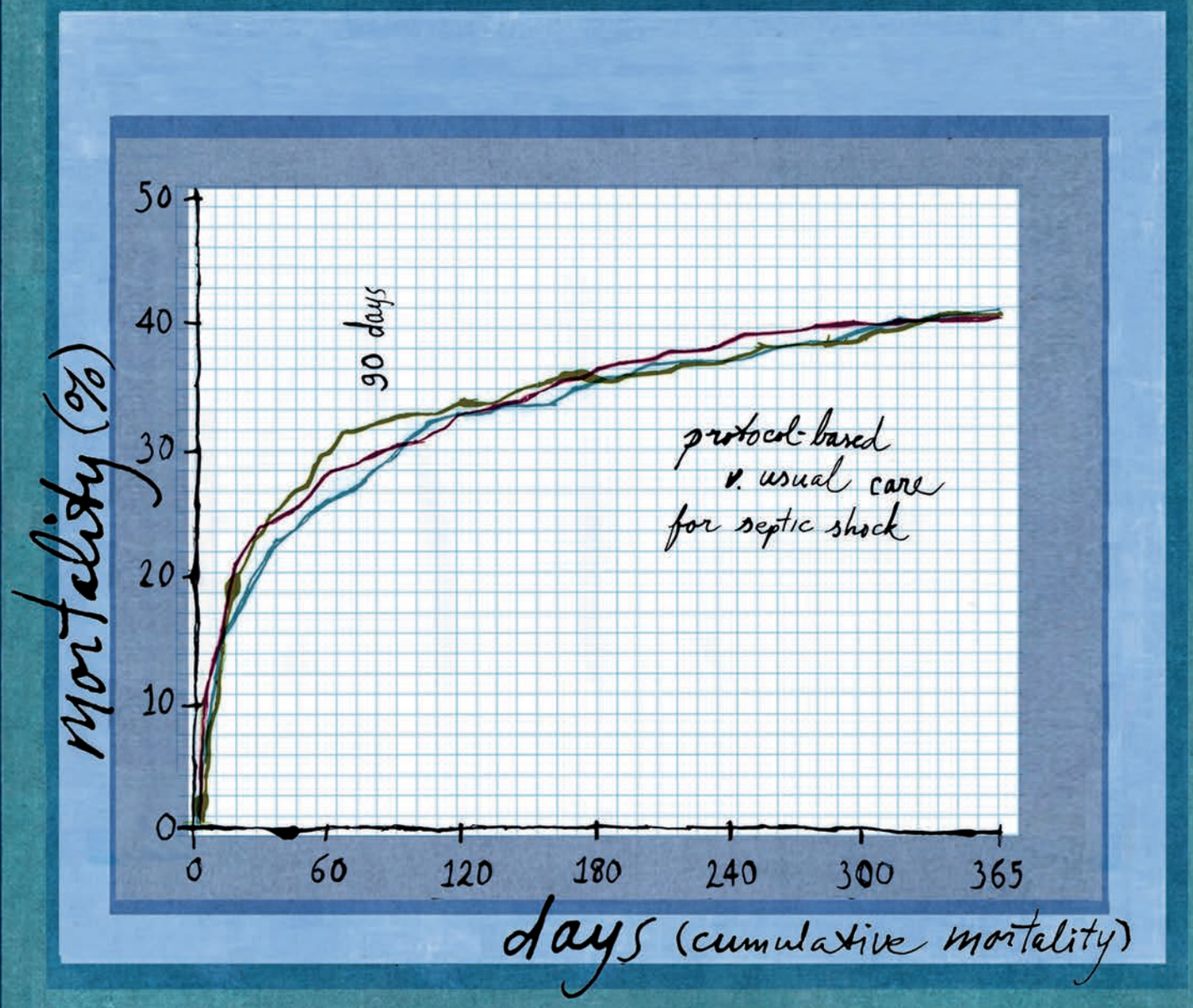
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2014

PITTMED



BIG IS BEAUTIFUL

WHEN LARGE TRIALS YIELD
UNEXPECTED RESULTS

GETTING PERSONAL-IZED

I enjoyed the summer e-version of *Pitt Med*, especially the @PittMedMag archive posting about Albert Ferguson, as I played "Ferg" sweeping up the OR in the movie our class made for Scope and Scalpel in 1981. I saw that your cover story for this issue was on personalized medicine ["Tailor Made"], and (though I trained in radiology) I actually practice the original version of personalized medicine, acupuncture, which was developed in China thousands of years ago.

An interesting follow-up article would be how the computerized version that Michael Fitzgerald depicted in his article can be integrated with a holistic approach to facilitate optimal healing. I spoke to Pitt med students this September about this.

Larry Burk (MD '81, Res '85)
Durham, N.C.

The writer is the cofounder of Duke Integrative Medicine. He can now be found at Healing Imager, PC, and www.larryburkmd.com.

EDUCATION IS THE BEST MEDICINE

Just a note in response to the Summer 2014 issue's "Overheard: Sticker Shock" discussion with Elisabeth Rosenthal on the cost of care.

The cost of medicine in the United States is one-fifth of our budget and soon will be one-fourth. This is about two to three times that of other industrial nations, and all of their systems are moaning of increased costs.

The best way to cut costs is to expand our preventive medicine efforts.

Education is the best preventive medicine. My advocacy is to put health education in our K through 12 curricula. However, it needs to be aggressive, progressive, and all-inclusive. The concept will work!

A tribute to medical doctors: A large poll was taken to see how many of us would participate in such an effort; the results—90 percent!

Robert McPeake (MD '57)
Indian Wells, Calif.

CORRESPONDENCE

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

Pitt Med
400 Craig Hall
University of Pittsburgh
Pittsburgh, PA 15260
Phone: 412-624-4152
Fax: 412-624-1021
E-mail: medmag@pitt.edu
pittmed.health.pitt.edu

For address corrections, or to change your print/online subscription preferences:

Pitt Med Address Correction
ATTN: Andre Burton
M-200K Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
Phone: 412-648-9090
E-mail: medalum@medschool.pitt.edu

PITTMED

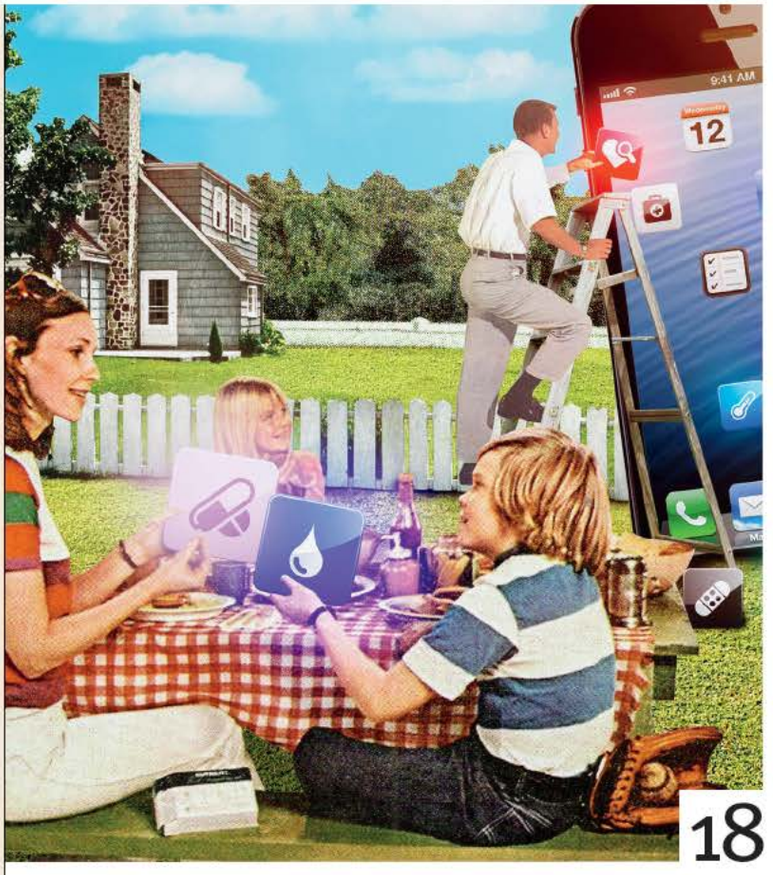
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2014
VOL. 16, ISSUE 3


7

DEPARTMENTS


33

40 1/2



18

FEATURES

CONTRIBUTORS

TIM GROEN [Cover] splits his time between the Netherlands and New York City. For our cover—a handmade graph—Groen drew the lines with a pen dipped in ink to reproduce the original provided from the investigator. The watery, subdued hues were inspired by Josef Albers, the influential German artist and educator. More often, Groen (pronounced *grow-en*) produces psychedelic, retro images, often collaged together from old issues of *Mademoiselle* and *Good Housekeeping*. "Sometimes I can't help myself," he says, "and I just buy like a year's worth of old magazines that obviously nobody else wants." Groen loves that manual work of cutting and gluing but finds digitization exciting, too. "You can crank out all these variations and experiment with color." His upcoming projects are an interview for *Frame* magazine—he writes, too—and a gallery exhibition of his work ("all manual!" he says) in New York City, opening in 2015.

ELIZABETH ANNE MAY ["A Doctor with 'High Touch'"] studied journalism at Ohio University and then spent years as a staff writer and editor for institutions like the University of Pittsburgh (contributing to *Pitt Magazine* and other publications) and as a freelance writer. Her food and lifestyle features have appeared in newspapers throughout the country. She has been blogging about faith and her family and selling inspirational photos for about two years now at seasonswithsoul.com. May grew up on a berry farm in Ohio—which is also a good place to get pumpkins, apparently. Her girls sold a bunch this fall out of their home in Peters Township, Pa. Half of their proceeds went to the Cure JM Foundation. (In case you want to catch the sale next year: large pumpkins $5, medium pumpkins $3, Indian corn bunches $2.)

COVER

The results of a large, multicenter trial on sepsis care have intensivists rethinking what's important. Large trials often have this power. This ink-penned graph by Tim Groen was reproduced from one provided by Pitt's Derek Angus, the lead author on the sepsis study.

PITTMED

PUBLISHER
Arthur S. Levine, MD

EDITOR IN CHIEF
Erica Lloyd

ART DIRECTOR
Elena Gialamas Cerri

SENIOR EDITOR
Elaine Vitone

ASSOCIATE EDITOR
Robyn K. Coggins

CONTRIBUTING EDITOR
Chuck Staresinic

INTERN
Nick Moffitt

PRODUCTION MANAGER
Chuck Dinsmore

CIRCULATION MANAGER
Andre Burton

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

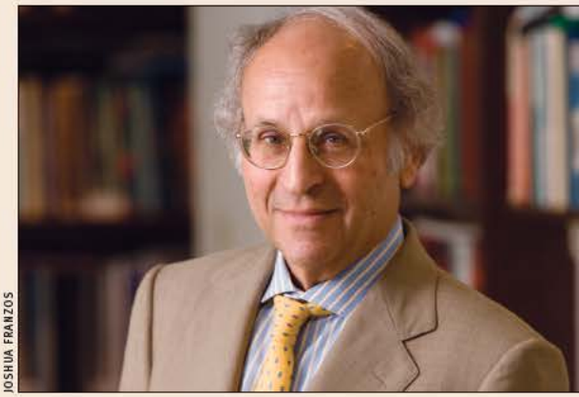
EDITORIAL ADVISORS
Jeremy Berg, PhD
Michelle Broido, PhD
Nancy Davidson, MD
Paula Davis, MA
Joan Harvey, MD
David Kupfer, MD
Joan Lakoski, PhD
David Lewis, MD
Margaret C. McDonald, PhD, MFA
David Perlmutter, MD
Maulin Shah, Class of '17
Steven Shapiro, MD
Peter Strick, PhD
Bennett Van Houten, PhD
Simon Watkins, PhD
Marshall Webster, MD, Res '70

UNIVERSITY COMMUNICATIONS
Kenneth Service
Cindy Gill

University of Pittsburgh

Pitt Med is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with University Communications. It is produced quarterly for alumni, students, staff, faculty, and friends of the School of Medicine. PR 6729

When I returned from
so many journeys,
I stayed suspended and green
between sun and geography -
I saw how wings worked,
how perfumes are transmitted
by feathery telegraph,
and from above I saw the path,
the springs and the roof tiles,
the fishermen at their trades,
the trousers of the foam;
I saw it all from my green sky.
—Pablo Neruda, "Bird"


JOSHUA FRANZOS

As Pablo Neruda's bird does, this is a time for us to suspend the moment, view our landscape, and observe the particular.

An April 2014 *PNAS* article by several of today's leading scientists—Bruce Alberts, Harold Varmus, Shirley Tilghman, and Marc Kirschner—urges a new approach to federal funding for biomedical science. Our funding system is infirm and the prognosis is certainly not good if our government fails us. The situation is becoming even more difficult as academic medical centers deal with dwindling clinical revenues—the major source of our leverage as we partner with federal support, i.e., the National Institutes of Health.

Only 17 percent of NIH research grants were funded in 2013, down from 32 percent a decade ago. Even established investigators with top-ranked proposals have been denied funding. The situation is even worse for young scientists. In response, researchers are mainly submitting conservative grant proposals with short-term goals (in this "golden age" of science, as Alberts notes!).

Alberts el al. offer a possible antidote quite similar to one I suggested in the late '80s, also a time of declining NIH support, though mild compared to now: Our nation should focus on supporting not our most promising projects, but rather our most promising and accomplished scientists—the person, not the project.

This would give investigators time to think and imagine, rather than chase after grants, as well as the chance to take risks in the lab.

Both the Howard Hughes Medical Institute Investigator and MacArthur Fellows programs recognize the value in investing in people. Hughes requires that its investigators have a demonstrated track record of pushing their field very substantially forward. That criterion has worked well for evaluating midcareer and senior scientists. It is stickier to determine who among our junior scholars are capable of cutting-edge work. But it can be done. Here I repeat some of the observations that I made 24 years ago (*The New Biologist* 2, 207, 1990).

There are various stripes of intelligence, of course; great science is often done by people who have more than mathematical/logical intelligence. If you want to determine the course of a trafficked organelle, for example, aesthetic and spatial abilities would help. Likewise, interpersonal intelligence, to articulate ideas and collaborate with colleagues, seems essential.

We want investigators who can absorb the fount of knowledge they've inherited while also being capable of openness, independence, and boldness, even in the face of attack. And there's no substitute for diligence. Breakthroughs require both sudden inspiration and a chronology of hard and meticulous work.

Then there are the more subtle facets of the creative mind. Thomas Kuhn spoke of seeking out those who can think both convergently and divergently at once, and who are free of angst in doing so.

Like other geniuses, the poet Neruda sees similarities among the disparate, or as Samuel Johnson wrote, "The yoking together, by violence, of unlike things." Consider how Neruda ends "Bird": *I had no more alphabet/than the swallows in their courses/the tiny, shining water/of the small bird on fire/which dances out of the pollen.*

We must invest in great human potential, in the promise of shimmering pollen, in those small birds on fire.

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

Devoted to noteworthy happenings at the medical school

NEW "FLU" REVIEW

Recent findings from two teams at Pitt may bring new treatment options for patients with alpha-1 antitrypsin deficiency (ATD), a genetic disorder that afflicts the lungs and liver. In ATD, a protein called ATZ amasses in liver cells, causing inflammation, cirrhosis, and sometimes cancer.

David H. Perlmutter (MD chair of pediatrics, the Vira I. Heinz Professor and Distinguished Professor of Pediatrics, as well as a professor of cell biology) and collaborators discovered that fluphenazine, an antipsychotic typically used for patients with schizophrenia, reduces buildup of ATZ in mammalian cell line models and a mouse model.

Furthermore, Stephen Pak, PhD assistant professor of pediatrics, and Gary Silverman, MD/PhD Twenty-Five Club Professor of Pediatrics, Cell Biology, and Physiology, in studies of the primitive worm *C. elegans* found similar results after screening a variety of potential treatments with the worm. Fluphenazine, or "flu," encouraged breakdown of ATZ through autophagy (the cell's degradation, recycling, and general cleanup process), whereas other protein-busting drugs were less effective. Their discovery suggests that autophagy is a good target for further treatment.

A previous Perlmutter study revealed similar tidying properties in another unusual source—an antiseizure and mood stabilizing drug called carbamazepine. Autophagy factors into at least two more rare liver diseases; so a breakthrough for ATD patients could mean help for others, too.

The best part? These drugs are already approved for use in humans. That means clinical trials should start soon.

—Robyn K. Coggins

KATHERINE LEWINSKI/GETTY

Sprout It Out

Eat, or drink, your broccoli. Here's why.

For decades, Pitt's Thomas Kensler and colleagues from Johns Hopkins University had been working in rural China to try to stem the high levels of liver cancers linked to aflatoxin, a fungal-derived carcinogen found in many dietary staples there. They'd devised a broccoli-sprout tea that showed promise as an antidote. Then farming practices changed, people became wealthier, and, happily, the incidence of exposure to aflatoxin abated. However, air and water quality in the area had diminished considerably. So Kensler's team decided that they would see if those potent sprouts could help locals fight off air- and waterborne carcinogens.

The sprouts seemed to be highly effective. A study of 291 people in a rural area 50 miles north of Shanghai demonstrated that drinking a fruit juice enriched with custom-made, broccoli-sprout powder enhanced the excretion of benzene, which is carcinogenic. (Kensler, PhD professor of pharmacology and chemical biology and of environmental and occupational health, notes that eating sprouts would probably work too, but the team couldn't guarantee fresh supplies throughout the 12-week study.) What makes broccoli sprouts so good at flushing out noxious stuff? A compound found in broccoli called sulforaphane elevates enzymes in our tissue to get rid of carcinogens before they have a chance to disrupt the DNA-repair process. In animal models, Kensler has shown that the compound is effective when animals are first exposed to benzene—kicking it out of "barrier" cells in the linings of the airways, gastrointestinal tract, and liver—but not once the toxin settles into fat deposits.

