important thing he does. He turned the experiment into a high school science curriculum, a National Science Foundation-funded effort he calls EvolvingSTEM. Using the harmless bacterium *Pseudomonas fluorescens*, ninth-graders in New Hampshire—and, as of last school year, the Pittsburgh area’s Peters Township—have been conducting their own bead-transfer experiments and watching wrinkly, studded, and ruffled mutants arise.

“I mean, there’s nothing like *doing* science, right?” says Cooper.

“Many of [the teens] are doubtful about whether they *can* do it, but the protocol is so simple that most people wind up succeeding, and it builds a lot of confidence that they can do bench science.”

A scientist true to form, Cooper has used surveys to compare EvolvingSTEM students against controls. The former had better learning outcomes. And they said they were more motivated to consider STEM fields, too.

There are other reasons this is his favorite pet project: These experiments completely undermine any suspicion of evolution, says Cooper. And a thin-to-nonexistent understanding of evolution really limits the understanding of life sciences as a whole—which has consequences.

It’s easy to forget how clonal we *Homo sapiens* really are. Just 200,000 years ago, for example, there was just one mitochondrion among our species. Every single one of us descends from the same maternal ancestor who spun out a second one, likely under some pressure to survive.

And so we *do*.

When we lose sight of our origins, it is to our detriment, Cooper says. “We tend to focus on the little differences among individuals rather than a broad commonality.” ■

PATIENTS, DOCTORS, AND RESEARCHERS FACE A
TERRIFYING DISEASE TOGETHER | BY GAVIN JENKINS

MUTUAL SUPPORT

Jerry French had never heard of idiopathic pulmonary fibrosis (IPF) when a doctor diagnosed him with the disease three years ago. It took French months to understand and accept what was happening: The interstitium—the space between alveoli and the bloodstream—in his lungs was thickening with scar tissue, making it difficult for oxygen to reach the capillaries. His lungs were stiff and couldn't properly inflate, diminishing his breathing capacity. It was going to get worse, and a lung transplant was the only cure.

For two years, French's internist had been treating him for a sinus infection. Despite a nagging cough, French, now 72, worked full-time in commercial contracting and construction. He played church-league softball and was active around his Clarksburg, W. Va., home. The statistics he and his wife learned from the pulmonologist were shocking: the median life span for IPF patients after diagnosis is three to five years.

PHOTOGRAPHY | TOM M. JOHNSON

The support group at the Simmons Center helps researchers as well as patients. LEFT: IPF patient Jerry French on his West Virginia property.



The idiopathic aspect—that no one knew the cause—was “devastating” to French. Genetic and environmental links have been found, but, French says, he wanted to put his “finger on what it was that did this.”

Like more than half of all IPF patients, French became depressed following the diagnosis. He sat in front of the television, obsessing over what would happen to his lungs and how it would feel. His wife, Katie French, encouraged him to get off the couch and do something. Anything.

He eventually listened and pulled out of

ence room. Nearly every patient breathed with the help of an oxygen tank. Most IPF patients are older than 50; the disease forces many to slow down. Some end up retiring early.

Jared Chiarchiaro’s keynote talk that day was called “Planning for Your Future with Your Loved Ones.”

Chiarchiaro, assistant professor of medicine, began his remarks with a question: “How many of you had never heard of IPF before you or your loved ones were diagnosed?”

Twenty-three hands shot into the air.

Chiarchiaro’s lecture focused on acknowl-

support group and other programs at the Simmons Center, says that the community atmosphere has inspired volunteerism among the patients. In 2003, Charles Ward, a 75-year-old retired firefighter, asked to talk to Lindell after a support group meeting. He was wondering, *After he died, could he donate his lungs for research?* Naftali Kaminski, then the center’s director, looked into it.

He learned that Ward’s lung had to be donated within six hours of his death. The timeframe would help doctors keep lung tissue in the best possible condition so they could

In 2003, Charles Ward, a 75-year-old retired firefighter, asked to talk to Lindell after a support group meeting. He was wondering, *After he died, could he donate his lungs for research?*

the fog by attending IPF support group meetings hosted by the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease at UPMC.

IPF can be terrifying. To address this, the Simmons Center started the support group program, among the nation’s first for IPF patients, in 2001.

A community of patients, their caregivers, and medical professionals has arisen from the gatherings. Today, the community not only supports patients and their families, but advances the work of University of Pittsburgh doctors and scientists, as well. Patient participation has yielded precious research resources, including the largest IPF tissue bank in the country.

The Simmons Center is named after a prominent Pittsburgh businessman and his wife. Following Dorothy Simmons’s death from IPF in January 2001, Richard Simmons donated \$5 million to the University of Pittsburgh to create the center; he stipulated that educating and supporting IPF patients be a priority along with finding a cause and a cure.

The monthly gathering is catered. Patients take turns talking about how they are doing. Then it starts to feel more like a college seminar, with physicians and other scientists explaining their research and fielding questions. At April’s meeting, 23 patients and caregivers sat around tables assembled in the shape of a horseshoe in a Scaife Hall confer-

encing death, talking to relatives about it, and planning for end-of-life care. The one patient who arrived alone said that he wished his wife had attended. “She still thinks I have 10 years,” he said to the group. “We’ve got to have this conversation.”

Other recent meetings have focused on clinical trials and stem cell therapy. Following each lecture, there is often an icebreaker. Once a year, the meeting includes a lab tour.

“Everyone there becomes family,” says Wesley Plietz, a retired postal worker from Glenshaw, Pa., who was diagnosed with IPF a decade ago. Plietz, 75, received a double-lung transplant seven years ago but still attends several meetings a year to share his story and give advice. After a lung transplant, patients have a 50 percent chance of living five years. Plietz tells people at the meetings that he has beaten the odds because he never forgets to take a rejection pill or vitamin. He jokes that he’s a pill peddler.

The meetings have even attracted patients who don’t have IPF. Skip Mortimer, 74, suffered from emphysema and bronchitis before a lung transplant six years ago. Mortimer, a Weirton, W. Va., resident, started attending the monthly meetings in Pittsburgh two years before the procedure because he’d heard that the group was supportive and active. He still attends and now gives a ride to a friend who has IPF.

Kathleen Lindell, PhD and RN research assistant professor of medicine who runs the

isolate live cells to study. After Ward died, Kaminski and Lindell created the country’s first rapid tissue (then known as “warm autopsy”) donation program for lungs. Rapid tissue donation was common with prostate cancer and neuromuscular diseases, but it had never been tried with lungs, says Lindell.

To date, 85 Simmons Center patients have participated, and French plans to donate after he dies. “If we’re working with researchers, why not do something more?” French says. “Because they can definitely do something more with the tissue.”

A number of labs have used Pitt’s banked lung tissue, as well as blood samples, in their research. In the 16 years since its founding, Simmons Center researchers—under the leadership of Kaminski and former medical director James Dauber, as well as current Simmons director Daniel Kass and medical director Kevin Gibson—have published 350 papers. Some of those are among the most cited in IPF literature.

One Pitt study, led by Ana Mora, associate professor of medicine, on scarred lung tissue samples revealed mitochondrial abnormalities in IPF patients. Mora’s team found that the abnormality was linked to aging and an enzyme deficiency that eventuates in fibrosis.

Kaminski and Gibson, a professor of medicine, discovered the first validated peripheral blood biomarkers for IPF. Such biomarkers should help doctors predict how IPF will progress in each case.



Wesley Plietz had a double-lung transplant for IPF seven years ago; he's beaten the odds. After a lung transplant, patients have a 50 percent chance of living five years.

That's important because an IPF patient's condition can plateau for years and then quickly deteriorate to acute exacerbation, which Kass, who is an associate professor of medicine, describes as falling off a cliff. Those patients might die within weeks.

Another investigation involving Simmons patients could change how doctors think about the disease. For years, the conventional wisdom was that IPF had nothing to do with inflammation. According to Kass, there was not a lot of inflammation evident in biopsies when pathologists looked under the microscope.

"So they thought it was a disease of scarring that never ends," Kass says. "And nothing appears to provoke that scar."

But Steven Duncan (Fel '85), a former associate professor at Pitt who is now at the University of Alabama at Birmingham (UAB),

thought the arguments against inflammation in IPF seemed specious, given how most fibrotic diseases have an inflammatory component.