The team is now planning a trial to see whether ingesting broccoli-sprout-enriched juice actually lowers cancer incidence in humans. *—Erica Lloyd*

CAMI MESA

Overheard

Med Honcho

You can call her "vice dean"—**Ann Thompson**, an MD, assumed the "day-to-day dean" role at the School of Medicine this October, as Steven Kanter left to assume a deanship in Missouri. As such, she'll oversee associate deans, work with the curriculum committee on teaching strategies, and ensure the medical school stays top-notch; in other words, she'll keep Pitt med's educators and students, in her words, "magnificent."

Thompson, professor of critical care medicine and pediatrics, previously served the med school as associate dean for faculty affairs. (She earned an "Ask Ann" following in that role for her effectiveness in helping junior faculty navigate challenging career paths.) She has also been chief of pediatric critical care and director of the pediatric intensive care unit at Children's Hospital of Pittsburgh of UPMC.

How has your previous work prepared you for this new gig?

One of the good things about coming out of intensive care into this role is that the ICU is kind of a microenvironment of all the health care professionals that are crucial in the care of patients. . . . I have an appreciation for the contributions of everybody else on the team, and I think that'll help draw in people from the other schools of the health sciences to find ways for students to do at least some of their learning together.

What's important to you as vice dean?

Encouraging [teachers] to be innovative, letting them take the lead, and then finding the best ways I can to support them.

We've been working really hard to improve our recruiting practices. We've interviewed nearly every member of the faculty who identifies him/herself as an underrepresented minority faculty member to find out what would make them more comfortable here, what they think would help us attract others. I remember, as one of 12 women in a class of 120, it was kind of lonely.

What would you say to med students about becoming a doctor right now?

Being a doctor is one of the best jobs in the world. It's this incredible mix of complex, rapidly evolving science and medical knowledge [with] a really rich interaction with society as a whole and the opportunity to impact individual people's lives in a way that very few other people [have a chance to do].

I would want to know whether a student gets excited about that science and that place in the larger society and still is really interested in being someone's physician. Do they really want to care for people? That's me as a clinician. Those are the things that have been important to me, and I want people to show me that those things are important to them. *—Interview by Robyn K. Coggins*

Name Dropping

Jeffrey Gordon, an MD, is this year's Dickson Prize in Medicine recipient. Gordon delivered the Dickson Lecture during Pitt's annual science festival, Science 2014—Sustain It!, which ran October 1 through 3.

Gordon's research has focused on the role of the gut microbiota in nutritional status. Through this lens he studies childhood undernutrition in low-income countries and obesity in adults living in Westernized societies. He has shown that children suffering from defects in the program of assembly of their gut microbiota have microbial communities that appear less mature than those of healthy children of the same age. This immaturity is not corrected with existing therapeutic food interventions. New types of therapeutic food interventions, at earlier time points, could help, he says. So might seeding intestinal ecosystems with collections from naturally occurring human gut microbes. Yet, Gordon says, "It's important that we educate one another about the potential benefits but also the need for caution when we start to manipulate our microbial communities." Gordon is the director of the Center for Genome Sciences and Systems Biology at Washington University in St. Louis.

The science festival also brought these speakers to Pitt. (A heck of a lineup.)

Jonathan Rothberg, a PhD and chair of the board of the high-tech startup 4Combinator, delivered the Provost Lecture. Rothberg is known for developing cheaper, high-speed DNA sequencing as founder of 454 Life Sciences, a biotech company that spearheaded the Neanderthal Genome Project and was the first to sequence an individual human genome.

This year's Mellon Lecturer was **Stuart Orkin**, an MD, Harvard's David G. Nathan Professor of Pediatrics, and a Howard Hughes Medical Institute investigator. Orkin's work has significantly advanced genetic research of blood diseases. Notable discoveries include identifying key genetic blood mutations and fetal-to-adult hemoglobin switch regulators.

Jeannie Lee, an MD/PhD, Howard Hughes Medical Institute investigator, and Harvard professor of genetics (and pathology), presented the Klaus Hofmann Lecture. Lee's work has advanced understanding of epigenetic regulation by long, noncoding RNA as well as the molecular mechanisms of X chromosome inactivation. *—Emily DeMarco*

It's a Wrap

This May, the Clinical and Translational Science Institute sponsored the Pitt Innovation Challenge (PInCh), a competition that asks "creative minds to tackle difficult health issues." One of the victors was the team that created Sealion—a time-released, biodegradable polymer applied to bandages that protects growth-factor activity and promotes healing.

"This technology may be a major advantage in wound care because of its ease of use by the patient and potential to provide better outcomes," says J. Peter Rubin, MD chair of the Department of Plastic Surgery, who consulted with the Sealion team.

Bioengineering grad students Noah Johnson, Chelsea Stowell, and Mirrah Almira, along with bioengineering PhD alum Eric Jeffries, won a $100,000 prize to propel their invention to the market—and the clinic.

Bioengineering, chemical engineering, and surgery prof Yadong Wang, a PhD, introduced them to the healing polymer that set the team searching. "We started looking into what's the most pressing issue in the wound-healing field and [determined that was] diabetic ulcers," says Johnson.

About 25 million Americans have diabetes and nearly 15 percent have an open sore from the disease. Uncontrolled infections in diabetic ulcers can lead to amputation or even death.

But what do sea lions have to do with it? "The technology uses ionic interaction between the polymer and growth factors so I was thinking *ion*, and it also *seals* the wound," says Jeffries. Hence, Sealion (and a cute logo). —*RKC*

For more PInCh innovations, see p. 20.

CATHERINE LAZURE

CANCER INHIBITOR PROBED

Shannon Puhalla, an MD assistant professor of medicine at Pitt, has seen some of her patients throughout her entire seven years here. "They tend to be very proactive, very involved in their care," she says. Many of them have the 5–10 percent of breast cancers with BRCA1 and BRCA2 mutations; those cancers are notoriously stubborn to treat. Her recent work, with support from the National Cancer Institute, examines a drug called veliparib, a PARP inhibitor that kills tumor cells by interfering with DNA-strand damage repair.

Puhalla's team found a 40 percent response rate for veliparib as a single treatment. Her trials tested proper dosing for the drug in 88 patients and analyzed tissue biopsies in 25 of them, both pre- and post-treatment, to see how tumors responded.

"A 40 percent response rate is pretty good, but that still means that 60 percent of people didn't respond. The question is, why is that and do we need to design better studies for those patients? What are the mechanisms? Is that something we can target? That's the challenge."

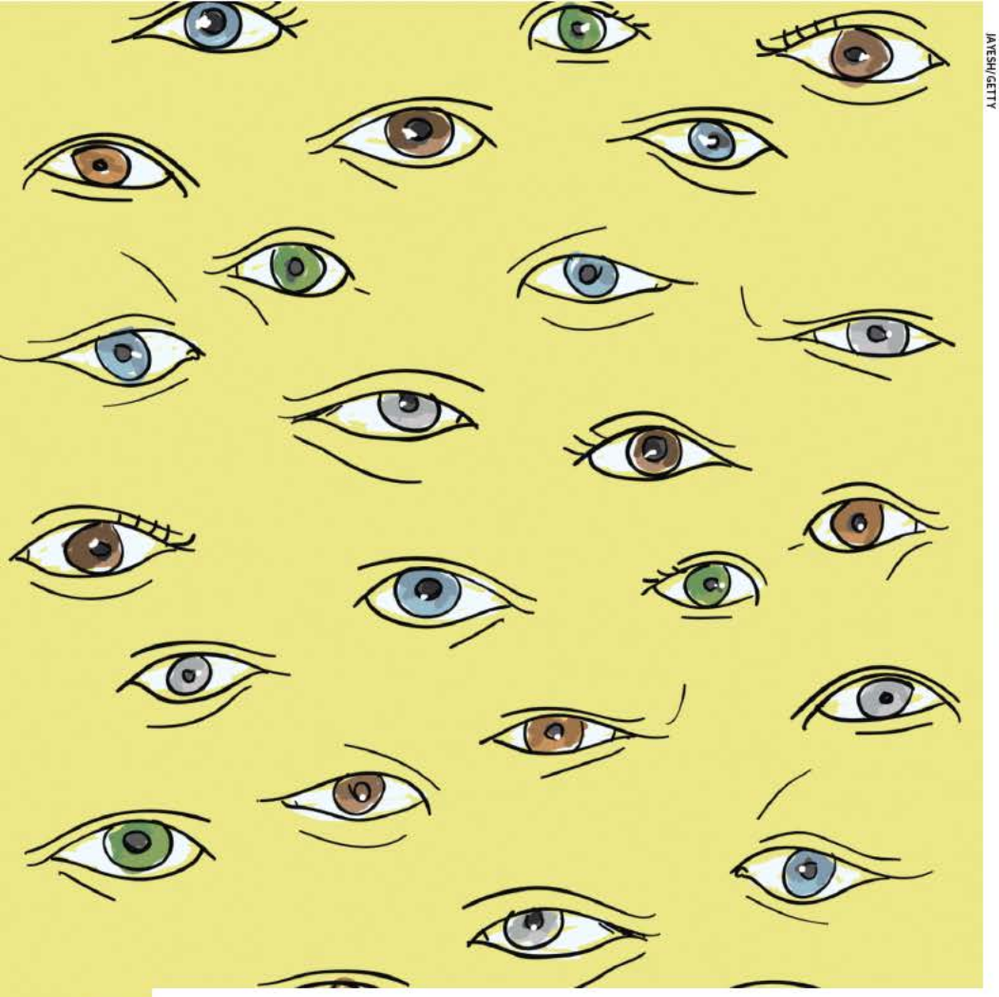
Phase 2 studies will examine whether blasting tumors with chemotherapy to damage their DNA, then using veliparib, will deliver a one-two punch to breast and ovarian cancers. She's also leading a PARP inhibitor study in patients with early stage cancer who have already had surgery or chemotherapy. They will receive olaparib, a PARP inhibitor similar to veliparib, as a preventive measure. Puhalla hopes studies with larger sample sizes will lead to commercialization of the drugs. —*RKC*

FLASHBACK

November 14 marks the 125th anniversary of the departure of Pittsburgh-born journalist Nellie Bly (who was born Elizabeth Jane Cochran) on her 72-day recapitulation of the journey in Jules Verne's *Around the World in 80 Days*.

APIC/HULTON ARCHIVE

Bly's most notable exploit, however, was her *New York World* exposé of conditions at the Women's Lunatic Asylum on New York City's Blackwell Island. Feigning mental illness, the reporter encountered inhumane treatment of patients who were sometimes as sane as she was. Her account caused such an outcry that the city swiftly enacted reforms.



JAYESH/GETTY

BROWN-EYED GIRLS SING THE BLUES

Inna Belfer, an MD/PhD, heard an intriguing story from her Pitt colleague, Jan Smith, MBChB clinical professor and clinician emeritus of anesthesiology. His brother, an oral surgeon in South Africa, noticed that dark-eyed women seemed to feel more pain during procedures. In those patients, "they expect some problems with anesthesia, analgesia," says Belfer, associate professor of anesthesiology and of human genetics.

Might observable traits be tied to pain tolerance? Belfer's recent work suggests this may be the case.

In her ongoing studies of healthy pregnant women at Magee-Womens Hospital of UPMC, Belfer had been issuing pain surveys, collecting psychosocial data, and performing quantitative sensitivity testing to see whether a woman's pain levels—particularly chronic pelvic and back pain—changed throughout and after pregnancy. Then she decided to keep track of eye color as well.

She divided her existing study into dark- and light-eyed groups—the former included brown and hazel, the latter, blue and green. Her results were in line with previous data and Smith's story: Dark-eyed women experienced more pain, as well as more depression and anxiety, and less improvement in those conditions overall. However, the light-eyed group experienced more sleep disturbance.

"We don't know yet, with all our pain-related studies, how exactly pain, mood, and sleep overlap," Belfer says. "What causes what? . . . The indication is that the relationship is complex."

Belfer hopes to test more diverse women in the future (this study was limited to White patients). Then her team will develop a patient questionnaire that includes a constellation of observable traits. It's personalized medicine light, she says, without the expense and time required for genetic sequencing.

Next, she'll test pain in post-mastectomy patients. "Addressing the question of why there is so much individual variability and differences within the same pain condition, within the same pathophysiology or etiology—this is one of the questions that I am so curious about." —*RKC*

Next Generation

Erica Nakajima, a fourth-year med student at the University of Pittsburgh, is one of four medical fellows the Howard Hughes Medical Institute nominated as Academy of Achievement delegates. She participated in the academy's International Achievement Summit this September, which pairs international leaders with young scholars.

Nakajima, part of Pitt's Physician Scientist Training Program, is also first author of a recent *PLOS ONE* publication on real-time quantification of tumor metabolism. She was mentored by Bennett Van Houten (the Richard M. Cyert Professor of Molecular Oncology and PhD professor of pharmacology and chemical biology) and Ashok Panigrahy (MD chief of pediatric radiology and associate professor of radiology).

Leah Manchester, a third-year Pitt med student, won the Society of Critical Care Medicine's 2014 Neurology Specialty Award. The honor recognized her abstract titled, "Correlation of Cerebral Blood Flow and Apparent Diffusion Coefficient in Pediatric Cardiac Arrest." Her work stemmed from a summer research project in Pitt's pediatric neurocritical care program under the mentorship of Ericka Fink, an MD associate professor of critical care medicine and pediatrics.

Fourth-year med student Shu Yang Lu received a Young Investigator Award at the Joint International Congress of the International Liver Transplantation Society, European Liver and Intestine Transplant Association, and Liver Intensive Care Group of Europe in June. He presented his accompanying article on rapid blood coagulation testing during liver transplantation. His faculty mentor on this project is Tetsuro Sakai, MD/PhD associate professor of anesthesiology. —*RKC*

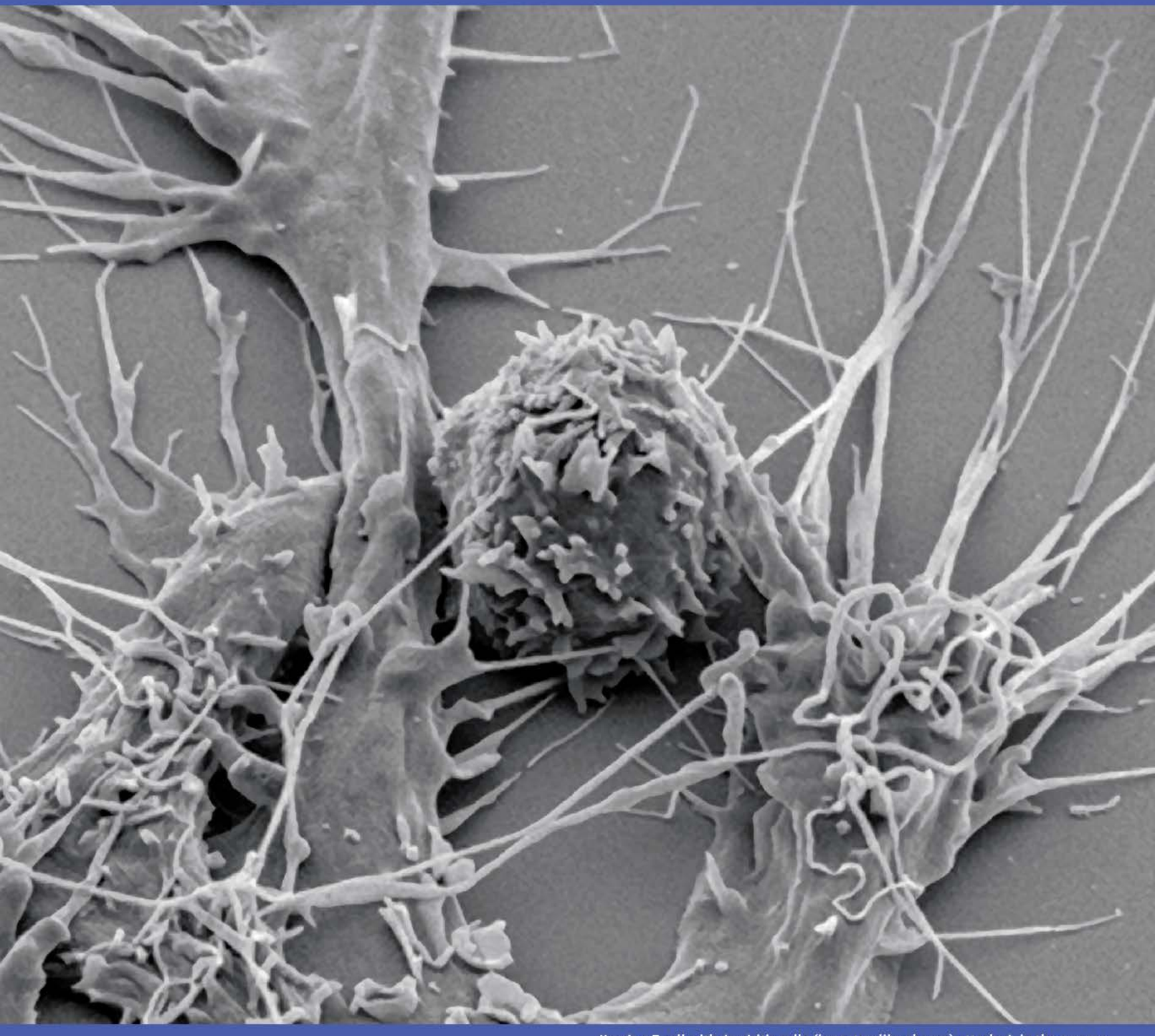
WHAT A WONDERFUL WORLD

Thirty-five years ago, as an obstetrics/gynecology resident, Carey Andrew-Jaja worked with an attending physician who loved to sing and occasionally serenaded newborn babies as he worked.

Andrew-Jaja, a Pitt clinical professor of obstetrics, gynecology, and reproductive sciences who is known for going about his own work with an infectious joy and an engaging smile, recalls what his singing colleague said when he retired: "He asked me, 'Andy, do you sing to your babies?' And I said, 'No, that's your stuff.' He said, 'Go ahead. Do it.' And so I took it over. He passed the baton to me. I started to sing to my babies ever since then, and I do it every single time."

Andrew-Jaja was just appointed president of the medical staff at Magee-Womens Hospital of UPMC. But he has been a memorable influence on Pitt medical students and residents for many years. And in summer 2014, he became a YouTube sensation when a video from the previous year went viral. In it, he croons "Happy Birthday" and "What a Wonderful World" to newborns at Magee. The video has been watched more than a million times and was covered by news outlets around the world. Scores of colleagues and patients' families responded with personal stories of their meaningful interactions with "the singing doctor," as he is known around the hospital.

Of the infants he welcomes into the world, in the video, Andrew-Jaja says, "They are special. Each of them is an individual, and I've delivered thousands and thousands of babies. When I'm singing to those babies, I think: *I'm singing to a future important person*. That's the credit I give to them." *—Chuck Staresinic* | *Video still, UPMC*



Here's a T cell with dendritic cells (long, treelike shapes) attached, in the process of transinfection. Pitt researchers are exploring what happens when dendritic cells have less cholesterol. They think that might protect against transinfection.

HIV'S HOV

THE SECRET SHORTCUT TO FAST AND FURIOUS INFECTION

BY HEATHER BOERNER

Somehow, about 1 in 300 people who contract HIV are able to live disease-free for decades without medication. In these nonprogressors, as they're called, the virus replicates so slowly that it never reaches the tipping point of full-blown AIDS infection. Researchers have puzzled over these rare cases for some 30 years, hoping to find some unique biological signature that might hold the key to a vaccine, to no avail—until now.

In the May issue of the journal *mBio*, a team led by the University of Pittsburgh's Charles Rinaldo—a PhD and chair of the Graduate School of Public Health's Department of Infectious Diseases and Microbiology, who also has an appointment in the Department of Pathology in the medical school—may have figured out at least part of the reason these people are able to keep the disease at bay.

Researchers have long suspected that HIV must be using some kind of shortcut to spread through the body so rapidly. Rinaldo found that this is indeed the case—and that nonprogressors naturally shut down that shortcut, called transinfection. They're able to do this because the white blood cells they use as sort of a canal system (dendritic cells, which have long extensions) don't have enough cholesterol to allow the virus to penetrate and spread. "Cholesterol forms lipid rafts," says Rinaldo. Those rafts ferry HIV, carried by dendritic cells, to helper T cells, which are then infected with the virus. Without the lipid, the raft breaks down, and HIV stays put, replicating steadily but slowly at the site of the infection.

For a scientist who has studied HIV since the early 1980s, the results were stark.

"Lab results aren't usually all or nothing," says Rinaldo. "But this one was. We didn't believe it. We repeated it many times."

They sat on the results for several years until they could figure out why the dendritic cells didn't transmit HIV and create the explosion of virus in T cells that progressors experience. The breakthrough came when a visiting professor shared the work he'd been doing on cholesterol and transinfection. Working with cells from uninfected people, he'd found that if you alter the cholesterol in the dendritic cells and then add HIV, transinfection stalls.

Then Rinaldo's team pulled blood samples from the nonprogressors—this time, testing the cholesterol levels in their cells. Though nonprogressors had normal levels of cholesterol in their T cells, their dendritic cells were deficient.

And if they added cholesterol to these deficient dendritic cells? Transinfection happened seamlessly, and the infection took the fast lane.

The samples came from men who were members of the longstanding Multicenter AIDS Cohort Study, or MACS, which Rinaldo started in the '80s. Most of the samples were of blood long ago infected with HIV. However, two of the eight nonprogressors they studied had first enrolled in MACS before contracting HIV. Tests on the stored blood cells of those men from before they were infected showed dendritic cells with the same inability to transinfect T cells. "This was the key finding in the whole study," Rinaldo says. "This is very likely a genetic trait. Our study was the first to show in a natural infection of HIV in humans that transinfection is significant."

The next steps: Find the biomarker for low-cholesterol dendritic cells and recruit healthy people with the mutation for studies on how cholesterol and transinfection function both in HIV and in other diseases.

"We have to be careful about being overly confident—this virus never ceases to surprise me," Rinaldo says. "But these people's bodies are trying to tell us something. We have to listen." ■

COURTESY CHARLES RINALDO LAB

INSIDE TRACT

One way to head off HIV's downhill slide toward AIDS may start in the gut. That's what research funded by the National Institutes of Health and published in the June issue of *The Journal of Clinical Investigation* revealed.

"You see, HIV ravages the gut, causing a vicious cycle of inflammation, kicking up gut microbiota and sending it out into the rest of the body through damaged intestinal linings," explains Pitt's Ivona Pandrea, MD/PhD professor of pathology. "All this fuels HIV replication in the T cells, hastening the slide toward AIDS; it can also cause increased blood clotting, which leads to HIV comorbidities like heart disease.

"But if we can keep the microbiota where it belongs in the gut and calm the inflammatory response, maybe we can slow the progression of HIV and reduce the incidence of heart disease," she says. Pandrea did this with pigtailed macaques. Using sevelamer (a drug used in people with chronic kidney disease) to bind microbial lipopolysaccharide (a key component of the microbial wall) and prevent microbes from escaping the gut in a process called microbial translocation, Pandrea and her team found that they could reduce inflammation, decrease replication of the virus, and reduce coagulation levels.

"It's not a miraculous treatment for HIV," she says. "But we've directly proven the relationship between microbial translocation and immune activation. From a pathogenesis point of view, it is important." *—HB*

BERT HARDY ADVERTISING ARCHIVE/GETTY

GINS OF THE FATHERS

ALCOHOL AND THE NEXT GENERATION

BY ALLA KATSNELSON

COURTESY JENNIFER BOMBERGER LAB

It's something pediatricians are taught to discuss with their young patients: Alcoholism runs in families, they counsel, so if yours has a strong history of this condition, you should be especially careful about drinking. But researchers' efforts to pin down specific genes that contribute to this heritability have largely come up short. "Nobody has found a smoking gun that says, *This is a gene that causes alcoholism*," says Gregg Homanics, a professor of anesthesiology at the University of Pittsburgh (with a PhD in animal science). He and Andrey Finegersh, an MD/PhD student in his lab, decided to try a slightly different tack. "We thought that maybe in alcoholics, drinking a lot would cause some changes in what controls the genes—and that is what gets passed down to the next generation," says Homanics. The findings from the resulting study were published in *PLOS ONE* in June.

The idea that parents' life experiences can have effects on their children's biology is not new. For example, studies show that famine in one generation tends to increase the rates of obesity and diabetes in subsequent ones. These effects are not caused by changes in the genes themselves, scientists think, but in chemical markings at specific spots atop DNA that regulate how genes are expressed—or epigenetics.

With regard to alcoholism, a flurry of studies two decades ago reported behavioral differences in the offspring of animals exposed to alcohol. But researchers back then did not yet have a good understanding of epigenetics and could not explain what they found. Now, scientists studying alcoholism are coming back for a closer look. It has long been known that addiction can influence how genes are expressed, and because addiction takes years to develop, heavy drinkers may be especially susceptible to racking up such modifications.

Homanics and Finegersh speculated that exposing mice to alcohol would make their offspring less sensitive to it and therefore more likely to imbibe, since that's what seems to be happening in humans. But to their surprise, they saw the opposite. They had male mice inhale alcohol vapor for five weeks, then bred the animals with females that had no exposure to the substance. The resulting pups grew up to be more sensitive to alcohol's effects on motor control and reduction of anxiety, not less, and were actually more likely to avoid it than were the control animals.

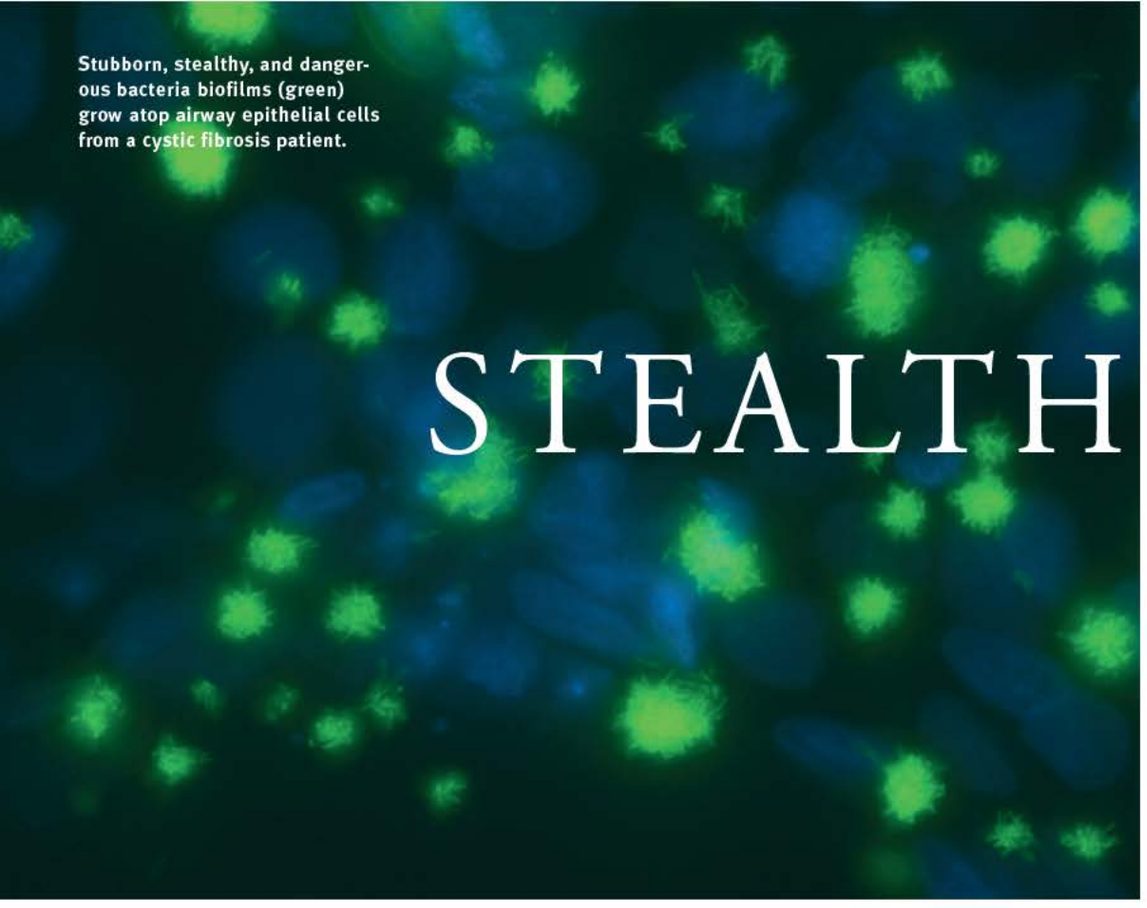
They also showed differences in epigenetic markings on a gene called BDNF, which has been associated with drug-taking behavior; that change took place in an area of the brain called the ventral tegmentum, which is thought to be involved in addiction. Strangely, though, only male offspring, not female, were affected.

The researchers don't yet have a good explanation for what they found, but Homanics notes that researchers at the University of Pennsylvania reported very similar results in a study of cocaine published last year. One potential explanation, he says, is that this inherited disinterest evolved as a protective mechanism. "So if an animal is exposed to some toxin, for example, then [its] offspring may be less inclined to consume whatever has that toxin in it," he explains.

If that were the case, and if the result transferred to humans, then developing alcoholism would require somehow overriding such a mechanism.

But another explanation is much more prosaic. "We are not able to model all aspects of alcoholism in mice with just one or two tests," Homanics says. "So maybe we just picked the wrong test." (Their studies so far have measured alcohol's effect on anxiety levels and coordination, as well as what happens when the mice have unlimited access to the substance.) His group is continuing to investigate behavior and epigenetics of alcohol exposure with the mouse model and its offspring.

Homanics says, "What our study shows is that there is a lot we don't know about the effects of alcohol that we need to think about—how it might influence not just drinkers themselves but [also] the kids they are going to have." ■



Stubborn, stealthy, and dangerous bacteria biofilms (green) grow atop airway epithelial cells from a cystic fibrosis patient.

STEALTH MODE

THE RED OCTOBER OF CYSTIC FIBROSIS

BY LILY DAYTON

Pseudomonas aeruginosa—which is found in soil, mud puddles, and even the crevices of showerheads—isn't a problem for most healthy people. However, this opportunistic bacterium is quick to invade the airways of those with chronic lung diseases like cystic fibrosis (CF) or chronic obstructive pulmonary disease. By late adolescence, the lungs of 80 percent of CF patients are permanently colonized by *P. aeruginosa*. Some 80 to 95 percent of CF deaths result from respiratory failure from various lung infections. "The thought—[regarding] cystic fibrosis patients—is that it's this infection, and really a robust but ineffective immune response to it, that causes a lot of damage in the lungs," says Jennifer Bomberger, PhD assistant professor in the University of Pittsburgh Department of Microbiology and Molecular Genetics. In a series of papers throughout the past six years, Bomberger has uncovered mechanisms that may explain how *P. aeruginosa* pulls this off:

Essentially, by going into stealth mode.

For its studies of host-pathogen interactions, Bomberger's lab team uses a unique model, culturing airway epithelial cells that come straight from lungs that have been removed from UPMC transplant patients suffering from chronic lung disease. (They also culture cells from donors with healthy lungs to use as controls.) The researchers then grow the cells together with *P. aeruginosa* on a plastic membrane, its underside bathed in medium and its topside exposed to air. The cells behave as though they were in the lung.

Using live-cell imaging, the team watches as *P. aeruginosa* produces colonies of bacterial biofilms—slimy, mushroom-shaped structures that are a hallmark of chronic lung infection—in the mucus layer that lines these epithelial cells. *P. aeruginosa* itself is highly resistant to antibiotics, and the biofilm colonies it forms create a physical barrier that is antibiotic resistant, as well.

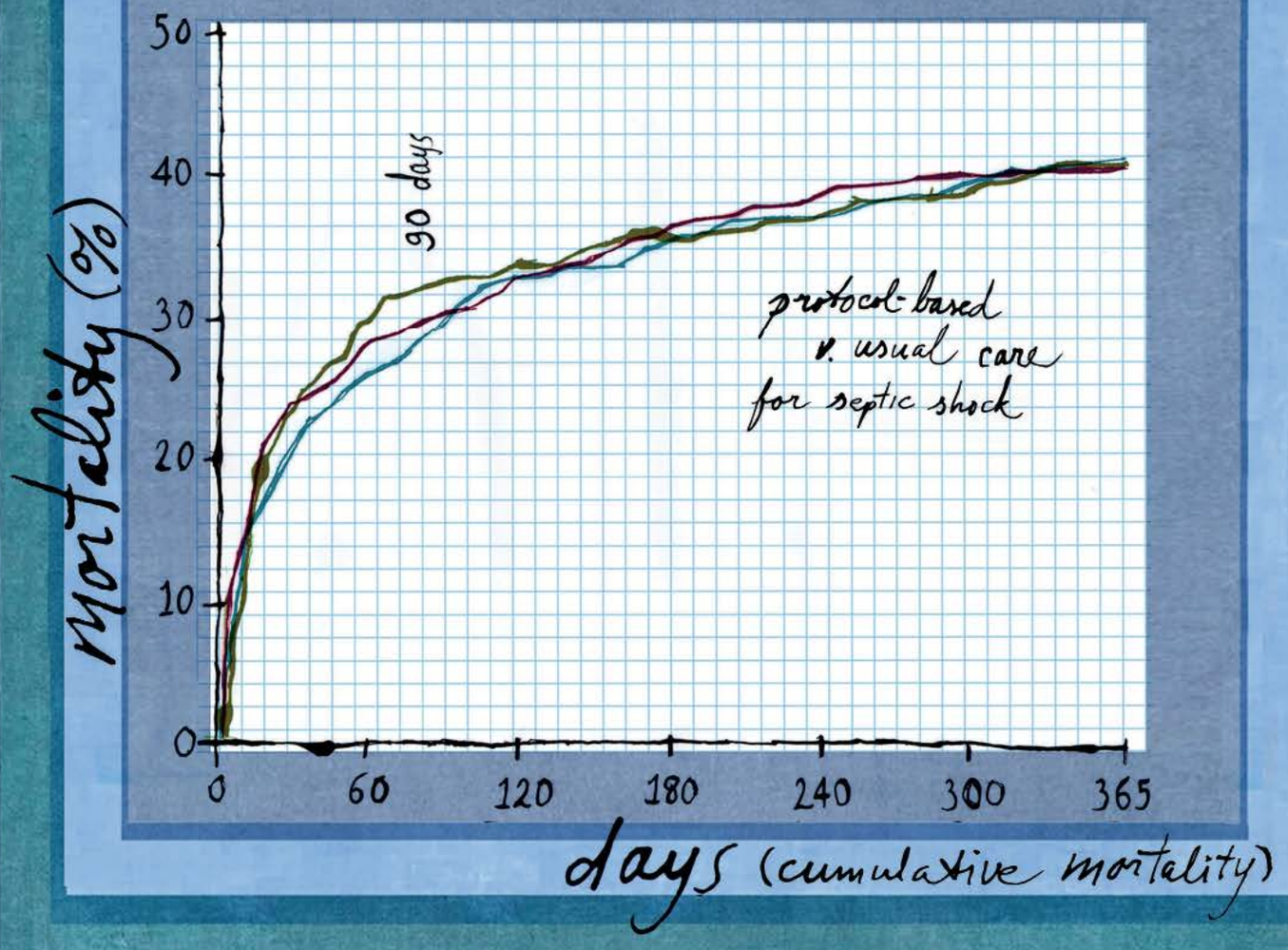
Bomberger has shown how *P. aeruginosa* delivers numerous virulence factors across the mucus layer and into host cells. The bacteria release vesicles from their membranes, which fuse with certain membrane molecules of host cells. This way, *P. aeruginosa* avoids having direct contact with the host, Bomberger explains. At the same time, within biofilms, the bacteria change their gene expression to stop producing virulence factors, allowing them to fly under the radar of the host's immune system. Bacteria near the center of biofilms also drop to a lower metabolic state.