Duncan suggested that IPF should be treated like an autoimmune disease, such as lupus or rheumatoid arthritis. Through the course of two years, Duncan and Michael Donahoe, Pitt professor of medicine and executive vice chair of clinical affairs, treated 10 Simmons Center patients who were hospitalized because of acute exacerbation. The doctors ordered plasma exchanges for the patients to deplete their bodies of autoantibodies. The work was supported by UPMC. Duncan says that, after one year, the new treatment was effective in more than 50 percent of cases; before this, patients did not respond significantly to any treatments.

"When it salvaged them, it was like a

miracle," Duncan says. "People who were critically ill would get up to leave the hospital days later using either low-flow oxygen or no oxygen."

Later this year, doctors at Pitt, UAB, Temple University, and Harvard University will begin a National Institutes of Health-funded multicenter trial using this method of treatment.

Simmons Center research associate John Sembrat, who contributed to the mitochondria study, says talking to patients at the monthly meetings keeps him motivated during those late nights in the lab.

"I always think: *How can you even breathe with a lung as damaged as that?* And then I get to meet these people, who are carrying around an oxygen tank. Every day, they're waiting and waiting for some kind of cure, some kind of help."

Mary Camphire, who was diagnosed with IPF two years ago, was at the April meeting with her husband, Jack. She called Chiarchiaro's talk the most difficult discussion she had attended and described her ride home to Edinboro, Pa., as "terrible." But after talking with her husband about the meeting for a couple of days, she was glad they'd gone.

"It opened my eyes," says Camphire, 75. "I guess you try to put things out of your mind when they're not in your face, and that brought it to the surface."

During the meeting, everyone shared what they hoped for most at the end of life. People wished to not be a burden on their loved ones and to have a painless death.

There were lighter moments, too, like when the couples shared what they did on their first dates. Jack Camphire had invited Mary to a jazz concert. However, she'd turned him down for dates so many times before that he hadn't bought the tickets. So he rushed to get them.

A couple of times, the mood in the room threatened to turn dour, and French turned it around.

At one particularly serious point in the discussion, he looked at his allies around the table and said, "We should be passing around a bottle of Crown [Royal]." Everyone laughed. ■



The Brain Bank's Julia Kofler makes characterized tissue available to labs throughout the world.

IN MEMORY

THE TRUTH THE DEAD KNOW

BY NANCY AVERETT

PHOTOGRAPHY BY TOM M. JOHNSON

At 15, Gina Rugari was like a lot of girls her age: She liked manicures, sleepovers, and school dances. She loved her dog, Bella Rina, and dreamed of traveling to Paris. In other ways, though, Gina was atypical. She was born with Krabbe disease, a neurological disorder that might have taken her life before she turned 1. Instead—thanks to a medical breakthrough—she lived another 14 years.

When Gina died in 2015, her mother, Anne Rugari, donated Gina's brain and spinal cord to be used for research at the University of Pittsburgh. That gift has advanced research on Krabbe disease, which causes depletion of myelin in the brain's white matter and in the spinal cord. Eventually, nerves in those regions can no longer conduct electrical impulses normally, and they die.

"Gina had such a unique brain," says Rugari. "She was one of the first infants to get an umbilical cord blood transplant for Krabbe disease, so I knew that when she passed away, it would be very valuable for researchers to have it."

Gina's tissue was housed and examined at Pitt's Neuropathology Brain Bank. Rugari donated Gina's tissue through the Program for the Study of Neurodevelopment in Rare Disorders at Children's Hospital of Pittsburgh of UPMC. Julia Kofler, director of the Brain Bank, often hears from families directly: "At least once a week, someone contacts me and asks me about donating."

"People want to know more about what happened to their loved ones, and they want to be helpful to research," says Kofler (Res '10), MD assistant professor of pathology at Pitt.

Kofler earned her medical degree in her native Vienna. She started her career as a physician in the emergency department who also researched the neurological damage that can occur in patients surviving a cardiac arrest.

"The brain is an extremely complex organ, and I've always been fascinated by it," Kofler says. So fascinated, in fact, that she moved to the United States and completed another residency, this time focusing on neuropathology. In her role at the Brain Bank, Kofler makes characterized tissue available to labs throughout the world. Her staff includes a pathology fellow and pathology assistant; they are on call 24 hours a day, seven days a week, to perform autopsies.

Kofler's neuro-colleagues here speak reverently about the service she provides. "Julia is

a huge resource," says Chris Donnelly, PhD assistant professor of neurobiology. "Having her expertise to help validate our research is really, really important. A lot of labs don't have access to someone like that."

Yet Pitt's bank has often operated on a wing and a prayer. Grant funding for brain banks is hard to come by; the National Institutes of Health, for instance, offers limited direct funding for such repositories (though it does support banking for Alzheimer's disease research). Kofler has often had to string together support from multiple sources—grants as well as various departmental and hospital funds—to run the repository.

So Kofler was thrilled last fall when she learned that Pitt's bank had been selected to receive part of a Henry L. Hillman Foundation grant in support of the University's Brain Institute. "It's been a huge help and stabilizing factor for our financial situation and allowed us to expand our banking initiatives," she says.

Most of the 1,600 specimens at the bank have come from participants in Pitt's Alzheimer Disease Research Center. The repository also houses specimens representing amyotrophic lateral sclerosis (ALS), Parkinson's disease, and pediatric neurodegenerative diseases, such as Krabbe. Kofler is now partnering with Pitt's Brain Trauma Research Center to further studies on traumatic brain injury and chronic traumatic encephalopathy (CTE), the degenerative condition that has afflicted football players.

The existence of the bank—and the bonus of having a director who is also a neuropa-

thologist—helped lure Donnelly here from Johns Hopkins University in 2015. Donnelly focuses on understanding ALS at the molecular level.

When Donnelly needs to validate what he's seeing in his petri dish, he turns to Kofler. He recently, for instance, identified a defective cellular pathway in the stem cells of patients who have a mutation that leads to ALS. Donnelly wondered if this impaired pathway might also exist in ALS patients without the mutation. So he asked Kofler if she could find evidence of the defective channel in her ALS tissue samples. She did, including in tissue from some patients who did not have the mutation.

"It's an ongoing study," Donnelly says. "But what it potentially means is, if we can figure out a way to correct the problem with that pathway, we might find a way to treat subsets of patients who have this disease."

Similar validation is building understanding of Krabbe disease. Gina's brain and spinal tissue, for instance, confirmed what animal studies had shown: an umbilical cord blood transfusion can halt disease progression, but more so in the brain than in the peripheral nervous system. Gina's peripheral system showed disease progression, and this is most likely why she died, notes Maria Escobar, Pitt associate professor of pediatrics. Escobar is director of the Program for the Study of Neurodevelopment in Rare Disorders and had been Gina's doctor at Children's Hospital since the girl was born.

Rugari now educates parents of children with Krabbe disease about brain donation to further Escobar's research. To date, nine families have participated. Escobar expects those donations will offer insight as she probes for a potential new treatment.

The progress is gratifying to Rugari.

In addition to losing Gina, Rugari lost an infant son, Nicholas, to Krabbe disease. He died in 1987.

"I was told back then, 31 years ago, that Krabbe is so rare there's never going to be any research, cure, or treatment for this disease," she says.

"I just said, 'No way.'"

Editor's Note: For research on CTE, the Brain Bank is looking for tissue donors who were boxers, played football, were in the military, or experienced concussions. Call 412-624-9415.



ILLUSTRATION BY PETE GARCEAU

THE INHERITANCE

**A FAMILY ON THE
FRONT LINES OF THE
BATTLE AGAINST
ALZHEIMER'S DISEASE**

In 2009, writer Niki Kapsambelis took on a story assignment that changed her life.

It was an article for the University of Pittsburgh Alzheimer Disease Research Center's newsletter; Kapsambelis was asked to write about a family from North Dakota, the DeMoes. The family was partnering with Pitt's William Klunk, MD/PhD professor of psychiatry and neurology, and Chester Mathis, PhD professor of radiology. The scientists had developed Pittsburgh Compound B, an agent used for imaging brains in living patients to identify buildup of a sticky protein (called beta-amyloid) associated with Alzheimer's disease.

Five of the six DeMoe siblings carried the gene for early onset Alzheimer's. Their father died from it, as did their paternal grandmother.

Kapsambelis met the family at Pittsburgh's Omni William Penn Hotel. At that time, two of the siblings, Brian and Doug DeMoe, who'd worked in the oil fields like their dad, were starting to experience symptoms. The men were then 48 and 44, respectively. Brian was unable to make the Pittsburgh trip.

After meeting the DeMoes, Kapsambelis got into her car to drive home and found herself shaking. "I just felt they had a much more important story than a newsletter article," she told the Pittsburgh Post-Gazette.