Like *Red October*—a fictitious nuclear-missile-armed submarine that stalks coastal waters undetected, thanks to a stealthy propulsion mechanism—*P. aeruginosa* evades the host's defenses as it attacks cells.

"We've shown using this model that we can't solubilize enough antibiotic to kill [the bacteria] when they grow like this," says Bomberger.

Her data also suggest that a co-occuring viral infection dramatically enhances the ability of *P. aeruginosa* to form biofilms. During a viral infection, the host's innate immune response plays a critical role in defending against the virus. But while the immune system is fighting one pathogen, it leaves an Achilles' heel that's vulnerable to secondary infection. In the majority of cases, *P. aeruginosa* takes hold in the lungs of patients soon after they contract a virus. Bomberger is trying to elucidate this process of co-infection to target the early stages of *P. aeruginosa* colonization. In addition, her lab is developing a biofilm-disrupting agent she hopes will prevent *P. aeruginosa* infection in CF patients. "If we can figure out a way to prevent or at least prolong the time until patients get this chronic infection, we can help their disease course," says Bomberger. ■

Editor's Note: *Watch for more groundbreaking developments on CF in our next issue.*



PROTOCOL-BASED EGDT (RIVERS)
PROTOCOL-BASED STANDARD THERAPY
USUAL CARE

LARGE TRIALS CAN DIVULGE UNEXPECTED RESULTS

BY JENNY BLAIR

BIG IS BEAUTIFUL

Large clinical trials often reveal important treatment nuances or even refute results of smaller trials.

A small 2001 landmark study by Pitt fellowship alum Emanuel Rivers showed that an aggressive protocol for treating severe sepsis saved many lives. A large, multi-center study published this year by Pitt's Derek Angus and others suggests that the importance of the Rivers protocol was its demonstration that sepsis should be sought out, diagnosed, and treated with as much urgency as a gunshot wound. Once doctors get and act on that message, the treatment used doesn't seem to matter so much (see graph opposite page).

Imagine it's 1998, and you're the doctor in charge at an emergency department. You look in on an elderly woman who has arrived from home by ambulance. She's pale, her forehead moist, her eyes unfocused. Her pulse is fast and her blood pressure low. An X-ray shows pneumonia, which has probably led to systemic inflammation and the overwhelming, immensely complex immune response known as severe sepsis.

What do you do with this patient? You can give her antibiotics for the pneumonia. You can give her IV fluids—and maybe even mechanical ventilation or medications—to try to raise her blood pressure. Oxygen might help. Definitely a hospital admission.

ILLUSTRATION | TIM GROEN

You think back to a recent journal article about the search for drugs to interrupt the sepsis response (a response that often does patients more harm than the infection that sets it off). No such drug is available yet, though. In fact, you're only too aware that not much seems to lower the 40-plus-percent mortality rate in sepsis patients. Discouraged, you order fluids and antibiotics and ask the on-call intensivist to see her.

Not long after the date of this scenario, sepsis care changed dramatically. A look at how it did so can tell us something about how biomedical research lights the way, however imperfectly, for physicians at the bedside. How do physicians know what they know—or what they think they know?

In 2001, a University of Pittsburgh–trained critical care specialist at Detroit's Henry Ford Hospital published a landmark paper on sepsis care in *The New England Journal of Medicine*. Emanuel Rivers (Res '87), an MD and MPH, and his colleagues studied 263 patients with severe sepsis and septic shock, comparing mortality in patients treated within six hours with a strict bundle of interventions called early goal-directed therapy (EGDT) to that of patients treated with a simpler group of interventions, one that left more decisions up to the clinician's judgment.

Patients treated with early goal-directed therapy, which included intravenous fluids, medications to raise blood pressure, continuous monitoring of blood oxygen and blood pressure by dint of internal catheters, and even blood transfusion—all aimed at specific blood pressure and oxygenation goals—did better than patients treated with the simpler interventions. Their rapid heartbeats slowed, their blood pressures rose from low levels, their blood oxygen levels improved. And they survived at higher rates, with a remarkable 16 percent lower risk of dying in the hospital than the other group.

The results offered emergency and intensive-care physicians new hope. Pitt's Donald Yealy, an MD (Res '88, Fel '89), professor and chair of the Department of Emergency Medicine and professor of clinical and translational science, recalls the frustration regarding sepsis care in the pre-Rivers era.

"Almost all of the research up until that point didn't show any one thing was particularly helpful," Yealy says. "People often had the approach that, once sepsis occurred, you could do supportive care; but really, it was out of your hands. . . . It's not that patients were ignored, but it seemed like nothing mattered all that much."

Was determining exactly how to proceed less important than simply proceeding? Emergency physicians and intensivists badly needed a study to answer that question.

But after Rivers, sepsis didn't seem so hopeless after all. Pitt's Derek Angus, an MD and MPH, Distinguished Professor, Mitchell P. Fink Professor, and chair of the Department of Critical Care Medicine, calls the Rivers paper "the shot heard 'round the world."

That shot was no magic bullet—it showcased a precise, stepwise series of largely uncontroversial treatments, swiftly administered. And it seemed to work. As other researchers rushed to replicate the exciting results, some hospitals adopted the protocol outright. The Surviving Sepsis Campaign launched in fall 2002 and issued its first set of guidelines in 2004; these noted the success of the Rivers protocol and recommended that physicians use its goals. Rivers, as that iconic paper is known among emergency physicians, has been cited more than 3,000 times since its publication.

Still, not everyone was sold yet. Angus says he and his Pitt colleagues viewed the Rivers study with "equipoise."

"It was a great proof-of-concept study. But it was a single-center study, and so there were important questions about whether the findings could be validated," Angus says.

Some physicians hesitated to adopt Rivers because the protocol is no picnic. It effectively brings the intensive-care unit into the emergency department, so it requires a lot of resources. Clinicians must place a central venous line and an arterial line—as well as intubate, ventilate, sedate, and paralyze sicker patients—with all the careful monitoring those procedures require. Everything takes place along strict numerical parameters; the clinician works to optimize oxygen levels, blood pressure, and red blood cell levels to specific goals. Titrating blood-pressure support medication requires an eagle eye and a careful hand. The blood bank, too, has to stand by on notice.

"For a while, since [Rivers'] evidence was all that was available, I think people thought that this was the ideal or the singular best pathway," Yealy says. "The problem is that it's very difficult to deliver. . . . Many people, I think, considered the use of it, but found it difficult to implement in their own setting."

Some physicians wondered, too, whether to chalk up the study's dramatic results not so much to its protocol as to the axioms on which that protocol was built: that sepsis should be sought out, diagnosed, and treated with as much urgency as a gunshot wound. Was determining exactly how to proceed less important than simply proceeding? Emergency physicians and intensivists badly needed a study to answer that question.

They had to wait more than a decade. But in May 2014, Angus, Yealy, and numerous collaborators published a large, randomized, controlled trial that compared septic-shock patients treated with a Rivers-like protocol to patients treated with either of two other simpler approaches—one a protocol and one a "usual care" option that left decisions up to the doctor. All three groups received early diagnosis and treatment, reflecting the post-Rivers consensus that such action is key. The study, called the Protocolized Care for Early Septic Shock (or ProCESS) trial, found no significant survival difference among the groups of patients, who numbered 1,341 people at 31 hospitals. The mortality rate hovered between

21 percent (Rivers protocol) and 18.2 (other protocol-based therapy) at 60 days. (That's in-hospital deaths; the p. 12 graph shows cumulative mortality at 90 days.) ProCESS lends weight to what many physicians have long thought: Once patients get appropriate early diagnosis, antibiotics, and fluids, there may be more than one right way to proceed.

"What we've shown is that . . . how you [treat sepsis] is much less important than the commitment to looking for it and to staying on top of it as early as possible and as aggressively as possible," says Yealy.

R. Phillip Dellinger, an MD and critical care specialist at Cooper University Health Care in Camden, N.J., is one of the leaders of the Surviving Sepsis Campaign, which still recommends a Rivers-like protocol for septic shock, including placing a central venous line. Dellinger says protocols can be particularly effective in community hospitals and wherever a major study isn't goading clinicians to extra vigilance; and he suspects ProCESS's "usual care" patients probably received care similar to what a protocol would call for. Still, he calls ProCESS "a study to be applauded," because it "really speaks to the power of early identification and early treatment of septic shock and severe sepsis."

Yealy draws the same message from ProCESS. "Our trial does not refute Rivers. It actually clarifies it," he says. "Now we think of sepsis like we think of trauma, like we think of stroke, and like we think of heart attack. You have to get moving; you have to do things. That was really the durable message of Rivers."

"Our trial does not refute Rivers. It actually clarifies it," Yealy says.

Large trials often clarify small trials in this way and sometimes overturn them. For many medical questions, small single-hospital trials are all that clinicians have to go on. But they're seldom the last word on a subject.

"When it's one small initial trial, it's very difficult to make that become a standard operating procedure or become part of a protocol," Yealy says. "The first study sets the promise of benefit. But it's rare for it to answer the question completely."

Cautionary examples abound. Physicians once routinely prescribed hormone-replacement therapy for postmenopausal women, a recommendation they based on small observational studies. Because women's lipid levels fell with hormone replacement, physicians reasoned, the therapy would help prevent heart disease. Then came the Women's Health Initiative. More than 16,000 women randomly received either hormone replacement or placebo; the hormone-replacement groups suffered a much higher risk of stroke.

Similarly, oncologists once held out hope that beta-carotene supplements could reduce mortality in lung cancer patients; large studies disappointed them. Intensivists took notice when a single-center study of critically ill patients seemed to show a significant benefit to tight blood-sugar control. (That was rather large, at 1,500 patients.) Eight years later, though, a 42-hospital study of 6,100 patients found that tight control led to higher mortality.

In short, though even large studies can be poorly designed, it's especially risky to base the standard of care on small or single-center early studies. Cause and effect are more easily confused, for one thing. High blood sugar may not worsen critical illness but merely indicate its presence, so attempts to control it could be misleading. Selection bias, confounding variables, and lack of blinding or controls can skew results in small trials, too. Some simply don't enroll enough patients for their results to be statistically compelling. And some smaller trials have compelling numbers, but because of an anomaly (like a genetic trait common to the regional population but not the population at large), they don't hold up on a large scale.

Joseph P. Costantino (a DrPH) knows what is and isn't enough to hang your stethoscope on. He is a professor of biostatistics at Pitt Public Health and director of the Statistics and Data Management Center for NRG Oncology Foundation, a major National Cancer Institute grant recipient that conducts multi-institutional clinical cancer trials.

"A lot of the information that we have in evidence-based medicine comes from prospective, nonrandomized studies by people just looking at records and assessing who got a treatment and who didn't, and then comparing the two groups," Costantino says.

So-called observational studies like that can certainly be useful. But because these studies don't randomize patients, hidden factors could influence results. The randomized controlled trial is considered the gold standard in clinical research for determining cause-and-effect relationships.

"I'm a firm believer in the randomized controlled trial as the best way to seek the truth," Costantino says.

A subtler factor can also contribute to disparities between large and small trial results, according to Edward Chu, an MD professor of medicine and of pharmacology and chemical biology, who has spent his career conducting clinical trials of investigational cancer drugs. That factor is meticulousness. Chu says that investigators conducting early phase or other small studies may be more careful compared to those running larger, late-phase studies, and that makes an important difference.

"Even though they're all working off the same playbook in terms of eligibility criteria, exclusion criteria, I think that level of scrutiny, perhaps the attention to detail, may not be quite as great" in late-phase studies compared to smaller ones, Chu explains.

Less experienced investigators running small trials, he says, tend to follow protocols closely when enrolling patients, whereas seasoned investigators may exercise more judgment about whom to enroll.

Ironically, this slight sloppiness is more representative of how a treatment is likely to be used in the "real world," Chu suggests, making large trials better predictors of a treatment's efficacy.

The long delay between Rivers and Angus certainly wasn't for lack of interest. Conceiving a large multicenter trial and seeing it through to completion is an immense task.

Angus and colleagues designed their follow-up sepsis study in 2005, shortly after wrapping up another one. They secured funding in 2006. It took 18 months to set up the study sites, as institutional review boards examined and approved the study protocol and collaborators learned how to administer it. Patient enrollment took another five-plus years. Crunching the data, by comparison, went quickly.

That schedule is, unfortunately, typical. Enrolling patients can be the rate-limiting step. With rarer diseases, like certain cancers, enrollment can drag because the right patient only comes along occasionally.

Angus says doctors often also mistakenly view clinical trials as distractions or even as being at odds with good patient care. Convincing them otherwise could greatly accelerate the pace of research.

It can be hard, too, to convince people to try new treatments that seem daring. Such reluctance slowed landmark studies comparing lumpectomy plus radiation to total mastectomy in breast-cancer patients, the first of which was launched in 1976 by the National Surgical Adjuvant Breast and Bowel Project (NSABP) under the direction of Pitt's Bernard Fisher (MD Distinguished Service Professor of Surgery). Fisher hoped to demonstrate—and ultimately did—that the first, less invasive option was as safe and effective as the second. But few patients wanted to be the first to take that chance.

"Getting women and physicians to agree to be randomized to a study where you're going to do a little bit of surgery compared to this radical surgery—when, for years, the belief was 'The more surgery the better'—was very, very difficult," Costantino notes.

Besides delaying medical progress, such hesitancy can undermine the quality of results. By the time the Rivers trial was approved, funded, and under way, new research had emerged suggesting that its blood-transfusion threshold was too strict. It's hard for researchers to design the ideal research protocol when the standard of care evolves out from under them.

"There's no question that these trials are incredibly labor intensive and expensive," Angus says. "There's a tremendous penalty that we constantly pay in terms of the delay to knowing the answer and the precision to which we know the answer, simply by having clinical trials be logistically burdensome."

Cancer researchers, at least, are finding ways to speed things up, thanks to what we're learning about cancer biology.

Typically, clinical researchers test new medical treatments in three phases. In phase 1, a few patients receive the new treatment and researchers test safety, dosage, and side effects throughout the course of several months to a year. Phase 2 trials focus on the treatment's efficacy in a few dozen or several hundred patients over about two years. Phase 3 trials last much longer; they randomize hundreds or thousands of patients to receive the new treatment or one or more standard treatments.

Pitt has earned an outstanding reputation in phase 3 clinical trials for cancer. For instance, its NSABP conducted the original studies of lumpectomy for breast cancer, as well as landmark research into breast-cancer prevention and treatment with tamoxifen. (In early 2014, the NSABP merged with two other research groups, the Gynecologic Oncology Group and the Radiation Therapy Oncology Group, to form the NRG Oncology Foundation.)

And now the pace and logistics of cancer trials are changing. Tumors result from mutations that release the brakes on a cell's growth and division. Two patients with the same cancer diagnosis may have very different mutations; and as sequencing technology improves, it's getting easier to detect and categorize cancers by specific mutation. Many new drugs are aimed precisely at those specific mutations, and researchers expect many more to emerge, potentially transforming cancer treatment.

Studying such drugs means tracking down a group of cancer patients who share the relevant genetic anomaly. Though that sounds difficult, it also presents a golden opportunity. Those studies will require fewer patients than studies of a less-precise drug would—and the results will be more relevant.

Recognizing this, the National Cancer Institute reorganized its clinical trials structure in March 2014 to link cancer centers around the nation in a National Clinical Trials Network (NCTN). (NRG Oncology is one of five of its adult patient "network groups" in the United States and Canada.) The network is intended to speed up late-phase trials by allowing member institutions to collaborate and pool resources.

"Some of these subtypes are so small that there aren't many patients out there, so you do need to have a large collaborative effort," says Costantino. "If one group is doing a study, it's open to the entire system, and the entire system is encouraged to participate."

Large trials often clarify small trials and sometimes overturn them.

Members will share a data-management system and a single institutional review board, both of which are expected to shave time off trials. In April, the University of Pittsburgh became one of 30 recipients of a Network Lead Academic Participating Site grant, which is set aside specifically for the NCTN. At about $5 million, the grant will fund cancer trials under the leadership of Adam Brufsky, an MD/PhD professor of medicine and codirector of the Comprehensive Breast Cancer Center.

NCI isn't overlooking early phase trials, either. To coordinate phase 1 and 2 trials of investigational cancer drugs and of biomarkers that could help physicians detect

patients most likely to benefit, it created the Experimental Therapeutics Clinical Trials Network, or ETCTN, in early 2013. Chu is principal investigator on a $4.25 million ETCTN grant; Pitt is one of 12 centers in the nation to receive a grant of this kind.

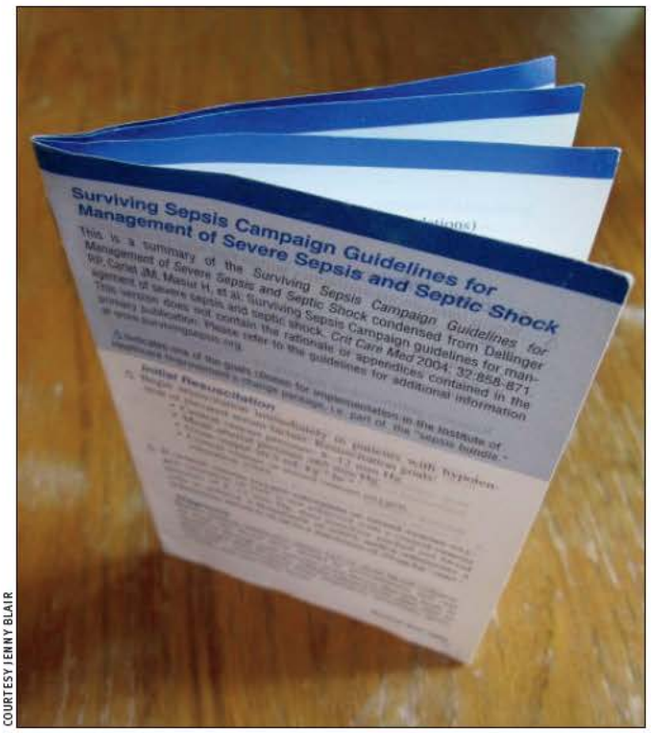
There's reason to think that tests of new cancer drugs could go rapidly. Case in point: ceritinib, a drug the FDA approved to treat a subtype of nonsmall cell lung cancer after it performed spectacularly in a multicenter phase 1 trial that tested an unusually high number of patients. (More typically, a phase 1 cancer trial might come up with 80 to 100 patients; this one had 163.) Early phase trials, then, can be enough to demonstrate both safety and efficacy if researchers can enroll plenty of patients with the relevant mutation.

Ceritinib, Chu says, may herald a new paradigm of drug development.

"They had a genetic mutation. They have a genetic test. They have a drug that targets it. And, poof—in phase 1, [an] incredibly positive clinical benefit," Chu says. "It's going to be the poster child."

Bringing together multiple centers with early phase expertise is critically important, Chu adds. The arrangement takes advantage of each center's strengths. Pitt, for example, brings strengths in drug metabolism, clinical pharmacology, imaging, and pathology, among other areas. UPMC also has a broad patient base, which makes it easier to find the right patients for any given study.

"In the end, the whole is greater than the sum of the individual parts," Chu says. "Then there's real synergy."



COURTESY JENNY BLAIR

The intensive Rivers protocol (described in the pamphlet shown) for treating sepsis was the "shot heard 'round the world" for doctors to take action on sepsis.

Sepsis researchers like Angus don't have the oncologists' luxury of dividing patients into genetic subsets—not just yet, anyway. They are finding other ways to push their research ahead.

Reaching across borders is one strategy. Large though the Angus study was, it enrolled only enough patients to detect a potential 6 to 7 percent difference in mortality between protocols. One of those protocols might still have an edge over the others—just a few percentage points perhaps, but enough to be worth knowing. So Angus plans to pool data from the ProCESS trial with those of two other large sepsis studies. One, called ARISE, was led by Rinaldo Bellomo, an MD and another Pitt-trained intensivist (Fel '93), who teaches at the University of Melbourne and Monash University. Bellomo et al. reported on October 1 in *NEJM* no difference in mortality (18.6 v. 18.8 percent at 90 days) between the Rivers protocol and usual care. That study—with 1,600 patients mostly from Australia and New Zealand—was even larger than ProCESS. The other multicenter trial, ProMISe, takes place in the United Kingdom. With such a huge patient pool across so many centers, small but potentially lifesaving subtleties in sepsis care should be detectable.

Keeping in touch with patients over time and re-examining samples collected during the study can bring more valuable insights. Angus will follow ProCESS patients for years to learn more about long-term sepsis survival. Other researchers across the nation, including Pitt's Brian Suffoletto, MD assistant professor of emergency medicine, are examining ProCESS blood samples to investigate the role played by the endothelial cells lining blood vessels in sepsis.

And new large-scale studies continue to be born. Associate professor of critical care medicine David Huang, an MD/MPH, who trained at both Pitt and Henry Ford Hospital, is leading a new multicenter study of procalcitonin, a marker of inflammation, to see whether it can alert doctors to early stage pneumonia. If so, that would make decisions about prescribing antibiotics easier.

Though the process of understanding sepsis has been arduous, we can take heart. The mortality rate has plummeted since 1998. That's thanks to studies both large and small (especially the study by Rivers).

Angus hopes that physicians will become more receptive to the idea of involving their patients in research studies. The National Cancer Institute reports that just 3 percent of cancer patients are enrolled in clinical trials. Angus believes that trials would run 10 times faster if just 10 percent of eligible patients were to enroll instead.

So whether you're a doctor or a patient, add "study enrollment" to your to-do list. Medical progress needs you. ■

Editor's Note: *Writer Jenny Blair, an MD, trained in emergency medicine. She says that as a resident a decade ago, she made hundreds of index cards "that served as mnemonics/reminders of this and that." The Rivers protocol was too complex to fit on a card, so she carried a folded-up sheet of paper instead. She still has it today.*


9:41 AM
Wednesday
12
73°
Mail
Safari
Music

THERE'S A REMOTE INTERVENTION FOR THAT—
OR THERE WILL BE

AN APP A DAY KEEPS THE DOCTOR AWAY

Nearly a third of Americans say they can't live without their smartphones—what if they could live better because of them?

Pitt people are building apps to help us take control of our health. At the same time, the University has established a new center to explore the nuances of social and digital technologies in terms of how they affect patients and providers.

On April 3, 1973, Martin Cooper, a Motorola division manager, stood on a street corner in Manhattan and placed the first cell phone call to his rival at AT&T's Bell Labs. The first cell phone conversation wasn't documented, but Cooper reportedly said: "I'm ringing you just to see if my call sounds good at your end." His cell phone weighed about 2.5 pounds. It took another decade for cell phones to become commercially available and another 19 years before the first text message was sent. (The first incarnation of the Internet made its debut just four years before Cooper's milestone call.)

We don't have to bring you up to date on the rest of the story. Ninety percent of our population now uses cell phones, the majority of which are smartphones. Digital, particularly Internet-driven, technology has changed how we live, how we work, how we represent ourselves, how we communicate, what we carry in our pockets and handbags. Many hope it can help us manage our health. Yet what exactly is going on at the intersection of health and this technology is, well, a bit cloudy.

ILLUSTRATION | JESSE LENZ

A CONSTANT PRESENCE

Brian Primack—an MD/PhD associate professor of medicine, of pediatrics, and of clinical and translational science at the University of Pittsburgh—is the newly appointed assistant vice chancellor for research on health and society and director of the University's new Center for Research on Media, Technology, and Health.

"Our brains developed over millions of years of evolution for a certain kind of world and a certain kind of life," he says. "Now, we're literally spending the majority of our waking hours doing activities that have only been around for the past couple of decades at most. With these huge social and technological changes, we should really see what kinds of impacts they might have on health."

MARK BOLSTER/UPMC

Brian Primack will help us navigate the cloudy nexus where health meets personal digital technologies.

Much of the research that relates to these issues focuses either solely on positive impacts or solely on negative impacts of technology on health, says Primack. His hope is that Pitt's new center will provide collaborators from throughout the University with resources to look critically at the enormous, complex nexus of health and technology while helping to develop effective remote interventions.

"We can leverage these technologies to do unbelievable things that we've never been able to do before," he says.

"There's now an app on my phone that I can put on my chest, and it will do an EKG for me. Then I can set it to automatically send it to my cardiologist. That might improve detection of a potential problem if I have chest pain. It might help reduce costs so I don't have to incur a $1,000 or $2,000 bill." However, there are drawbacks to people giving themselves EKGs, he notes. A layperson might take an EKG incorrectly or miss other problems that a physician could detect. Because it's far cheaper to use an app than to get an EKG at a hospital, patients might be inclined to choose the less costly, easier option when they should really meet with their PCP. In other words, an app a day might keep the doctor away, but when and how should it? As we move forward, Primack says, it's essential to research the impact of the tech-based health care interventions that we develop, which is no easy task given how quickly technology is evolving.

"We can't just reduce a human being to an EKG tracing," says Primack. "In some ways there is no substitution for seeing a person in the flesh. There are a lot of times when a person has an EKG that's totally normal, but there's something about what they're saying, or the way they're saying it, that can bring us more concern and can help us clinically make a different determination. There is concern about losing that." All innovation has unintended consequences, Primack points out, which is why it's important to have research and critical thought involved with technological development, especially when it affects our health and health care. —*Kristen Cosby*

Lots of people at Pitt and elsewhere are realizing that the little computer you probably carry around with you can help you stay (or get) healthy. It's a realm that's ripe for apps, and we got a peek at some under development at the med school and other health science schools. Several of these were finalists or winners of the first Pitt Innovation Challenge (PInCh), a competition orchestrated by Pitt's Clinical and Translational Science Institute with support from the Office of the Provost and the University's Innovation Institute. PInCh provided three $100,000 prizes and three $25,000 prizes for the development of promising solutions to health care problems.

DON'T DO IT: QuitNinja

ISSUE: Suppose you want to quit smoking. You throw away your cigarettes, your ashtrays. You make promises to people you love and to yourself. At the end of the first day, you pass someone smoking on the street. More than anything, you want a cigarette. All your good intentions disappear. Wouldn't it be easier if you had a nonjudgmental friend by your side day and night to remind you of all the reasons you wanted to quit? Wouldn't it be great if that friend were pocket size and could replace that pack of cigarettes in your jacket?

APP: Enter QuitNinja, developed by a team of researchers at Pitt led by Ellen Beckjord (PhD/MPH assistant professor of psychiatry and of clinical and translational science) with help from Pitt's Saul Shiffman (PhD professor of psychology) and Vignet Corporation's Praduman Jain and David Klein. Smokers with an urge to light up can send a message to the app and receive an intervention—maybe a positive message about the benefits of quitting, a suggestion about how to change the immediate environment, or a personal motivator, like a photograph of the kids. QuitNinja helps people during those "weak" moments.

AWARDED: $100,000 PInCh Prize and Beckjord's $660,000 KL2 research grant from the Clinical and Translational Science Institute.

WHAT'S NEXT: An upgraded QuitNinja will incorporate an artificial intelligence component. The

app will actively gather data on the smoker through a Q&A. In addition, QuitNinja will passively gather data that pinpoints the time of the urge, the locale of the user, and the amount of time lapsed from the last cigarette; it will then predict when the user will have another urge to smoke. In the future, QuitNinja could be adapted for other behaviors that require self-regulation. The app is being beta tested by a group of 30 smokers. Pilot trials begin in early 2015. *—Kristen Cosby*

HELP FOR GOOD AND BAD DAYS: SPark

ISSUE: The medication schedule and dosage for patients with Parkinson's can be complicated and variable. The meds are time sensitive, lasting only a few hours, and have different effects on different people. Those effects might vary depending on whether the patient is having a "good" or "bad" day. Patients often are left to guess when they need to medicate. That's rough enough for people who don't have a neurological disorder—imagine having to negotiate all the physical and emotional challenges of a disease that makes your body's movements unpredictable from one hour to the next.

QuitNinja is like a pocket-size friend that can remind you why you want to quit smoking. (Illustration adapted from an app prototype.)

APP: SPark helps patients with Parkinson's disease remember to take their meds and administer those drugs more effectively. It also keeps a record of dosage so that when patients visit their physicians, they can spend less time trying to figure out what medication adjustments are necessary and more time on other challenges they might be having.

Parkinson's patients can experience "bad episodes" involving tremors and stiffness that endanger them. Standard smartphones and smartwatches have motion sensors embedded within them that, when employed by SPark, can determine when a patient's movements are becoming abnormal. SPark uploads their medication record and information about their body movements into a private record in the cloud that both patients and their care providers can access. Pitt's Samay Jain, an MD assistant professor of neurology specializing in movement disorders, is developing SPark with colleagues from Pitt's Department of Bioengineering, Carnegie Mellon University, and the Parkinson's Disease Foundation.

AWARDED: $100,000 PInCh Prize.

WHAT'S NEXT: An upgrade may include customizable alerts. In a pilot study of 24 patients with Parkinson's, SPark was able to detect tremors with more than 90 percent accuracy. The team will conduct four focus group studies to test the software. If SPark continues to predict the need to medicate with at least 90 percent accuracy, it will be rolled out for larger trials. *—KC*

JOINT DECISIONS: PIVOT

ISSUE: Consider the mighty anterior cruciate ligament (ACL). When it works well, it controls the back and forth movement of the knee, providing necessary stability. When it doesn't work, it's the scourge of many an athlete. Each year, about 150,000 people in the United States undergo ACL reconstructive surgery. The orthopod's classic diagnostic tool is the manual pivot-shift test, in which the examiner rotates the patient's extended leg toward the inside and then flexes the knee past 30 degrees to assess whether the tibia's position on the femur is lax or misaligned. The problem? The condition is subjectively graded on a severity scale. "Grade 1 in my hands may be grade 2 in yours," says Volker Musahl (Res '08), Pitt associate professor of orthopaedic surgery and bioengineering, as well as medical director of the UPMC Center for Sports Medicine.

APP: Musahl and his collaborators came up with PIVOT, an iPad app that video records the pivot-shift test as a physician performs it. Before the test, three markers are placed at strategic points on the side of the knee. The app then tracks those markers, and a built-in algorithm computes how much movement occurred during the test. "It's been validated in the laboratory on cadaver studies," says Musahl. "Now, instead of saying, 'This is a grade 1 or grade 2 pivot shift,' we can say, '[It's a] 2.6 millimeter shift.'" The app is currently being tested in an international multicenter clinical study involving four medical centers, including UPMC.

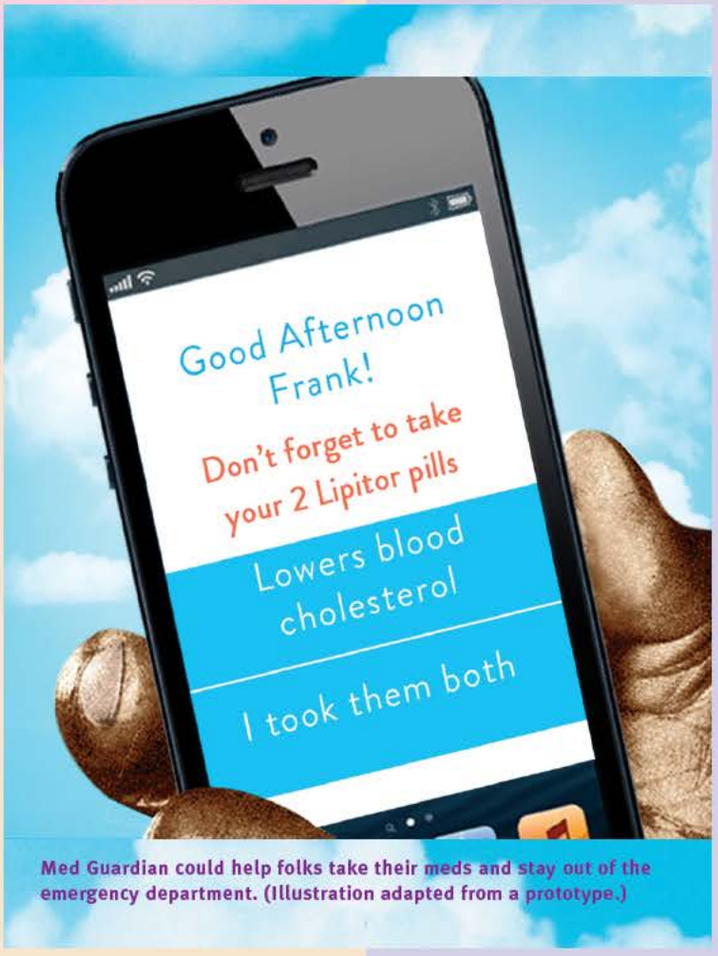
AWARDED: PIVOT received honors in 2013 from the Brazilian Congress of Orthopedics and Traumatology and the International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine.

WHAT'S NEXT: If the app, which has received a U.S. patent, proves its mettle in the multicenter trial, Musahl would like to get it to market so any orthopaedic surgeon can use it. PIVOT, he says, has other potential uses, including assessing injuries on the sidelines of athletic fields and tracking the success of rehab therapy. He expects that one day there will be an Android version. *—Sally Ann Flecker*

MORATORIUM ON MEDS MISUSE: Med Guardian

ISSUE: Half the drug regimens prescribed in this country aren't carried out as directed. People fail to take their medications for many reasons: expense, confusion, inability to feel the effects of the medication, or the presumption that they're cured (as is frequently the case with antibiotics). In addition, accidental poisoning from prescription drugs is a growing concern. In 2010, misuse of prescribed medications caused more than 35,000 deaths and more than 400,000 emergency department visits.

APP: Like SPark—the app for Parkinson's patients—Med Guardian should help patients keep track of their prescriptions. But Med Guardian is for a wider audience. Say you have type 2 diabetes, high blood pressure, and arthritis. You (or your pharmacist) could enter all of your scripts into Med Guardian, which would then upload that information to a database. When you needed to take your blood pressure medicine, an alert would appear on your smartphone showing you a picture of your blood pressure pills (so you know you're taking the right medication) and a description of the purpose of the medicine. You would then confirm that you'd taken it. That record could be uploaded to the cloud so that you (or a member of your family or a health care provider) could track your medication adherence online. You'd also get feedback about how successful you were at adhering to medication regimens.