Eight years and many, many interviews later, Simon and Schuster published Kapsambelis's book, The Inheritance, which weaves the DeMoes' story with a narrative of the history of the disease and related research, notably the work of Klunk and Mathis. Kapsambelis came to feel she was part of the DeMoe family; the DeMoes called her their "author-in-law."

We share edited excerpts of the book here. —Erica Lloyd

In her introduction, Kapsambelis describes the importance of what the DeMoes decided to do with their remaining years. She notes that researchers are searching for a way to predict who will get Alzheimer's so they can treat those people before they slip away.

... But to find such a treatment, doctors need a patient who is guaranteed, with 100 percent certainty, to get the disease—only then will they know whether an experimental treatment is successful, by testing it out on that person and then measuring its effect.

Those perfect patients do exist, as one tiny sliver of the population who stand distinctly apart from the rest. They are the people living with one of three known mutations that guarantee they will be stricken. Only about 1 percent of all Alzheimer's patients fall into this category. They are hit young: their average age of onset is between 30 and 50 years old.

These are the people we will thank when Alzheimer's itself becomes a distant memory.

By testing preventive drugs in this population, researchers hope that they will be able to translate a successful treatment before another generation is lost.

FAVORITE SON

Brian was living in a trailer on the outskirts of Tioga when his sister Karla and mother, Gail, began to think that maybe it was time to bring him closer to the center of town. They wanted to keep an eye on him as his memory and thought process deteriorated: Alzheimer's patients often wander and go missing, or people take advantage of them.

They found him a little one-bedroom

house just down the street from Doug's and a few blocks from Gail's. He moved in, bringing a stray cat that he'd adopted and called Missy, until he found out it was a male. Then he named it Mr. Missy. Brian's daughter, Kassie, found it ironic that her father, who'd hated cats throughout her childhood, was mellowing under the shadow of Alzheimer's to the point where he doted on his kitty. The first night he spent in his new house, he climbed onto the roof to rescue the cat, only to fall and break his legs in the process.

For a few years, Brian got by. In the aftermath of Trey Sunderland's firing from the National Institutes of Health, Karla was determined to steer her family to another research venue. She hoped Bill Klunk's work at the University of Pittsburgh would fill that void.

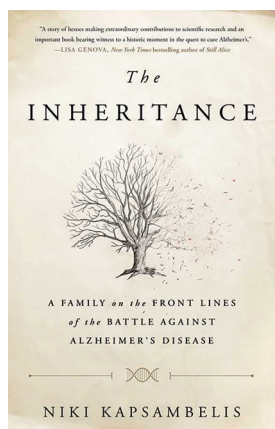
It would prove to be a fortuitous partnership. In Klunk, the DeMoe family finally found their champion: a man who cared about them as human beings as much as he cared about the scientific

knowledge he could gain from their unusual genes. Gail saw Bill Klunk as a man who would watch over her family in ways that she couldn't; his entire staff treated them like old friends. One by one, the DeMoe siblings trekked to Pittsburgh each year, undergoing a battery of tests and brain scans so scientists could see how the disease was progressing both biologically, inside their brains, and clinically, in their behavior.

The study paid for travel costs and provided a meal stipend and small honorarium; in return, each study subject had to schedule at least three days off from work and convince a partner to accompany him or her—a spouse or a close friend or family member who could objectively answer questions about the subject's day-to-day level of functioning. The study partners also had to schedule time off, and in some cases, they had to handle the rigors of traveling with an Alzheimer's patient.

Gail frequently traveled with her offspring, and Klunk and his staff came to know each of them intimately. When Gail's grandchildren grew into adulthood, most of them joined the study.

Though the tests were grueling, Klunk and his group worked hard to make the trip palatable. The subjects were encouraged to sightsee, attend ball games, explore the city. When the



COURTESY KARLA HORNSTEIN



The DeMoe siblings with their mother in 1986. BACK ROW, FROM LEFT: Jamie, Doug, Dean, and Brian. FRONT ROW: Karla, Gail (their mom), and Lori. Karla was the only sibling who tested negative for the gene for early onset Alzheimer's.

workday was over, the DeMoes and the doctor often ate dinner together. Klunk did this with many of the patients in his study, except for certain cases: If study participants chose not to learn their genetic status, he politely declined dinner, fearing he might accidentally tip someone off to what he knew.

Klunk admired the DeMoes for their courage and their selflessness. Their contributions gave science a window to a baffling disease. He would come to know three generations of DeMoes; he would witness their losses and triumphs, learn their deepest secrets and most paralyzing fears. He was humbled by their sacrifices and their trust in him. He would become their touchstone, a lifeline as they were battered by the relentlessness of the disease. Unlike anyone else they had met in the research world, he always made himself available, always returned their calls.

"There's only one family like the DeMoes," Klunk said. "They're the salt of the earth."

Brian made it to Pittsburgh twice to par-

Kim Johnston remembers teaching him to ride a three-wheeled bike, thinking it would help him get to Gail's more easily.

At 5-foot-2, Kim struggled to hold the small bike while Brian moved the pedals, forgetting to coordinate each push.

"Okay, now, now, now!" she yelled, as Brian started to get the hang of it.

"I can't!" he shouted.

"Can't never could," said Kim, borrowing one of Gail's favorite expressions, and Brian pedaled faster.

They wobbled down the street, past an oil company office; workers stuck their heads out of the window, fascinated at the spectacle of a burly man in a trucker cap shakily pedaling a bike several sizes too small for him while a short woman cheered him on like an exultant mother. By the time they reached Gail's house, Gail was outside, laughing so hard she had to cross her legs to avoid wetting her pants.

"That was probably one of the last times that I thought part of him was still in there,"

the other side of the state, Karla had been monitoring her brother's living situation. She called the woman who tended the Skol Bar and learned that Brian was sometimes emerging from the bar's restroom without pulling up his underwear. And Karla knew that the ugly incidents with Gail were escalating.

Because Brian was no longer married, his children were scattered, and Dean had been diagnosed with the mutation, Karla alone held the power of attorney over his affairs. It was up to her to decide what to do next. After consulting with Brian's children and some of his friends, she made the first of what would be many difficult choices. She decided her big brother would enter a memory care facility—one that was locked to safeguard against wandering. It was in Minot, 80 miles away.

Karla told Lori and a few other family members and close friends about her plan, but made sure to keep the news from Gail. No matter how hard it was for her to relive the terror and pain of her final years living with her husband,

"That was probably one of the last times that I thought part of him was still in there."

ticipate in Klunk's study before the disease claimed too much of his brain to make travel possible. His small world grew smaller; he walked across the street from his little house to the Skol Bar, which was populated and run by his friends. They made sure nobody stole from him; it would have been easy to take his money.

At the local drive-in, family friend Kim Johnston worked behind the counter and waited on Brian when he showed up for lunch. Knowing that too many questions flustered him, she placed his standing order for a Philly steak wrap without asking and took the correct amount of money from Brian's billfold when he silently handed it over to her. Then he'd settle into a table across from her and wait for his food, saying, "Ayup," like he was relaxing after a particularly hard day at work.

Brian had always been generous; now he bought small trinkets to give his mother. They were all he could afford, but he made the gesture to show her his affection. He walked to her house, often woefully underdressed for the harsh weather, loping along on his bum leg that had never quite healed right after the fall from the roof.

Kim said.

Once he was home all the time, he would spend hours playing the practical joke that had been a DeMoe family tradition for decades: canning cars. The trick never got old. As his disease progressed, it got more hilarious. He canned cars so often that the people of Tioga came to expect it when driving past Gail's house; a few times, he forgot to let go of the fishing line and nearly lost a finger.

And sometimes, though he loved her, Brian was uncharacteristically cruel to his mother. When Brian's mood swung low, he unleashed his temper on Gail, much the way his father once had. Though she knew by now that the viciousness was Alzheimer's, it was impossible for Gail not to take the abuse personally.

Occasionally, she brought him with her when she went across town to volunteer at the nursing home. Sometimes he slipped outside to smoke a cigarette while she was doing a patient's nails. That worried her because she knew he was a wanderer, and the nursing home wasn't a locked facility. What would happen to him when he was no longer capable of living on his own?

The answer came in February 2008. From

Moe, Gail could never have agreed to send her favorite son away.