Med Guardian could help folks take their meds and stay out of the emergency department. (Illustration adapted from a prototype.)

AWARDED: $25,000 PInCh Prize.

WHAT'S NEXT: The team—including Pitt med's James Kaus (MD '15), Olufunmilola Odukoya (PhD assistant professor of pharmacy and therapeutics), and several others—is developing the app's architecture, designing the clinical trial, and engaging in discussions with patients, pharmacists, and physicians about improving medication adherence with the app. The team intends to have the product ready for wider market release by January 2015. *—KC*

SIREN CALL: ThinkSepsis

ISSUE: Quick—name the most common condition prompting a call to the EMS. No, it's not heart attack, stroke, or even traumatic injury. It's sepsis, a deadly syndrome affecting more than 1 million adults in the United States each year and the number one killer of patients in the hospital. Still, it's not on everyone's radar. Patients present with fever, high respiration and heart rate, and, perhaps, confusion, which could point in many different directions. But every one-hour delay in the treatment of sepsis increases the risk of death by about 7 percent. So the more quickly sepsis can be diagnosed and treated, the better the chances of survival.

APP: Identifying and treating sepsis as early as possible—in the ambulance—is the goal for sepsis tool innovator Christopher Seymour, an MD assistant professor in the departments of critical care medicine and emergency medicine. He and his collaborators within those departments and at Pitt's Clinical and Translational Science Institute are developing ThinkSepsis to prompt first responders—including paramedics and firefighter EMTs—to recognize the signs and symptoms of septic patients. Not only that, but the app will report the symptoms and transmit the patient's biometrics to doctors at the receiving hospital or the medical command personnel who are helping the paramedics to activate a system of care.

AWARDED: $50,000 CTSI grant.

WHAT'S NEXT: Seymour expects a prototype to be built in the coming months. "EMS and medical practitioner awareness of sepsis is so lacking," says Seymour. "We think it's a really important area." *—SAF*

Everything's coming up remote interventions.

LET'S TALK/ CHAT/ POST/ SMS ABOUT IT

HEY KIDS, IT'S OKAY TO ASK: IOTAS

ISSUE: For the past 24 years, the Education Department of Planned Parenthood of Western Pennsylvania sponsored face-to-face peer education in resource classrooms within schools. A student with questions about sexual health could show up at a designated resource classroom and ask questions of a trained peer helper. A Planned Parenthood educator would be in the room to help, yet the students could exchange information in a private conversation. This kind of peer education has been effective in disseminating accurate information about sexual health among teens.

Then the kids stopped coming as much. It wasn't clear why, but we can guess: The Internet offers a lot of information that resource rooms used to; and maybe kids prefer that anonymity to talking about this stuff in person. Still, it's clear that teens don't mind texting, and they don't mind texting about sex.

INTERVENTION: Planned Parenthood's Katie Horowitz, Jose Garth, and other agency educators, with consultants from Pitt's Graduate School of Public Health (including Christina Mair, a PhD assistant professor of behavioral and community health sciences) as well as developers at Apps N'at, teamed up to create IOTAS, or It's Okay to Ask Someone, a text line about sexual health for high school students.

This is how it works. Say a girl wanted to know whether she could contract HIV from kissing. She could send a text to IOTAS. Through a customized app, Planned Parenthood educators would then screen the incoming question and deliver it to a queue for any of its 150–175 peer helpers. The peer helpers would access the queue from an app on their smartphones or from tablets provided by Planned Parenthood and select questions to respond to. Their supervisors would then review the answers, make suggestions, and approve the best responses. For example, "HIV can only be contracted through the exchange of blood, semen, vaginal fluid, and breast milk. You cannot get it from spit!" Approved answers and comments from the peer helpers would then get texted back to the teen who asked the question.

AWARDED: $25,000 PInCh Prize.

WHAT'S NEXT: The program will be piloted in four Pittsburgh high schools in the 2014–2015 academic year and marketed throughout Allegheny County in the summer of 2015. —*Kristen Cosby*

Pitt researchers are engaging young people and others through texts and online support groups to help them build healthy lifestyles and get them through tough times.

TEXTING V. BINGEING: TRAC

ISSUE: Binge, or hazardous, drinking is defined as the consumption of enough alcohol to raise blood alcohol level to .08 percent. (For men, that typically translates to imbibing five or more drinks within about two hours; women typically would have to have just four or more drinks.) Binge drinking is a common pattern of alcohol abuse among young people.

INTERVENTION: Imagine you are a college student. You tend to drink too much on Friday and Saturday nights. You aren't interested in quitting, but you'd like to control your party habits. Maybe your phone could help you.

Brian Suffoletto, an MD assistant professor of emergency medicine at Pitt, and his team have developed a program called TRAC (which stands for Texting to Reduce Alcohol Consumption) that uses texting to help reduce binge drinking among young adults who have already ended up in the emergency room and are considered at risk for the behavior. (That's about a third of young patients in the emergency department.) This system is the first intervention for binge drinking that's proven itself in a large, randomized clinical trial.

If you subscribed to TRAC, every Thursday at 4 p.m. you would receive a text message like, "Hey, it's the TRAC team checking in. Do you have any plans to drink this weekend?" If you reply that you won't be drinking, TRAC sends a message of positive reinforcement, maybe, "Good, you are healthier for it!" But if you say that you are planning on drinking, TRAC then asks, "Are you planning on having more than three (or four) drinks?" If you say yes, you are asked to set a short-term goal for the weekend to restrict your drinking to less than that. But if you reply that you have no plans to restrict yourself, TRAC then asks you to reflect on your choices and reminds you that drinking is associated with injury and illness. The program checks back in with you on Sunday at noon to review whether you've met your goals.

A clinical trial of 756 young adults at four emergency departments throughout Pittsburgh demonstrated that young people are more candid in their texts to TRAC about their drinking habits and their failures to meet their goals than they might be with a physician. After three months, TRAC users reported consuming fewer drinks per session and drinking fewer days per week. Suffoletto's team published its results this July in the *Annals of Emergency Medicine*.

AWARDED: A five-year $873,125 National Institutes of Health grant funds further research and development of TRAC.

WHAT'S NEXT: The TRAC team hopes to program the software so that it can text with its users while they are in high-risk situations, like at a party or a bar. The team enrolled Pitt undergrads in its studies of the app; it will continue to expand enrollment among Pitt students and other young people by partnering with other colleges and medical centers. —*KC*

TAKE YOUR SUPPORT GROUP WITH YOU: Online Treatment

ISSUE: Patients often turn to the Internet to build their support networks and answer their health questions. Unfortunately, the accuracy of the information that they find online isn't always reliable. Additionally, no one has ever studied the effects of health-related social networking on patients.

INTERVENTION: In October 2012, Pitt's Bruce Rollman (an MD/MPH professor of medicine, of psychiatry, of biomedical informatics, and of clinical and translational science) and his team launched Online Treatment for Mood and Anxiety Disorders, an Internet support group, or ISG, built for UPMC primary care patients who show signs of depression and anxiety. (A mobile-device-friendly version loads automatically for patients logging in on the go.) The ISG, which may be the first with ties to an organized health care delivery system, offers a forum for patients to commiserate over shared experiences—from sleep disturbances, to weight management, to how to talk to people in their lives about their illness.

In a randomized trial of 704 depressed and anxious patients from 26 UPMC-affiliated primary care practices, Rollman's team will compare the effectiveness of usual care, versus using the ISG on its own, versus using the ISG in combination with Beating the Blues (a Web-based cognitive behavioral therapy program). Beating the Blues replaces tried-and-true paper workbooks that help patients learn better ways to view and respond to challenges.

Online, patient engagement is much easier to track, Rollman notes.

So are patients' needs. For example, as the team monitored ISG discussion board comments from the patients (who are anonymous), they learned that there was a lot of interest in the topic of domestic abuse. So, the team created a page with relevant information and resources.

AWARDED: $2.6 million grant from the National Institute of Mental Health.

WHAT'S NEXT: Rollman's team opens the study blind in 2015. Preliminary results on patient engagement are "very encouraging," reports Rollman. He's hopeful that this model of a UPMC-branded support group might prove useful for other patient populations. —*Elaine Vitone*

TRANSPLANTING
THE SHLOMCHIKS TO PITTSBURGH

BY ELAINE VITONE

BLOOD BROTHERS

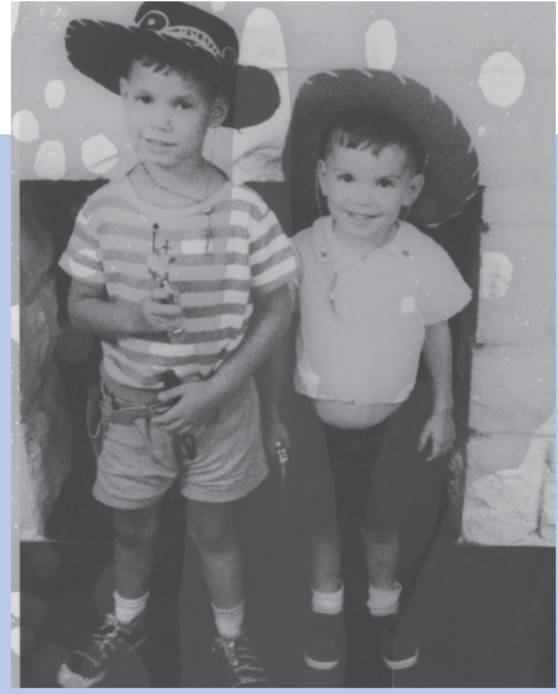
In the spring of 1962, in the suburbs of West Philadelphia, the Shlomchik family prepared for the arrival of their second child.

"Mark," Marlene said to their toddler, "you're going to be a big brother. You're going to have to take care of the baby."

The Shlomchiks were worried about the new addition to the family, and with good reason. Marlene was B negative, Seymour was O positive; and as a surgical resident (a future orthopaedist), he was well aware of what the antibodies in his pregnant wife's blood work meant. Her immune system—piqued and primed by the Rh-positive blood that had crossed the placenta into her system when she carried her first child—was now mounting an attack on her second.

PHOTOGRAPHY | CAMI MESA

Warren (left) and Mark Shlomchik in the immunology department's newly renovated space at Pitt.



Mark and Warren, c. 1964.

The couple arranged to deliver at Einstein Medical Center, the Philly hospital best equipped for what the baby would need—delicate exchange transfusions to remove his own blood and replace it with that of a donor. Given the risks—including brain damage—associated with coming into the world with high bilirubin levels and self-destructing red blood cells, time was of the essence.

Mark, a 26-month-old, took his new charge seriously. On the day his parents came home without the baby—a boy, Warren, who would stay in the hospital for seven exchange transfusions in all—Mark stood at the door, dismayed.

"Where's my brother?"

Fortunately, Warren not only survived, but thrived, turning out just as bright as his brother (which is saying a lot—Mark was giving his classmates astronomy lessons in kindergarten). And since the day Warren came home, "they've been really close brothers and best friends," their father says. "They've never been competitive with each other. They used to play tennis and never kept score."

Mark Shlomchik, an MD/PhD—a specialist in transfusion medicine when he wears his clinical hat and in immunology when he wears his academic hat—arrived at the University of Pittsburgh as the new chair of the Department of Immunology in October 2013. Best known for his discoveries in the essential biology of lupus, he was among the first to elucidate the roles of B cells and of toll-like receptors in autoimmune disease.

Warren Shlomchik—the taller, dark-haired brother who looks a lot like their dad, if their dad wore a ponytail—is an MD who studies the immunology of allogeneic stem cell transplantation, especially situations where the donor's immune cells attack the host's malignant cells or the host's body more generally. A hematologist/oncologist, he's making preparations to join his brother at Pitt in March 2015 as professor of medicine and director of Hematopoietic Stem Cell Transplantation and Cell Therapies for the Division of Hematology/Oncology and scientific director of Hematopoietic Malignancies for the University of Pittsburgh Cancer Institute (UPCI). (When his family joins him, Pittsburgh will inherit one of Connecticut's top dermatologists, Warren's wife, Stephanie Dietz.)

The Shlomchik brothers—to whom we'll refer by first names, for clarity—have a history of sticking together.

Mark went to college at Harvard. Then so did Warren. Mark went to med school at Penn. Then so did Warren. Mark spent much of the past 20 years working in one of the top immunology departments in the country, Yale. And Warren has done that, too.

And for much of that time, they've been scientific collaborators.

"We have a great time with it," says Mark. "We used to see each other practically every day."

"We no longer read each other's grants. But we read *sections* of each other's grants," says Warren.

Mark's predecessor, Olivera Finn, PhD Distinguished Professor of Immunology and of Surgery, and founding chair of immunology at Pitt, says there's nothing bittersweet about handing over the reins—it's "all sweet." New leadership means new resources and new faces in this department she built from scratch 12 years ago, when she recruited four basic scientists (young scholars fresh out of their postdocs, all of whom went on to make tenure on the first try, she notes). Finn calls Mark a prime choice for the job. In fact, in the '90s, when she was at Duke, she tried to recruit him.

At Yale, Mark and Warren were just down the hall from each other. But in Pittsburgh, Warren will be a few floors away, in the Thomas E. Starzl Transplantation Institute—not because anyone wants to break up the Shlomchik brothers, but because Warren will be close to collaborators there. Immunology at Pitt is expanding. And just as important, it's strengthening its ties to departments and centers across Pitt and UPMC. (Since he arrived, Mark has already been at the table for faculty searches in pediatrics, rheumatology, and oncology.)

These changes reflect a growing appreciation for immunology as central to virtually every part of medicine, from arthritis to transplantation, from asthma to vaccine development, and across a host of immune diseases and disorders affecting every organ system and every phase of life.

When we science scribblers write about immunology, we tend to lean on the same old, tired metaphor—war. And, as with many clichés, this one is popular because often, it fits: Antigen-presenting cells are something akin to intelligence officers, spotting pathogens and sounding alarms. B cells and T cells—the immune system's infantry—deploy and attack. Antibodies—like heat-seeking missiles—search and destroy. And when all goes well, the viruses and bacteria fall, and the body lives another day.

But at a certain point, the good-guys/bad-guys trope falls short—and so do scorched-earth approaches to disease. If you bomb all the body's bacteria into the Stone Age with antibiotics, the microbiome is left in ruins. If you shut down all of an autoimmune-diseased body's defenses with immunosuppressive drugs, then that body is a sitting duck for infection and for cancer. And if you obliterate tumors but wreck the body along the way, then it's all for naught.

As we're getting to know our basic biology better in the quest for more targeted therapies, we're seeing a much more nuanced picture: competing agendas, balancing acts. As one Stanford writer put it, the relationship between microorganisms and the bodies they inhabit is more like a "finicky marriage" than a war. Somehow, everyone must find a way to coexist under one roof—like a family. And a persistent curiosity for these underlying mechanisms has fueled both Shlomchiks' studies from the start.

In Mark's first year of med school, his immunology instructor invited him to work in his lab. And within the first few weeks of that summer job, Mark was hooked. So hooked that he decided to take a year off and apply to graduate school. So hooked that, when he was done with his PhD, he wasn't sure that he wanted to go back for his MD, he was having so much fun. By then he'd already racked up five first-author papers that would be published in journals like *Nature*—early studies on the origins of autoanti-

bodies that are still widely cited.

But go back to med school he did. His dad, among others, convinced him that being an MD/PhD would help him in the field he was so in love with, autoimmune disease research. ("And I was right!" says Seymour.)

When it came time to pick a clinical specialty, the study of blood, and all of the secrets it tells on the immune system at work, appealed to Mark. "Transfusion medicine is immunology in action."

To date, his longest-running collaborator, actually, is not his brother, but Ann Marshak-Rothstein, PhD professor of medicine at the University of Massachusetts—she's been a "critical" partner, he says. They met at an autoimmunity conference when Mark was a PhD student. Marshak-Rothstein went up to Mark's mentor, Martin Weigert—"a brilliant scientist," she says, whose lab was among the first in the country that could efficiently sequence antibody genes. Marshak-Rothstein had isolated from autoimmune mice some cell lines that secreted monoclonal antibodies that reacted with the mouse's own immunoglobulins, something that only happens in disease. She thought that sequencing could reveal a lot about the origins of the antibodies. She pitched the idea to Weigert at the meeting, but his plate was full, and he had to turn her down.

"But about 15 minutes later, Mark walked over and said, 'Just send me your cell lines. I'll sequence them,'" she recalls. It turned out to be worth everyone's while—to the tune of a *Nature* paper (1987).

The monoclonal antibodies, or rheumatoid factors, were the same sort that circulate in the blood of a mouse model of lupus, as well as in people with lupus and rheumatoid arthritis. After completing medical school and residency, Mark worked again with Weigert, this time to create a mouse with B cells only expressing rheumatoid factor receptors. The result was an ideal setting for studying the molecular play-by-play of a self-destructing immune system in the throes of lupus. Thirty years later, Mark and Marshak-Rothstein are still using the model for their studies.

In autoimmune diseases, the body is attacked by various stripes of autoantibodies, which might be thought of as specialized "heat-seeking missiles." Patients with lupus produce autoantibodies that attack DNA and RNA, we've long known, but the reasons why have eluded scientists. Of the hundreds of thousands of proteins and different molecules in the human body, why were DNA and RNA the preferred targets of the self-reactive B cell response in lupus? Although DNA and RNA dwell in cell interiors, they are constantly released from dying cells; many thought the link to cell death was important.

In 2002, Marshak-Rothstein and Mark Shlomchik unraveled this mystery. B cells that bind to immune complexes that contain RNA and DNA get an extra boost because of another class of receptors, called toll-like receptors (TLR), that can recognize either DNA or RNA. TLRs play a critical function by helping the immune system recognize DNA and RNA from bacteria and viruses—scientists used to think they could only recognize these pathogens. However Marshak-Rothstein and Mark discovered that DNA and RNA–specific B cells can use their surface receptors to bring these nucleic acids inside them, where the TLRs reside, to activate the TLRs. Once the B cell surface receptors are activated, the B cell goes turncoat, making antibodies to a patient's (own or "self") DNA and RNA, eventually leading to lupus.

This was big B cell news. Scientists had always assumed a B cell could only activate this self-destruct mode if signaled to do so by a T cell, but now it was clear that wasn't the case—the TLR could do the job, provided that the B cell recognized either DNA or RNA. B cells and T cells can either act alone or egg each other on in a vicious cycle, Mark and Marshak-Rothstein believe.

In 1994, in his first paper at Yale, Mark showed that B cells were far more insidious in lupus pathogenesis than anyone had ever imagined. Everyone thought they made DNA-targeting missiles (which turned out to be correct). But Mark showed there was another role that's probably even more important: B cells recruit T cells to kill host cells outright; these TLR-activated B cells could be the missing link to explain how both B and T cells get activated to cause lupus.

Since his arrival in Pittsburgh, Mark has initiated work on a new project funded by the inaugural Lupus Insight Prize, which he received in June 2013. Scientists had postulated that a factor (an enzyme called NADPH oxidase) could lead to inflammation and perhaps promote lupus. Mark's lab turned this notion around, revealing that a mouse model of lupus was actually highly protected from lupus by the enzyme.

He then recognized that women who lack the factor in half of their cells (it typically shows up in all of our cells) have a 10–20 times higher risk of getting autoimmune diseases. Subsequently, other labs have shown that having any one of a large series of relatively rare mutations in the gene that codes for the factor also increases the risk of getting lupus by a substantial margin. The $200,000 award will enable him to further probe his lab's findings in hopes of revealing new therapeutic targets.

Mark's focus on B cells in lupus has also driven him to investigate normal B cell immune responses, which are required to clear bacteria and viruses and for vaccines to work. Particularly intriguing in this regard are "memory" B cells that have responded to a vaccine, then live on, waiting to protect the vaccinated person if he or she should ever encounter the real virus that is the subject of the vaccine. Mark is now working to define the various subtypes of memory B cells. He also has a new project on B cell activity in infectious diseases, specifically influenza and salmonella.

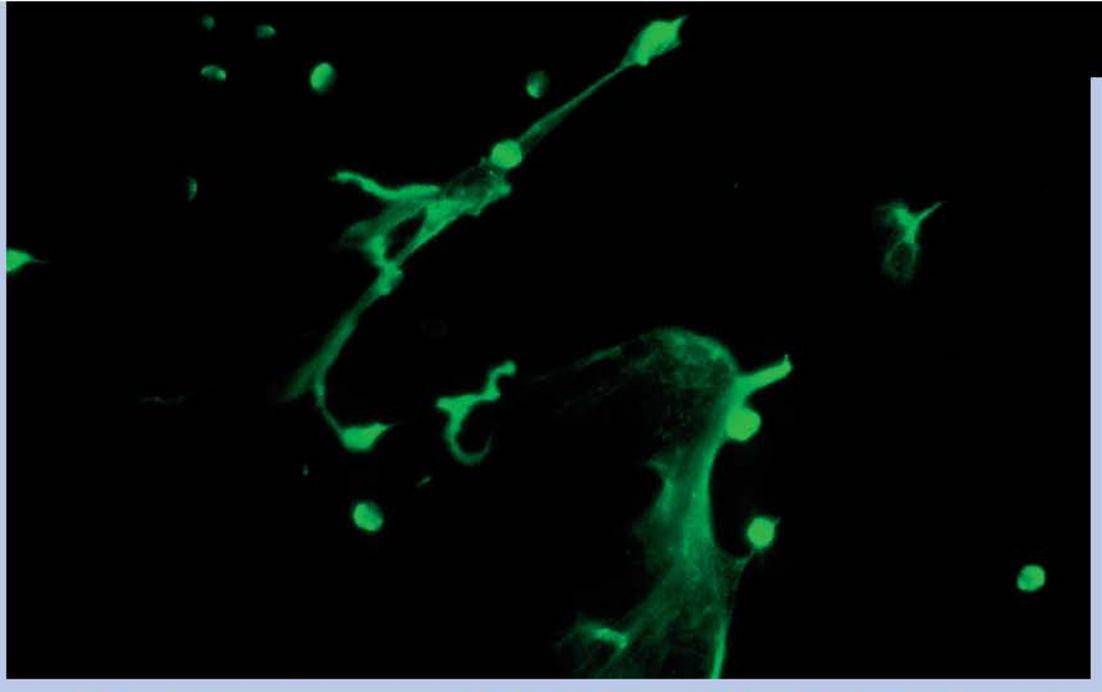
Mark is well-known for investigations like this—he'll often create new mouse models that enable him to figure out the roles of various autoimmunological minions. Some drugs that can be used for autoimmunity have been inspired by his studies of lupus in mice.

Oh, and did we mention that for the better part of the last 15 years, Mark has collaborated with Warren on his graft-versus-host disease work? Ask him about it, though, and he'll redirect you to his brother.

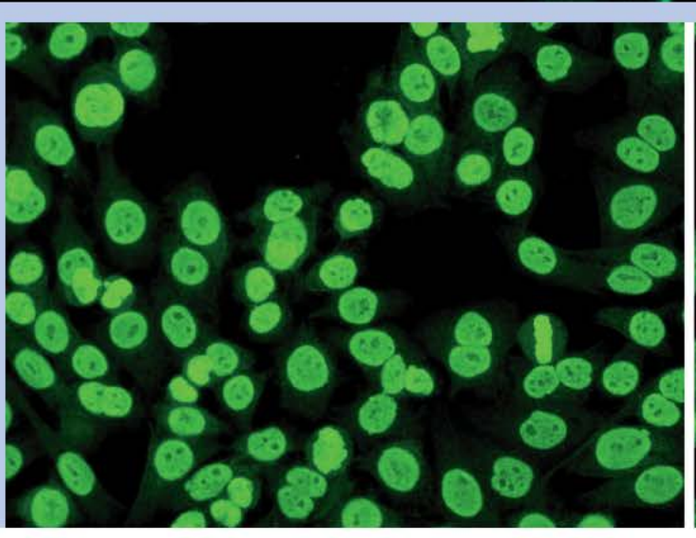
Similarly, if you ask either Shlomchik about their paper (*Immunity*, 2005) on Langerhans cells (immune cells in the skin), which they wrote with an MD/PhD mentee named Dan Kaplan, they give the credit to Kaplan. "I have a policy that when people do great stuff in my lab, they get to take that with them," says Mark. "Spawning new people is a big part of what we do." (Kaplan, he adds proudly, now has an endowed professorship at the University of Minnesota.)

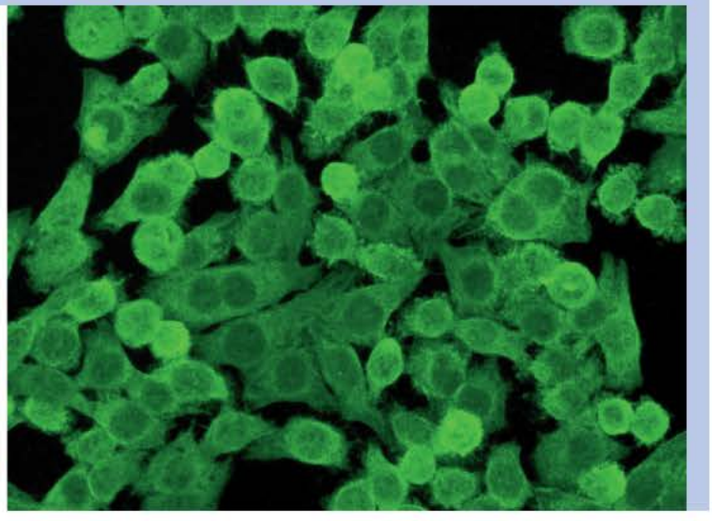
Needless to say, Mark has a broad repertoire—which will serve him well as chair, says his brother: "Mark knows a lot about a lot of things. He always has. Going back to reading the encyclopedia when he was growing up."

Among those excited to see Mark accept the chairmanship were Pitt's David Rothstein (no relation to Marshak-Rothstein), Pittsburgh Steelers Professor of Transplantation and MD professor of surgery, of medicine, and of immunology; and Fadi Lakkis, Frank & Athena Sarris Professor of Transplantation Biology as well as MD professor of sur-



TOP: A neutrophil (DNA in green) sets a trap known as a NET—wisps of nuclear material thought to ensnare pathogens. Allison Campbell, a student in Mark Shlomchik's lab, wondered whether, in the case of lupus, the presence of NETs might stimulate the immune system to attack its own DNA. Surprisingly, lupus-prone mouse models lacking the Nox2 gene (which allows them to create NETs) not only got lupus, but their cases were worse. BOTTOM: Blood cells from mice with lupus (left) have DNA-killing autoantibodies (green) in their nuclei. Blood from mice with lupus that lack Nox2 (right) glow mainly from their exteriors instead. The NETs and Nox2 actually protected the mice from the disease.





gery, of immunology, and of medicine, and scientific director of the Thomas E. Starzl Transplantation Institute. Both were recruited from Yale, like Mark (in 2009 and 2005, respectively).

At Yale, says Lakkis, Mark functioned very much like immunobiology was his primary appointment. (It was actually secondary; his primary appointment was laboratory medicine.) "He did things," says Lakkis, "that took a lot of effort to advance everybody's work in the department."

Like completely reorganizing a centralized flow cytometry core, notes his brother.

"He's a *doer*," says Rothstein.

Mark led the charge to renovate his department's space on the 10th floor of Pitt's Biomedical Science Tower East. (So far half of the floor is finished, and it's beautiful: an open-plan lab, separate office space, and lots of light throughout. "They actually cut extra window holes into the building," Mark says.)

Another Pitt example: Mark's faculty recruitment campaign since coming here. "Everyone nationally has noticed that as Mark was first setting foot here, he was already signing a very, very prominent researcher," says Rothstein. (That prominent researcher is Dario Vignali, a PhD, Pitt's new vice-chair of immunology, and UPCI's coleader of cancer immunology and of its Tumor Microenvironment Center.)

With Mark's Lupus Insight Prize in hand—and his lab now up and running in the clinical research powerhouse that is Pitt/UPMC—he's eager to take the insights he's gleaned from studies of basic biology in the lab and test them out in the clinic. He finds the prospect exciting, but it's a new area for him.

"How you do really effective human research and get insight into human diseases is not trivial. Thinking about it is humbling," he says. "There's a number of people who do this very effectively at the School of Medicine, so I'm hoping to learn from them."

On a warm afternoon in August 2014, in the student union of Pitt-Greensburg, which is about 35 miles from Oakland, students trickle in and out of the dining hall past a table with a banner that reads BE THE MATCH—promoting participation in the national bone marrow–donor registry.

Throughout the day, some 34 Greensburg students step up to dab the insides of their cheeks with cotton swabs; their DNA samples will be sent to a central lab in Minneapolis for processing. About one in 100,000 of such registrants matches up with a patient in need of a transplant who has no donor match within the family—as is the case about 70 percent of the time. Typically used in patients with leukemia, lymphoma, or aplastic anemia, this type of transplant is not without significant risk to the recipient; however, it is a chance for the patient to be cured.

"There's a lot of explaining," says Grace Huber, a community engagement representative for Be The Match. People commonly call it bone

marrow donation, but more precisely, it's a donation of hematopoietic stem cells, which come from bone marrow only 25 percent of the time. The rest of the time, the stem cells are harvested from circulating blood. (In this context, "stem cell" means immature blood cells—not embryonic cells.)

The field of stem cell transplantation is specialized, and there's a lot to explain—even when the person who walks up to her table happens to be an MD, says Huber. "They just don't know—unless [the person] happens to be a transplant doctor."

A doctor like Warren Shlomchik.

The same back-to-school week as the donor registry drive in Greensburg, the younger Shlomchik brother talks with this writer via phone, breaking for coffee while on clinical rotation at Yale-New Haven Hospital. He is a professor of medicine and immunobiology at Yale and codirector of the Yale Cancer Center's program in Cancer Immunology until March 2015, when he moves to Pitt.

Part of the original rationale for stem cell transplantation was to allow patients to receive high doses of chemotherapy/radiation therapy so as to kill leukemia cells that survived less intense treatments. These high dose therapies would, unfortunately, also kill the patient's normal blood cells. This toxicity could be "rescued" by giving donor blood stem cells (originally harvested from bone marrow) that were free of leukemia cells. However, even the earliest practitioners of this once exotic therapy recognized that immune cells (later revealed to be T lymphocytes or T cells) from the donor could attack patient's leukemia cells, Warren explains. "This was recognized in mouse experiments done in the late 1950s."

So with the transplanted cells, the patient receives immunosuppressants—not primarily to keep the body from rejecting the donor cells, as you might expect, since that's how it usually works when a patient receives a donor organ. In stem cell transplantation you're also trying to keep the transplant—the new immune system—from rejecting the body. This deadly complication, also caused by T cells, is known as graft-versus-host disease (GVHD).

Unfortunately, immunosuppressants leave patients vulnerable to infection. Nearly half of all deaths among transplant recipients are largely caused by GVHD and the consequences of immunosuppressive drugs used to prevent and treat it, notes Warren.

Warren followed a somewhat winding career path. As a college sophomore, a biochem major, he worked in a lab that studied gene expression in flies—at least partly for med school applications, at first. Yet Warren found he liked research so much he took a semester off from school to stay in the lab. Developmental biology fascinated him: hormones altering destinies, cell lines reinventing themselves. By then, the undergrad who'd always pictured himself as purely a clinician, like his dad, realized he wanted to do that *and* be a basic scientist.

Again, blood was a compelling story for a Shlomchik brother; Warren now practices hematology and oncology.

"Forming the different types of blood cells requires differentiation, very akin to what my interests were in college. . . . And likewise, cancer is an example of development that has gone wrong." He adds that some subliminal influence likely stemmed from his mother, as well—Marlene Shlomchik died of breast cancer his senior year of college.

After Warren graduated from medical school at the University of Pennsylvania, he did an internal medicine residency at Cornell/New York Hospital, then returned to Penn for a hematology/oncology fellowship (after a year as an emergency medicine doctor). His first year into fellowship, he read a paper in *The New England Journal of Medicine* that changed everything for him.

It was a series of bone marrow–transplant cases. The patients' leukemia returned even after their transplants—however, the patients were successfully put back into remission after receiving white blood cells from their donors. "I thought that was pretty amazing," he says. Some of the patients ended up with GVHD, however.

Though at this point Warren had planned to enter a lab that studied blood-cell differentiation, he altered his course. The idea he had at the time was to put a gene in the donor T cells that would allow them to be killed if GVHD developed. Warren learned from Mark that there were mice that expressed a "kill gene" in specific subsets of T cells, and together they began pursuing this approach in mouse models of GVHD in Mark's lab at Yale and in Stephen Emerson's lab at Penn. Warren also began working on putting a kill gene into the T cells, though by this time he learned that several other groups were fairly far along on this idea already.

Before working on this mouse model, the only immunology experience Warren had was the single course he'd taken in med school almost a decade prior. He and a close friend at Penn, who also was entering an immunology lab, together began teaching themselves immunology. Fortunately, throughout these self-directed studies, whenever Warren had questions, there was Emerson. And, well, he knew this other guy.

"My brother was very much my mentor," he says. "He had vast knowledge and experimental approaches and techniques."

The GVHD model was one of many collaborations to come between the brothers.

Warren's first big splash in GVHD started as a side project while he was still a postdoc. It had to do with antigen-presenting cells. These APCs, as they are called, take up pathogens, or cells that have been infected, and present them to T cells. In this way, the APC sort of alerts the immune system about undesirables (viruses and the like) in the neighborhood.

That's how it's supposed to work, anyway. But in the case of GVHD, stem cell recipients end up appearing to their own immune systems as though they have an infection in every cell.

Warren studied a class of donor cells, called CD8 T cells, that were known to cause GVHD. However, no one could say for sure just whose orders these cells were acting on. Were they getting their intel from the APCs derived from the donor's cells or from the recipient's? Warren's work suggested it was the latter—the hematopoietic-derived host APCs. These unexpected findings ran in *Science* in 1999.

"I would call it a paradigm shift," says Pavan Reddy, an MD who is the Moshe Talpaz, MD Professor of Translational Oncology at the University of Michigan. "[Warren] did some really creative experiments. Nowadays everybody does them; but back then, they were quite creative."

Reddy and Warren are close colleagues, and competitors, in the way you have to be when you're in such a small field. But the relationship smacks more of sibling than of rivalry. In 2006, Warren helped Reddy reshape a section of a grant application that hadn't gone over well with the reviewers. The edits ultimately got Reddy his first grant from the National Institutes of Health. ("As it turned out," Warren says, "Pavan has developed into one of the very top few investigators in our field who is translating his discoveries to the clinic. He certainly no longer needs help from me!")

Many years ago, Reddy, then a postdoctoral fellow, walked up to Warren at a national meeting and said something to the effect of,

So, you've come up with three of the most important ideas in stem cell transplant medicine in the last five years. What other ideas do you have?

Warren laughed and said, *Well, I'm not going to tell* you*!*

That "paradigm-shifting" *Science* paper, of course, tops Reddy's list of 3. Number 2, which also made ink in *Science* three years later, was Warren's collaboration with Italian scientist Andrea Velardi. They showed that natural killer cells—immune cells that had been known to destroy both leukemia cells and antigen presenting cells—could also be deployed to reduce GVHD in both people and mice.