The morning they decided to take him, Brian's sisters Lori and Karla—who were staying overnight at Gail's, ostensibly for an ordinary visit—met in the kitchen with Doug's daughter, Jennifer, as well as Kim Johnston. Gail woke to the sound of the gathering and wandered down the hall into the kitchen. When they told her what they were doing, she began to cry.

"Mom, I just know you would never want to let him go," Karla said gently, reassuring her that it was the only choice they could make. Karla accepted full responsibility for that decision, hoping to spare her mother some of the pain. Let Brian hate her; she could recover. Gail never would.

"It was awful," Karla said. "I didn't want her to feel that way."

The decision to move Brian to a locked facility—however pleasant the accommodations, however necessary the move—would be the first of many difficult turning points for Karla. With each decision, a limb of her family tree fell to her feet, her peace of mind eroding just a little more. —Niki Kapsambelis, © 2017. Reprinted with permission. ■

STUDENTS

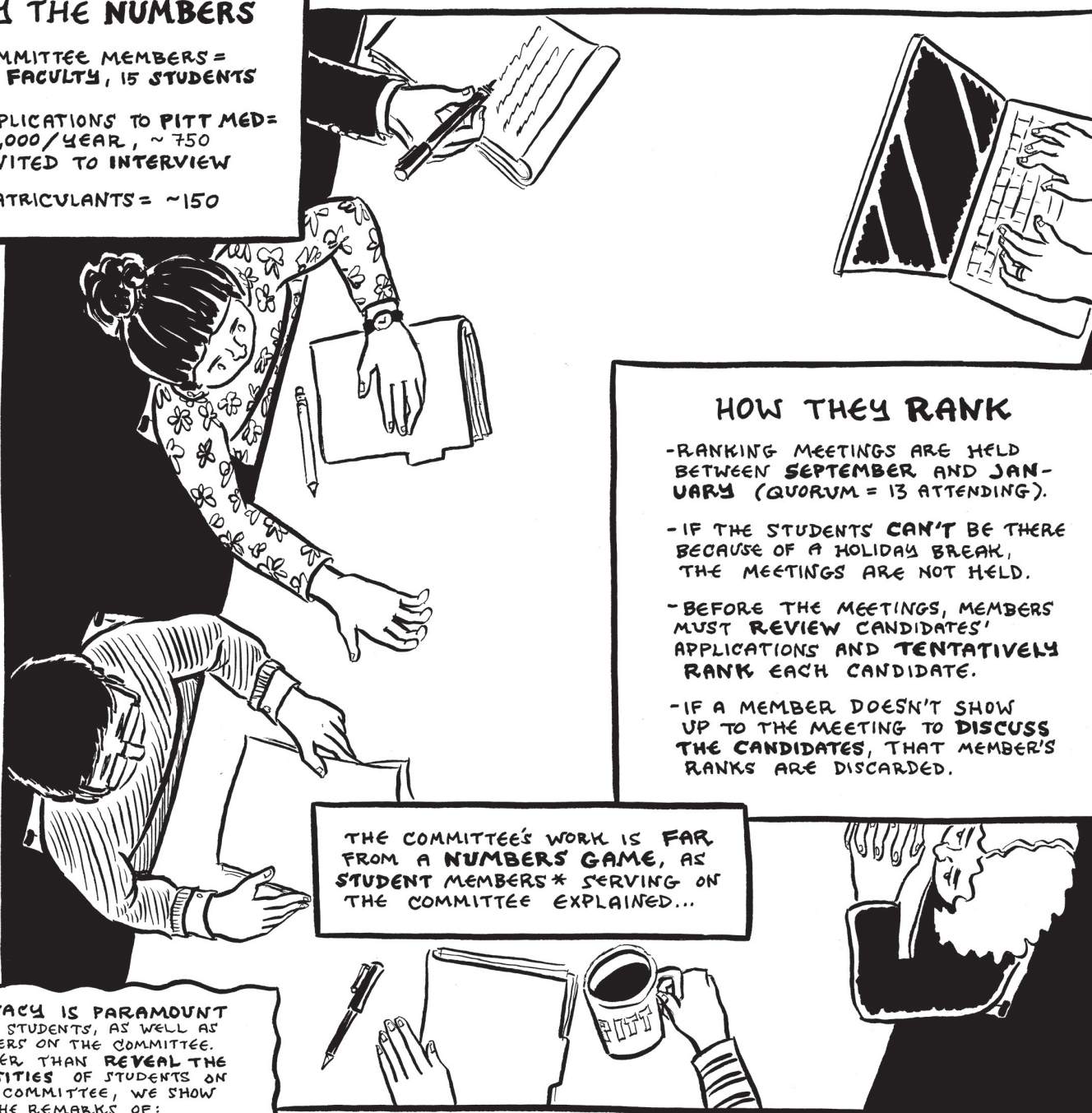
AT THE TABLE

SERVING ON THE UNIVERSITY OF PITTSBURGH MED SCHOOL ADMISSIONS COMMITTEE IS NO SMALL MATTER.

BY EM DEMARCO

BY THE NUMBERS

- COMMITTEE MEMBERS = 30 FACULTY, 15 STUDENTS
- APPLICATIONS TO PITT MED = ~6,000/YEAR, ~750 INVITED TO INTERVIEW
- MATRICULANTS = ~150



HOW THEY RANK

- RANKING MEETINGS ARE HELD BETWEEN SEPTEMBER AND JANUARY (QUORUM = 13 ATTENDING).
- IF THE STUDENTS CAN'T BE THERE BECAUSE OF A HOLIDAY BREAK, THE MEETINGS ARE NOT HELD.
- BEFORE THE MEETINGS, MEMBERS MUST REVIEW CANDIDATES' APPLICATIONS AND TENTATIVELY RANK EACH CANDIDATE.
- IF A MEMBER DOESN'T SHOW UP TO THE MEETING TO DISCUSS THE CANDIDATES, THAT MEMBER'S RANKS ARE DISCARDED.

THE COMMITTEE'S WORK IS FAR FROM A NUMBERS GAME, AS STUDENT MEMBERS* SERVING ON THE COMMITTEE EXPLAINED...

* PRIVACY IS PARAMOUNT FOR STUDENTS, AS WELL AS OTHERS ON THE COMMITTEE. RATHER THAN REVEAL THE IDENTITIES OF STUDENTS ON THE COMMITTEE, WE SHOW THE REMARKS OF:

STUDENT #1
LIKE THIS...

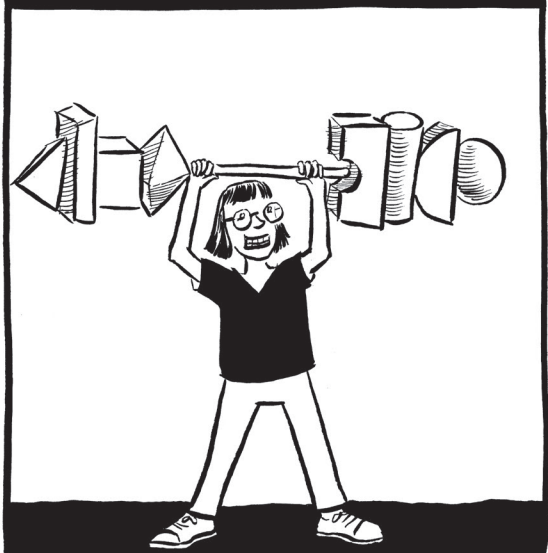
AND STUDENT
#2 LIKE THIS.

"WHEN YOU'RE APPLYING, YOU THINK THAT THERE'S A MAGIC FORMULA."

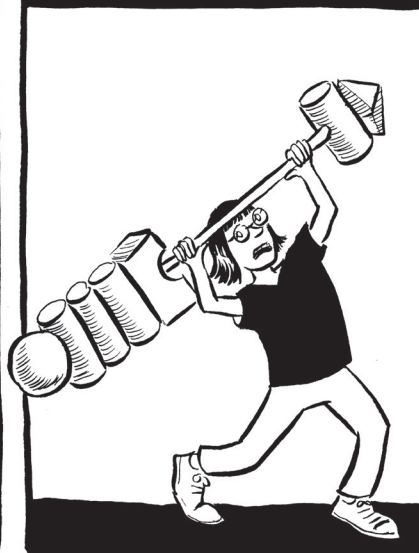


"YOU HAVE TO HAVE A UNIQUE, OUTSTANDING PACKAGE TO GET INTO MEDICAL SCHOOL-- SPECIFICALLY THE UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE."

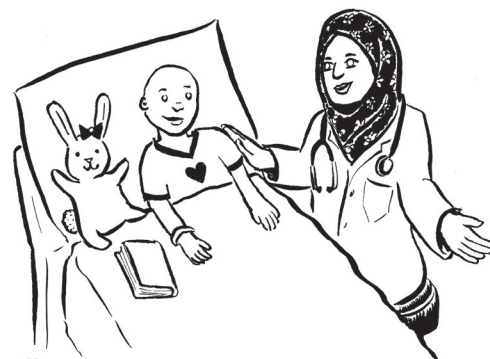
"NOT ONLY DO THEY LOOK AT MCAT SCORES AND YOUR GRADES, BUT THEY ALSO LOOK AT YOU AS A PERSON, AS A LEADER, AND YOUR INVOLVEMENT IN MEDICINE IN GENERAL."



"THIS IS A VERY RESEARCH-HEAVY SCHOOL... IF YOU DON'T LIKE RESEARCH, THEN THIS PROBABLY ISN'T THE PLACE FOR YOU."



"I LOOK AT THEIR PERSONAL STATEMENT TO SEE WHAT THE DRIVE IS TO BE A PHYSICIAN."



"YOU'RE NOT SEEING A LOT OF PATIENTS IN THE FIRST TWO YEARS... COMING INTO IT YOU NEED TO KNOW WHY YOU WANT TO BE A DOCTOR. OR ELSE IT'S GOING TO FADE REALLY FAST."

DURING INTERVIEW DAY...

SOME RED FLAGS THE COMMITTEE LOOKS FOR:

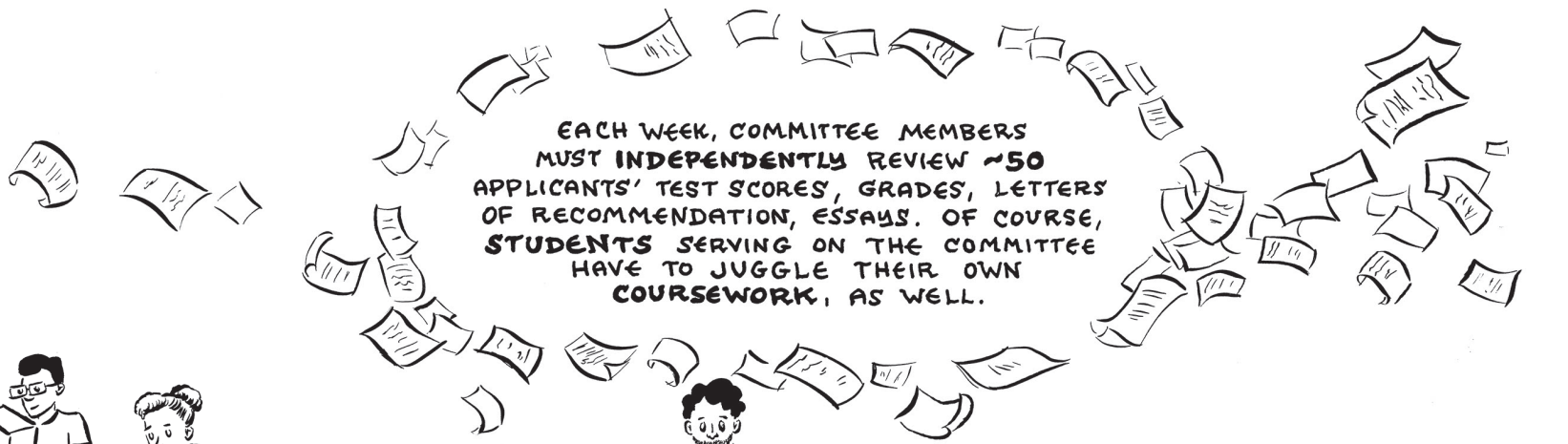
I CAN'T #\$.!?!%!
WAIT TO BECOME A DOCTOR!



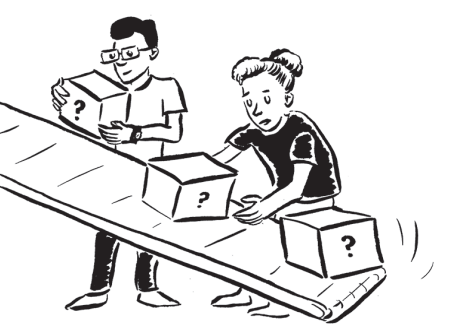
WOW-- HAVE YOU SEEN THE INCREDIBLE CAMPUS AT [INSERT OTHER MED SCHOOL NAME HERE]?



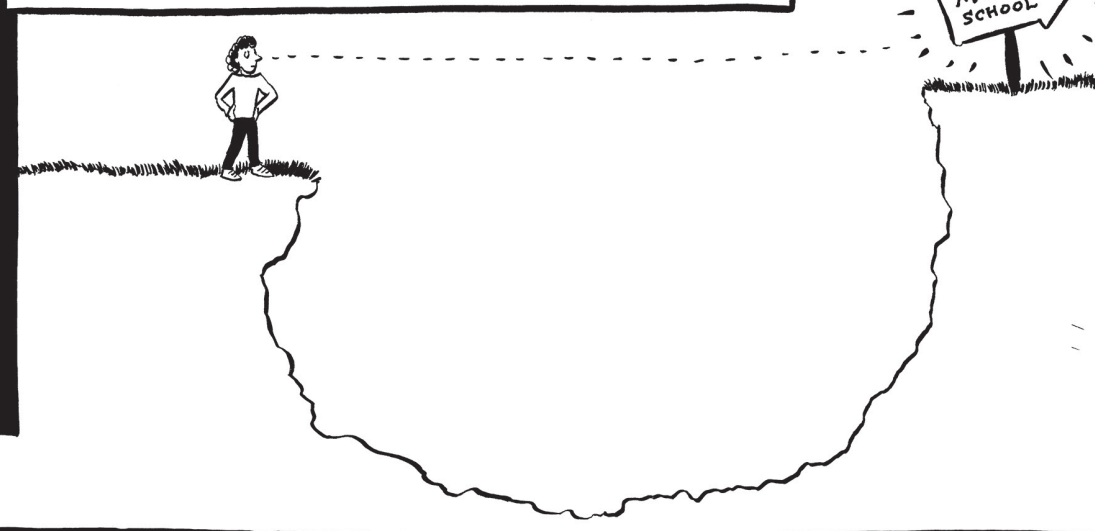
CANDIDATES ARE EVALUATED ALL DAY-- INCLUDING HOW THEY WORK WITH OTHERS ON A TEAM.



EACH WEEK, COMMITTEE MEMBERS
MUST INDEPENDENTLY REVIEW ~50
APPLICANTS' TEST SCORES, GRADES, LETTERS
OF RECOMMENDATION, ESSAYS. OF COURSE,
STUDENTS SERVING ON THE COMMITTEE
HAVE TO JUGGLE THEIR OWN
COURSEWORK, AS WELL.



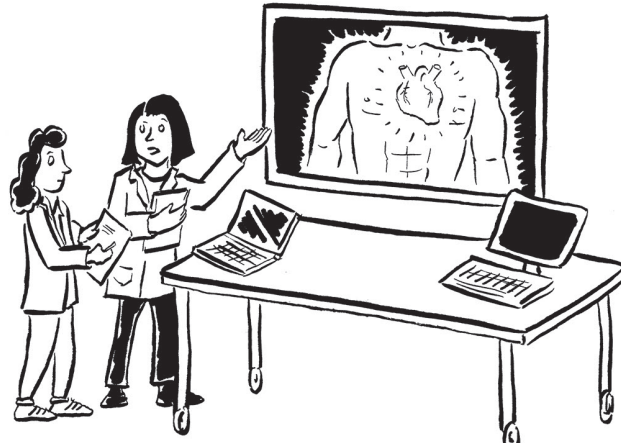

"IT'S A RESPONSIBILITY
... THIS CAN AFFECT
SOMEBODY'S CHANCES OF
BECOMING A PHYSICIAN.
-- AT LEAST AT THIS
MEDICAL SCHOOL."



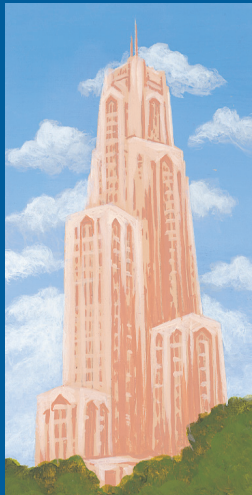
DURING THE MEETINGS, EACH MEMBER
CAN HIGHLIGHT ASPECTS OF A CANDIDATE'S
HISTORY, BACKGROUND, OR PERSONALITY THAT
MAY NOT BE APPARENT TO OTHER MEMBERS...

"[DIVERSITY] ON
THE COMMITTEE IS VERY
IMPORTANT... YOU WANT
TO MAKE SURE THAT
THERE ARE PEOPLE ON
THE COMMITTEE WHO
UNDERSTAND
THOSE APPLICANTS--
AND MAYBE UNDER-
STAND SOME OF THE
EXTRA HOOPS THEY
MAY HAVE HAD TO GO
THROUGH TO EVEN GET
TO WHERE THEY ARE
TO EVEN APPLY."

MEDICAL
SCHOOL



"IF YOU REALIZE
WHAT MAKES YOU
DIFFERENT, THEN YOU
WILL BE BETTER
AT **SHARING** THAT
WITH THE **CLASS**--
BETTERING US AS
A **WHOLE**. BECAUSE
WE'RE LEARNING FROM
OUR **TEXTBOOKS**,
BUT WE'RE ALSO
LEARNING FROM
EACH OTHER."



CLASS NOTES

'70s

Psychiatrist **Sharyn Ann Lenhart** (MD '74) says sexual harassment in the workplace occurs like pockets of air pollution—the atmosphere at one company may be clean, but the climate at the company across the street could be foul. Lenhart, author of *Clinical Aspects of Sexual Harassment and Gender Discrimination* (Taylor and Francis), says the differences in climate result from an organization's leadership. She has devoted her career to clearing the air—and the mind—for those affected by sexual harassment and gender discrimination. Lenhart holds a clinical academic appointment in psychiatry at Harvard University and is a senior attending psychiatrist at McLean Hospital/Massachusetts General Hospital as well as a consultant for employee assistance programs and legal cases. The resident of Concord, Mass., is also leading efforts to improve the community's mental health resources as a member of the town's Comprehensive Long Range Plan Committee.

'80s

Richard Shure (MD '82) remembers his first orthopaedic surgery experience fondly: still a med student, Shure assisted the then-attending **Freddie Fu** (MD '77, Orthopaedic Research Fellow '79, Orthopaedic Surgery Resident '82) in the O.R. Thirty years later, Fu is chair of Pitt's orthopaedic surgery department, and Shure, an expert in hand and microsurgery, has operated



Shure

on some of the biggest names in athletics, including Brandon Marshall, who at the time was a wide receiver with the Denver Broncos. In his first game back after surgery, he caught a record-breaking 18 passes. Shure also operated on Darrell Armstrong, a point guard for the Orlando Magic who, after his surgery, won the NBA's most improved player of the year award and Sixth Man of the Year Award (1998–99). But perhaps the biggest name (and hand) of Shure's career is Shaquille O'Neal's. Now retired, Shure occasionally works as a legal consultant.

In 2008, when **Jeanne Jordan** (PhD '88) became the first laboratory scientist to be recruited to the Milken Institute School of Public Health at George Washington University (GWU), she built the school's first research lab from scratch. To her amusement, the virologist and microbiologist was named a professor of epidemiology and biostatistics. "I don't know a thing about epi-bio," Jordan says. "I'm a lab person." But she wanted to convince her new colleagues they would benefit from interdisciplinary collaboration.

Since then, Jordan has worked on many federally supported projects with department colleagues. In a National Institutes of Health-funded effort, Jordan and physician Amanda Castel study molecular surveillance of HIV, with the goal of doing near-real-time next-generation sequencing of HIV to assess drug-resistant mutations. Jordan, director of the sequencing core for the D.C. Center for AIDS Research, recently received an R01 award from the NIH to pursue a more accurate means of predicting anal dysplasia in the MSM (men who have sex with men) population living with HIV, a prospect that could reduce unnecessary biopsies.

Jordan, now codirector of GWU's



Jordan

master's degree program in public health microbiology and emerging infectious diseases, credits her doctoral mentor, the late Julius Youngner, for showing her "how to do good science and how to be transparent and ethical. ... He was just amazing." (See Youngner obit on page 39.)

What's it like running the largest academic clinical research organization in the world? According to **Eric Peterson** (MD '88), director of the Duke Clinical Research Institute, the role is as multifaceted as it is fulfilling.

"We do lots of what we hope is really good, cutting-edge knowledge generation," says Peterson, noting the institute's publication output of more than a thousand papers annually, its 1,200 employees, and more than \$280 million in research revenue. Peterson is also a contributing editor for the *Journal of the American Medical Association*; he regularly sees cardiology patients; and he is the Fred Cobb Distinguished Professor of Medicine at Duke University.



Peterson

'90s

Gloria Beim (Sports Medicine Fellow '96) of Gunnison, Colo., knew she wanted to be an orthopaedist after having multiple knee surgeries at age 16. Now she's on the world stage. While volunteering at the Olympic Training Center in Colorado Springs in 2001, she garnered attention for her dedication to the athletes; she was subsequently invited to work at the Olympics (Athens, London, and Sochi), World University Games, Pan American Games, and, most recently, the 2016 Paralympics in Rio de Janeiro, where she was chief medical officer for Team USA. Beim attended every men's wheelchair basketball game and saw them win their first gold since 1988.



Beim (right) with gold medalist Michael Paye in Rio

'00s

Dave Stukus (MD '02) is dispelling myths, one tweet at a time. Stukus, an associate professor of pediatrics at Ohio State University, specializes in allergy and immunology at Nationwide Children's Hospital. Recently, he partnered with the podcast *PediaCast* for the hospital's health care communications and social media curriculum. The 12-episode series focuses on social media and medicine, with the aim of helping laypeople navigate digital space. "The majority of patients are going online to seek medical information, but the information they find is often unreliable," Stukus says. "We wanted to provide a blueprint to help." Medical media mavens may stream the podcast at pediacastcme.org/hcsm/. You can also follow Stukus on Twitter at @AllergyKidsDoc for a steady feed of Mythbuster Mondays.

'10s

As both a researcher and clinician approaching the final year of her critical care medicine fellowship at Johns Hopkins University, **Corrine Kliment** (MD '11, Cellular & Molecular Pathology PhD '11) is all about the lungs. Her research, primarily focusing on chronic obstructive pulmonary disease, seeks to find new protective pathways in cigarette smoking-related lung injury. Kliment says this research "goes back and forth from bench to bedside very easily." Her work was recently recognized by the American Society for Cell Biology as one of the "Best Cell Stories" of 2015. During her time at Pitt med, Kliment studied the basic science of pulmonary fibrosis. She then completed her internal medicine residency at Harvard Brigham and Women's Hospital in 2014.

Michael Best (MD '11, Anesthesiology Resident '15) did a six-month tour in Afghanistan last year with the U.S. Air Force. There, he served as disaster chief within his group and was called into action to treat patients after a suicide bomb attack at Bagram Airfield. Best also works as an attending anesthesiologist at St. Louis University Hospital in Missouri, helping to train medical personnel on airway skills, ventilator management, and initial resuscitation; he has served as the vice speaker for the Resident and Fellow Section of the American Medical Association.

—Cara Masset, Rachel Mennies, Susan Wiedel, Kylie Wolfe, and Elaina Zachos

LEON L. HALEY JR.

DEAN AT JACKSONVILLE

Growing up in Pittsburgh, Leon L. Haley Jr. (MD '90) dreamed of becoming the first African American sportscaster on network television. "But that changed when I mixed basketball with a trampoline," he says. Having missed a slam dunk, young Haley wound up with a torn meniscus—and an awakening fascination with medicine.

As a student at Pitt med, he completed a summer program working afternoon shifts at the emergency department at St. Margaret's Hospital. The variety of injury and trauma cases that came through the door inspired him to pursue emergency medicine. He completed his residency at Henry Ford Hospital in Detroit, Mich., followed by a master's in health services administration from the University of Michigan.

From there, Haley moved to Atlanta, where he rose through the ranks to professor of emergency medicine at Emory, as well as the university's executive associate dean for clinical affairs for Grady Memorial Hospital. During his tenure there, he implemented a rapid medical evaluation process that shortened emergency medicine patient waiting times by 45 minutes and reduced the length of stay for the patients with the least pressing cases by three hours. The process also drastically decreased the number



Haley

of patients who left without receiving care—by 50 percent.

In September, Haley was named dean of the College of Medicine, professor of emergency medicine, and vice president for health affairs at the University of Florida–Jacksonville.

As he looks to the future, Haley says teaching clinicians how to function in a digital environment will be critical. He emphasizes analytics, economics, and a push toward preventive medicine.

Luckily, Haley didn't always appreciate the latter. A bit of prevention in his basketball years might have been a game changer. —Kristin Bundy

New & Improved!

Are you tired of outdated Web site drudgery? Sick of logging on and wondering, *Hey, where's the beef?* Try the Medical Alumni Association's refreshing new site. Even *Mikey* likes it!

When you visit maa.pitt.edu, you'll find it's everywhere you want to be: connecting with classmates (when you care enough to send the very best), registering for Medical Alumni Weekend and other events (Calgon, take me away!), and giving back to your alma mater and its current crop of students (we bring good things to life). It just keeps going and going and going ...

While you're at it, connect with [@PittMedAlum](#) on [Facebook](#), [Twitter](#), and [Instagram](#). They're *grrrrrrrrreat* ways to stay in touch.

SHERILYN GORDON-BURROUGHS

AUG. 23, 1968–MARCH 19, 2017

Sherilyn Gordon-Burroughs (Fel '95) was fresh out of her residency at Howard University when she landed a research fellowship at Pitt. "It was her tenacity, determination, and curiosity that struck me," says Henri Ford, former surgeon-in-chief at Children's Hospital of Pittsburgh of UPMC,



Gordon-Burroughs

who supervised her and remained in close contact throughout her career. "I tried to convince her to pursue pediatric surgery, but transplant medicine really captured her."

Gordon-Burroughs became a nationally recognized liver transplant specialist, associate professor of surgery at Houston Methodist Hospital, and director of the hospital's general surgery residency program. She was also the hospital's designated institutional official, overseeing all 40 of its residency programs, and served as assistant dean for graduate medical education at Texas A&M. She died in March, the apparent victim of a murder-suicide. She was 48.

Gordon-Burroughs was a role model in a field where women are rare and women of color are rarer still, a colleague told the *Houston Chronicle*. "She was beloved because she was approachable and kind and thoughtful, someone who was always willing to take time out of her busy schedule to help students," said Patricia Turner, director of member services for the American College of Surgeons and a surgical residency classmate of Gordon-Burroughs's.

Ford, now vice dean of medical education at the University of Southern California, urged many of his own students to continue their training with Gordon-Burroughs. "I was very impressed with the quality of the surgical

residents that she had recruited," says Ford, who was a visiting professor at Houston Methodist in 2016. "It was a great source of pride to see the second research fellow who ever worked in my lab ascend and be on the trajectory to achieve even more recognition as a leader in the field."

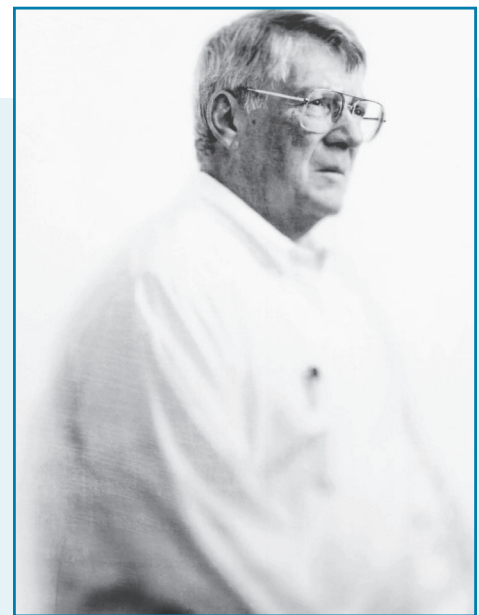
"Her loss is particularly tragic," he adds. "I lost a friend, and we've lost a rising star in the society of black surgeons and academic surgeons in general."

A fund has been established to support Gordon-Burroughs's preschool-age daughter and her guardians. Visit bit.ly/sgb2017 for details. —Sharon Tregaskis

HERBERT L. NEEDLEMAN

DEC. 13, 1927–JULY 18, 2017

In the early 1960s, Herbert Needleman was a self-proclaimed "cocky" resident at Children's Hospital of Philadelphia, and a young girl, we'll call her Vanessa, was admitted to his ward with severe lead poisoning. She had eaten the lead-based paint peeling from her inner-city home, and her story was all too common. Her brain had swollen to a point where she was dangerously near death. She didn't cry, didn't smile, just lay there, comatose. Needleman treated her with the only drug available to counter lead poisoning. Soon, she woke up crying, and Needleman breathed



FRANK WALSH

Needleman

a small sigh of relief. Within a few days, she smiled the sweetest smile Needleman could remember. He felt proud, even smug. When he knew the girl was going to make it, he turned to her mother and calmly told her she had to move from her home.

"If Vanessa eats more paint," he said, "there's no question she'll be brain damaged."

Her mother shot Needleman an angry look and snapped, "Where can I go? Any house I can afford will be no different from the house I live in now."

Needleman's smugness vanished. "I realized," he said, "that it wasn't enough to make a diagnosis and prescribe medication. I'd treated her for lead poisoning, but that was not the disease—the disease was much bigger and

IN MEMORIAM

'40s

EDWARD I. FABRY JR.
MD '47
MAY 22, 2017

'50s

CLETUS G. PELKOFER
MD '50
JUNE 10, 2017

JERRY N. BOSNAK
MD '52
APRIL 20, 2017

PAUL M. HAVER
MD '52
JUNE 17, 2017

RICHARD R. RITTER
MD '58
JUNE 13, 2017

ROBERT H. WILKINS
MD '59
MARCH 31, 2017

'60s

DAVID DIXON PORTER
MD '61
APRIL 16, 2017

WILLIAM W. EVERSMAAN JR.
MD '63
JAN. 28, 2017

JOHN E. OTT
MD '63
APRIL 24, 2017

DAVID A. MCEWEN
MD '65
MAY 3, 2017

'70s

ALLEN M. GOORIN
MD '72
APRIL 14, 2017

EVERETT A. CANTRELL
MD '74
APRIL 13, 2017

LOIS B. SHANE
RES '76
JAN. 8, 2017

'00s

BRENO DA ROCHA LIMA
RES '09
MAY 24, 2017

FACULTY

LEONARD A. SEPT
MD '63
JUNE 6, 2017

BARRY C. LEMBERSKY
RES '84
APRIL 13, 2017

caused by forces embedded in the child's life. Her disease was where she lived and why she was allowed to live there."

In those days, the Centers for Disease Control and Prevention had determined that children with 60 micrograms of lead or more per 100 milliliters of blood met the definition of having been lead poisoned. Back then, 20 percent of inner-city children had blood lead levels of 40 to 50 micrograms per 100 milliliters, and that was considered normal. This made no sense to Needleman. *Listen*, he said, *if we know for a fact that high-dose lead poisoning causes obvious problems—like coma, intellectual disability, and death—why should we assume that lower levels cause no injury to a child's brain?* He asked this question repeatedly for about five decades. Almost every time he did, he designed a study to examine it from a new angle.

Today, the CDC advises that "no safe blood lead level in children has been identified. Even low levels of lead in blood have been shown to affect IQ, ability to pay attention, and academic achievement. And effects of lead exposure cannot be corrected."

Needleman's life's work demonstrated that environmental lead exposure—even at low doses—is linked to cognitive deficits and behavior issues. The pediatrician and emeritus professor of psychiatry at the University of Pittsburgh died July 18 in Pittsburgh at the age of 89.

He joined Pitt in 1981 after leaving Harvard University. Two years earlier, in 1979, he'd published a landmark study in the *New England Journal of Medicine* showing that Boston-area children with higher accumulations of lead also had, on average, five or six fewer IQ points than those with lower lead accumulations who were of the same neighborhood, ethnic background, and economic status.

"That study really changed the whole way the world thinks about lead poisoning," Philip Landrigan of Mount Sinai, a long-time lead researcher who worked alongside Needleman, told *Pitt Med* in 2001.

"He really made the world consider the possibility that subclinical exposure to environmental pollutants could have a serious societal impact," said David Bellinger of Harvard. Bellinger and Needleman were also collaborators.

In 1996, Needleman conducted the first in-depth study on lead and delinquency. He measured bone lead levels in children and

collected reports of aggression and delinquent behavior from the subjects, their parents, and their teachers. The results of this study showed an association between lead and delinquency.

The lead industry and experts it paid questioned his work. Yet he continued to fight for the health of children. (His determination did not surprise people who knew him well. He was jailed in 1967, with pediatrician Benjamin Spock, for protesting the Vietnam War.)

For 40 years, through governmental committees, editorials, and other means, Needleman helped make the case against leaded gasoline. Needleman also pushed for lead to be removed from paint and for remediation of houses where lead paint was used.

"The thing about lead toxicity is it's completely preventable," he said.

—Compiled from Rebecca Skloot's 2001 *Pitt Med* feature "Houses of Butterflies" and *Pitt's* obituary.

JULIUS YOUNGNER

OCT. 24, 1920–APRIL 27, 2017

Julius Youngner perched on the edge of his chair, his back to a window overlooking the rainy streets of Pittsburgh. He pounded his fists on his desk and expounded on the importance of fighting infectious diseases. "I feel very passionate about this," he told a reporter. "You want to know why passionate? I'll tell you why passionate. You ever heard of influenza pandemics? 1918? Killed about 30 million? Or Asia? Hong Kong? That's why passionate."

Youngner was being interviewed for a Summer 2000 *Pitt Med* article about his work that led to type A and equine influenza vaccines and yielded more than 15 patents. Although the world-renowned virologist was impassioned about stopping pandemics, he was also soft-spoken about his own contri-

butions to doing so. When asked about his invention of trypsinization, a technique for culturing animal cells on a large scale—which made the killed-virus polio vaccine possible and ultimately changed the face of tissue culture investigation—he responded with characteristic humility: "Well, it was just a technical advance."

Youngner, Pitt's Distinguished Service Professor Emeritus of Microbiology and Molecular Genetics, died in April at age 96. During his 60-year career, he witnessed the birth and growth of the field of virology and always seemed to be on the edge or in the middle of the "next big thing."

After earning his doctorate in microbiology from the University of Michigan in 1944, Youngner was drafted into the army and selected to work on the Manhattan Project studying the effects of uranium salts on human tissue. He then worked at the National Cancer Institute until 1949, when he was recruited to Pitt to join Jonas Salk in the quest for an effective polio vaccine.

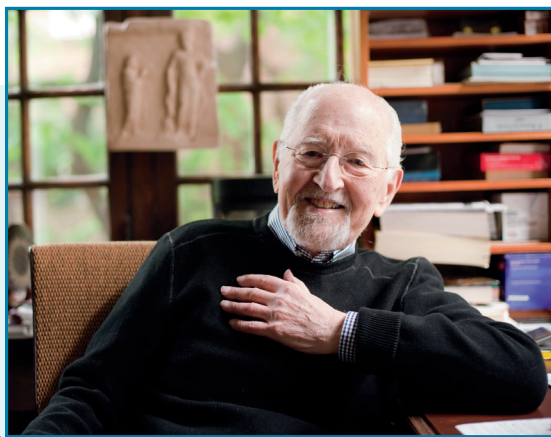
Youngner not only developed trypsinization for producing polio on a large scale; he also figured out how to inactivate the virus for the vaccine that was deemed a success in 1955.

The virologist went on to chair Pitt's microbiology department from 1966–1989. He became the first to demonstrate that non-viral agents could trigger interferon induction, which led to the idea that interferon could have important functions beyond its use as an antiviral. Interferon is now used in a variety of cancer therapies. His work on persistent viral infections made vaccines for type A and equine influenza possible.

Countless lives have been saved by Youngner's work.

—Adapted by Cara Masset from Rebecca Skloot's Summer 2000 *Pitt Med* feature, "To Stop Death in Its Tracks."

JOSHUA FRANZOS



ABOVE: Youngner. RIGHT: (Shown from left) Jonathan, Suzanne, and Matthew Youngner with the medical school's portrait of their grandfather.



HE GOT THE LEAD OUT

In the early '70s, 200,000 tons of lead were blowing out of the exhausts of American cars each year and poisoning our children. Then in 1976, the EPA began the decades-long phasing down, then complete phasing out, of leaded gasoline from the nation's roadways. That single act, which the research and advocacy of the University of Pittsburgh's Herbert Needleman helped make possible, did more than anything else to taper blood levels of the toxin in children. (See our obituary on the famed Pitt pediatrician and emeritus professor of psychiatry on p. 38.)

"Dr. Needleman was a key figure in persuading the Environmental Protection Agency to take lead out of gasoline," Mount Sinai's Philip Landrigan told this magazine in 2001.

There's more work to do, as disconcerting lead levels detected in water in some homes in Flint, Mich., Pittsburgh, and elsewhere, demonstrate. And lead in soil, dust, and paint chips is an even graver concern, says emeritus dean of Pitt's Graduate School of Public Health Bernard Goldstein. Needleman also sounded the alarm about lead-based paint hazards.

Goldstein warns of a poison of another sort, recalling a speech President Obama made in Flint. The president cautioned against stigmatizing children who've been exposed to lead. "If you are my age, or older, or maybe even a little bit younger," Obama said, "you got some lead in your system when you were growing up."

Children's lead levels today are typically about a fifth of what they were in Obama's youth, thanks to Needleman. —*Elaine Vitone*

CALENDAR

FOR ALUMNI & FRIENDS

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

MEDICAL ALUMNI WEEKEND

SEPTEMBER 15–16

Reunion Classes:

1957, 1962, 1967,
1972, 1977, 1982,
1987, 1992, 1997,
2002, 2007, 2012

HEALTH SCIENCES ALUMNI & FRIENDS RECEPTION

OCTOBER 4

San Francisco, Calif.

OCTOBER 5

Los Angeles, Calif.

For information:

Rachel Edman at 412-647-4241 or

rge6@pitt.edu

CLASS OF 1959

SCHOLARSHIP LUNCHEON

OCTOBER 13, 11 A.M.

Scaife Hall, Room 1104

HOMECOMING TAILGATE

OCTOBER 14 (THREE HOURS BEFORE KICKOFF)

Heinz Field, Red Lot 5A

SCIENCE 2017

OCTOBER 18–20

Alumni Hall and

Wyndham Pittsburgh University Center

For information: science2017.pitt.edu

PITT MED ALUMNI & FRIENDS RECEPTION

NOVEMBER 4, 6:30–8 P.M.

Boston, Mass.

Marriott Copley Place,

Berkeley Room

GETTY IMAGES



FOR REAL! TWEEN SCIENCE

Jeepers creepers, what color are your peepers?

It depends on the amount and pattern of melanin, or pigment, in the iris—the colorful ring around the black circle in the middle, your pupil. The iris's expanding and contracting are what control the amount of light that enters your eyes. The iris has two layers, and melanin is found in both, but it's the pigment in the front layer that determines your eye color.

The amount of melanin produced in the iris is determined by a person's DNA. Brown eyes have the most melanin, green not as much, and blue even less. Brown eyes are likely to run in your family if your ancestors came from a part of the world that receives the most sunlight, because melanin provides protection from the sun. If you have blue eyes, maybe your great-great-great-grandparents didn't need as much sun protection.

Some babies are born with dark-blue or slate-gray eyes. Then, at birth, the iris begins producing melanin, and eye color matures. The biggest changes occur between 6 and 9 months of age, but sometimes, eye color doesn't become permanent until age 3!

Sometimes, and this is very rare, the iris appears violet or red. What you're seeing is not a violet or red iris but the blood vessels behind it. This happens when there's little or no pigment.

Have you ever spied someone whose eyes were two different colors? That's yet another rarity. And there are even people whose eyes just *look* like they're two different colors, because one pupil is much larger than the other (usually because of injury). Apparently, color is more than meets the eye. —*Elaine Vitone and Kylie Wolfe*

Is there a topic you'd like For Real! to explore? Are you a teacher who would like to use Pitt Med in the classroom? Drop us a line: medmag@pitt.edu

THINK YOU KNOW US? THINK AGAIN.

1. *The Wall Street Journal*: Pitt is the #1 public university in the Northeast and 13th in the nation
2. QS World University Rankings: Best philosophy program in the world
3. Pitt's research expenditures top \$700 million annually
4. Top 10 nationally in NIH research support
5. Top 5 among U.S. public universities for 2016 Fulbright Scholars
6. 12 countries, 4 continents: Our medical and health sciences faculty serve the world
7. *Kiplinger's Personal Finance*: Pitt is one of America's best-value public colleges and the best value in Pennsylvania for the 12th consecutive year
8. *U.S. News & World Report*: Pitt is among the top 50 global universities
9. Among our alumni are Nobel Laureates, Pulitzer Prize winners, and recipients of MacArthur Fellowships, National Book Awards, the National Medal of Science, and many other distinguished awards
10. Our Cathedral of Learning is the tallest educational structure in the nation

PITT