And number 3? That's become something of an epic feat—a finding first reported 11 years ago that's finally made it all the way from the bench to the bedside.

The study has to do with T cells. Typically, in a cancer patient, T cells are transplanted from donors along with the donor's stem cells. The T cells promote engraftment, aid in reconstituting the immune system, and kill cancer cells. Unfortunately, they also cause GVHD.

When Warren first moved to Yale in 2000, he wondered whether different types of T cells behaved differently in GVHD. Would memory T cells—which develop from T cells that respond to infections and then stick around to protect you forever—respond differently from naïve T cells, which had never encountered infections of any kind before?

Working with their mouse model of GVHD, Warren and Mark discovered that memory T cells caused less GVHD but could transfer immunity from the donor to the host. The brothers published their findings in *The Journal of Clinical Investigation* in 2003. In subsequent work Warren showed that donor memory T cells could also mediate the graft-versus-leukemia effect (in which donor cells recognize leukemia cells and destroy them) and could transfer immunity to viruses from the donor to the host.

Warren and his collaborators at the Fred Hutchinson Cancer Research Center in Seattle (a.k.a., "the Hutch"), funded by a grant to Warren from the NIH Rapid Access to Intervention Development program, worked with a biotech company called Miltenyi to develop a way to get rid of the naïve T cells, leaving behind only memory T cells. The goal was to administer these memory cells along with stem cells during transplantation, sans naïve T cells. With funds from the Clinical Scientist Award in Translational Research, which Warren received from the Burroughs Wellcome Fund in 2007, and an NCI project award granted to researchers at the Hutch led by Stanley Riddell, an MD, the team is wrapping up a pilot trial of about 48 patients. Warren stresses that the Hutch team has done much of the work, notably MD/PhD Marie Bleakley: "She has been amazing."

The results so far are promising, Warren reports. The group will begin a larger-scale, NIH-funded clinical trial in Seattle and Pittsburgh in 2015.

Reddy is psyched about the possibilities, should this approach pan out: "You don't have to tinker with cells, you don't have to add a new drug. . . . You could get all the benefits without the downsides."

Immunosuppressants are a cruel irony in solid organ transplantation, too. The very medication that keeps the body from rejecting its life-saving organ can also open the door to both infection and cancer. Because stem cell transplantation is a rebirth of the immune system—really, a sort of resowing of the donor's immune system in the recipient's body—Starzl Institute investigators have been following Warren's work with interest. "If you're able to [safely] give a bone marrow transplant," says Pitt's Lakkis, "then you can turn around and transplant organs from that same donor without having to give any immunosuppressant.

"This is the most promising strategy for tolerance."

Lakkis and Rothstein have been collaborating with Warren since 2001—and have been lobbying to bring him to Pitt for years. Working together has been illuminating for all involved, as their fields face many of the same questions—because organ rejection and GVHD are mirror images of each other. Remember, in the former, the body rejects and attacks the organ. In the latter, the new cells reject the body.

The Yale/Pitt team has studied both processes at their most fundamental levels, using a powerful imaging tool called intravital two-photon microscopy—a window into the cellular doings within the living animal in real time.

Another reason Rothstein and Lakkis are counting down to Warren's arrival is the opportunity to witness the signature Shlomchik Brothers Brainstorm again. They're famous for this: Dispassionately scrutinizing every bit of the data, and then stepping back and seeing the big picture. Spotting the holes in the logic and then laying it all out, no hemming and hawing. Just: Here is *the* killer experiment you need to do to nail down the story.

Says Lakkis, "They'd come into your lab meeting, listen to your fellows' presentations, and say, 'Oh, why are you doing *that* experiment? Why not do this instead?' They will tell you that. And it will completely transform your work. But at the same time they've become good friends with people. . . . Very generous with mice, reagents, with ideas. There's no scheming. Just critical thinking."

"If you're able to [safely] give a bone marrow transplant, then you can turn around and transplant organs from that same donor without having to give any immunosuppressant. This is the most promising strategy for tolerance."

And then, says Rothstein, they'll check up on you: "When you go back to either of them months later, they remember exactly where you left off. It's like, *Okay, did you do that experiment?* They're both very much that way; just very, very bright."

"Pitt was pretty lucky to get both of them," says Reddy. "[In] the immunology world and the transplantation world, they're clearly superstars."

When Mark won the Lupus Insight Prize, his father flew up from Florida for the big event and took everyone out to dinner.

That night, and the night Mark won a clinical award from the Lupus Foundation 10 years earlier, Mark went up to the mic to receive his prize, and said, "This would not have been possible without the support of my father." Warren says he feels the same way about what he's been able to accomplish.

It's another classic move in this family—the Shlomchik credit-share. Toasting your progenitors. Paying it forward to your brethren. And to the new blood. ■

Daniel Kietz tries balancing with Julianne as he checks on her muscle strength and coordination in July.

A DOCTOR WITH "HIGH TOUCH"

IT'S THE LAST DAY OF SCHOOL AND THE 11TH NIGHT IN THE HOSPITAL

STORY AND PHOTOGRAPHY BY ELIZABETH ANNE MAY

It's not the last day of school we wanted. No ice cream social at the neighbor's to commemorate the start of summer. No Silly String celebration at the bus stop. Instead, I pick my 9-year-old up straight from school.

As she hugs friends, teachers, and the school secretary goodbye, we realize this day is a big deal. It's her last day of third grade and her final day at this school. Next year, she moves up to the big fourth- to sixth-grade elementary.

Today also marks the 11th night my daughter will spend in the hospital. The 12th time in the past 18 months she'll have an IV inserted. The 11th time she'll receive intravenous immunoglobulin. The 20th time she'll be treated with pulse steroids.

The milestones for me are less dramatic: It will be the 11th night I get to sleep fitfully on a hospital foldout, waking what feels like every few minutes to the symphony of beeps and vibrations and chimes of monitoring alarms. It will be the 11th time I am convinced I know everything there is to know about the hospital stay and find out I am wrong. It will be the 11th time I leave the hospital feeling confident I am not tired, only to find out the opposite the minute I walk through my front door.

Quiet pervades the admissions suite at Children's Hospital of Pittsburgh of UPMC when we arrive—not much going on here on a gorgeous June Friday at 4:30 p.m. After we're all checked in, the woman working the desk looks at me shrewdly: *You don't need an escort?*

Our records have given us away.

A few moments later, Julianne and I roll past the security guard near the inpatient-floor elevators like the pros we are. It's a dubious honor, to be this familiar with a hospital.

My daughter is one of a relative handful of children with juvenile dermatomyositis (JDM), a somewhat mysterious inflammatory muscle disease related to autoimmune dysfunction. In JDM, the immune system sets off an inflammatory response in the body's blood vessels. Two or three children per million have the disease.

JDM shows up in two key ways: a distinctive rash and weakness. The pinkish-purple heliotrope rash can appear on the eyelids, face, hands, and around the joints. Muscle inflammation causes fatigue: weakness near the body's trunk (thighs, upper arms, neck) and the torso itself.

There is no known cure for JDM (though we families hope for remission), and no one knows for certain what causes it. Experts speculate that genetic predisposition, along with an environmental trigger, can activate JDM. We certainly match the hereditary description, with autoimmune diseases on both sides of the family, including lupus, polymyalgia rheumatica, and psoriatic arthritis. (Even our dog has immune-mediated hemolytic anemia; Jasper has been in remission for the past few years. Our human family members have not been so lucky and still need medication to control their symptoms.)

While we can't know exactly what clicked Julianne's autoimmune system to this aggressive "on" position, getting it to switch off has proven elusive.

As the golden light of the late afternoon filters through our window in Unit 7B, I bustle around—getting Jules settled into her hospital bed, seeing if there are linens or pillows for me stowed in the cupboards, figuring out where the family pantry is and putting away our little insulated bag with favorite foods from home, and generally organizing myself for the long night ahead.

It's a mom thing, wanting to feel helpful; and in the hospital—and with this disease—I feel powerless.

It won't be long before we see Dr. Kietz, clinical director of the Division of Rheumatology, director of the hospital's rheumatology fellowship program, and an associate professor of pediatrics and medicine in the School of Medicine. A slim, neat man with slightly graying hair, glasses, and a faint German accent, Dr. Kietz always greets us with a smile, a handshake, and a little head bob, almost like a tiny bow. He'll examine Julianne, listen intently to our questions, ask us how things are going. He'll stay as long as it takes to answer everything—without a hint of impatience—laughing off my apologies. *I know I should let you go now,* I say, *but I just have one more question . . .*

The residents often scare us when they check in: *Who knows*, they say as if it's a long shot, *Dr. Kietz might stop by.* And my heart drops. What if he can't make it?

I should know better. We could be here on a Monday night or a Friday night, and Dr. Kietz is always here. It could be 6 p.m. or 9 p.m. or 8 a.m., but he shows.

The first time we met him, in the rheumatology clinic in October 2012, he immediately gravitated to Julianne, kneeling so he could be at her eye level, speaking with kindness and concern. He said: *I know you feel bad, and I know you're probably worried, but we're going to figure out what's going on and get you feeling better again*.

We ended up in his clinic a short two weeks after I first called our pediatrician, Stephanie Sussman (Res '11), with a perplexing set of symptoms. Feeling foolish, I said: *I'm calling about two unrelated issues. First, my daughter seems depressed. Second, she gets up off the floor funny.* I went on to explain how my then-7-year-old daughter seemed vaguely lethargic and unhappy, though she couldn't tell me why. I talked about how she got up off the floor like an old lady, turning around, getting on her knees, and slowly, almost arduously, pushing up to stand—yet, she said nothing hurt.

Dr. Sussman had us come in for an exam. The blood work she ordered put us on the fast track here. The markers that appeared in Julianne's blood painted a picture of significant inflammation.

My husband and I came to Children's armed with notes: Julianne was running a slight fever every day. She woke up tired, even after 12 hours of sleep. She couldn't sit "criss-cross applesauce." Climbing in and out of our low-slung van had become an issue.

Dr. Kietz examined Julianne. He looked with particular interest at the tiny, red-dotted rash at the base of her fingernails and at her eyelids (where we saw nothing unusual). He rubbed his thumbs across some faint red patches on her knees and elbows. He had her push her weight against his with her arms and legs.

Only about 15 minutes into the appointment, he gave us the diagnosis. We were shocked. We expected more blood work, additional tests, time to prepare ourselves. Dr. Kietz had seen this disease often enough to know its signs well. An MRI would later confirm his diagnosis.

He went on to explain the disease, the treatment, the prognosis. And, though we understood the potential outcomes—the disease course could run chronic; could be on-again, off-again, with flares or relapses; or could go into remission—the uncertainty fell hard. The intense path of treatment we would have to follow took weeks to really sink in. Dr. Kietz recommended a treatment plan of inpatient infusions once a month every month for seven months.

And, now, on this June day in 2014, we have been there and done that. From October 2012 to April 2013, we paid our dues in full with monthly hospital overnights. We expected to be done or, at the very least, progressing. It seemed we were—our girl was

Julianne at a dance recital. When she came out of remission earlier this year, her treatments allowed her to tap across the stage.

suddenly able to ride a bike without training wheels. And now, a relapse.

A light knock at the door interrupts my thoughts; the IV team is here. She's an ace, this nurse, and takes her time, looking for a nice, juicy vein. She offers Jules some freezy spray to help numb the arm. We say, *Why not? Let's try it.*

Another knock, and Dr. Kietz peeks in. I smile as he greets me and Julianne. *You can see I have no pull here,* he says in mock apology, gesturing to our view of a brick wall, instead of the picturesque Allegheny Cemetery or the city views our windows usually frame.

Next thing I know, he's rolling up his sleeve and grabbing the bottle of freezy spray we just told him about. *Watch as I heroically demonstrate on myself,* he says, and sprays the inside of his forearm. *Here, touch.*

I laugh and feel. It's cold.

In early April, when Julianne's JDM symptoms came raging back, she sat on the couch and cried. She knew exactly what would happen this time, and she dreaded it. She didn't want to go back to the hospital; she was especially nervous about the IV. She didn't want to feel weak and tired and miss school constantly. She didn't want to have to sit out gym or not play tag with her friends at recess. She didn't want to have to explain when her curious classmates asked, *Why?*

I didn't want to go back either. I wasn't ready for Plan B, because I liked Plan A: weaning Julianne off steroids and then, slowly but surely, lowering her once-weekly maintenance med (methotrexate) until she could quit it completely. The plan was remission with medication—and then remission without. The plan was *not* going back to a series of six hospital overnights, twice-daily steroid doses, once-a-week injections, plus a new medication. No thank you.

I sat next to Julianne on our worn chenille couch and said what I was supposed to say: I said I'd be there with her. I said we knew how to do this hospital thing now. I said she was so brave; the IV didn't even bother her anymore. I said it wasn't fun, but we had to do this to get her feeling better again.

I'm not sure what else I told her, but, mostly, I wasn't even buying it.

This evening, at the hospital, Dr. Kietz asks us if we want to walk down to the little overlook area on 7B; it's a favorite of his. It gives him a chance to see Julianne's gait and for us all to chat.

As we gaze out over the streets of Pittsburgh's Lawrenceville neighborhood (where Julianne's grandparents and great-grandparents grew up), Dr. Kietz muses about how the city comes alive in summer. *When the weather warms up,* he says, *everyone comes outside again. There are block parties and festivals—always something going on.*

He notices.

It reminds me of something nonfiction author Daniel Pink says. Pink tells us success in today's world depends not only on scientific or technical know-how but also on authenticity, connection, and creativity.

We long for someone to come along and do a job with excellence and empathy.

Pink calls this "high touch"—the ability to understand the subtleties of human interaction, to find joy in oneself and elicit it in others.

Tonight, we three stand still for a moment, here at this busy hospital. It's a place I've always assumed I'm unlikely to find joy and beauty and meaning, a place I rush to get into and out of as quickly as possible so we can get on with the rest of our lives. And I wonder if I've gotten it wrong.

Look! Dr. Kietz calls. He's noticed a little girl down below, twirling on the sidewalk. The tiny braids all over her head fly out, and she is dancing, spinning, a neon-orange blur of brief, pure, concentrated joy. ■

DOCTORS NEEDED

Kids with rheumatic conditions can log a lot of miles for care. A 2007 Department of Health and Human Services report to Congress notes that children with rheumatic diseases must travel an average of 57 miles to see a pediatric rheumatologist; the average is 25 miles for many other subspecialties.

Arthritis and other rheumatic conditions affect more than 300,000 children in America—making them among the most common childhood diseases—yet only about 300 pediatric rheumatologists currently practice in the United States. Many states have only one or two board-certified pediatric rheumatologists; eight states have none.

But Daniel Kietz, an MD/PhD—among the first recruits of Children's fledgling rheumatology service in 2003—has seen the landscape change dramatically in Pittsburgh. "Patients used to wait months to get an appointment," he recalls of the program's early days. "Now, we promise new patients an appointment within 72 hours." Children's division has seen exponential growth; it's now one of the country's most robust programs, with five full-time faculty members, basic and clinical research programs, a fellowship program, and a dedicated rheumatology social worker.

Kietz heads his division's three-year, ACGME-accredited fellowship program, which takes aim at the nationwide pediatric rheumatology shortage. The program boasts a National Institutes of Health–funded training grant exclusive to pediatric rheumatology and has trained 14 fellows to date. —*EAM*

CLASS NOTES

'60s

As a high school basketball standout, **Don Hennon** (MD '63) was heavily recruited by colleges around the country. But Hennon had "visions of becoming a doctor" and only visited universities with medical schools. Along with a litany of other statistical superlatives, Hennon holds the Pitt record for most points scored in a game (45) and is fourth on the Panthers' all-time scoring list, despite not playing his freshman year. His 40 years of working as a general surgeon in Franklin Park, Pa., were well worth turning down the NBA for an MD, he says. Now "retired," he divides his time between physicals for military recruits, a Bruster's Ice Cream franchise, and a cattle farm that he bought on a whim in 1985. Still the consummate competitor, he won Premier Breeder at the Pennsylvania Farm Show from 2005 through 2011.

'70s

Daniel Postellon (MD '70) says his career in pediatric endocrinology felt sort of like half-molecular biology, half-psychiatry. "You have to know a lot about how things work, and then convince [diabetic] teens to follow the rules and keep themselves healthy." The former associate professor of pediatrics and of human development at Michigan State University published mostly on diabetes and on congenital hypothyroidism, a preventable cause of intellectual disability. He helped to evaluate the blood test for it that's still part of routine newborn screening today and lectured widely on screening and treatment program implementation.

Since retiring in July 2013, Postellon has pursued sculpture full time in a small aluminum foundry he built in his backyard. This summer, he spent a month in Latvia creating a commissioned piece of public art as part of the Iron.Stone Symposium and Exhibition. "Sekimori Ishi" is his own take on a kind of ancient Japanese "Road Closed" sign—a stone-and-string marker one might find placed along a path. Postellon's version, measuring 5 feet tall and weighing 5 tons, has a bit more gravity—one interpretation, he says, is that it reminds us to stay on the right path. (Recently, a former patient, now in his 30s, emailed to thank Postellon for keeping him on track.)

Postellon with his sculpture, "Sekimori Ishi," in Latvia.

In August, **Dennis English** (MD '76), vice president of medical affairs at Magee-Womens Hospital of UPMC, launched a first-of-its-kind program for pregnant women with substance abuse challenges. In addition to prenatal care and delivery, the Pregnancy Recovery Center also provides comprehensive services to prevent withdrawal, minimize fetal exposure to illicit substances, and support recovery through counseling. "We are in a collaborative effort with other care providers and insurance companies to help improve these situations for the babies and the mothers," he says. With the coordinated efforts of these partners, which include UPMC, Gateway Health, and United Healthcare for Families and Communities, "the [chance] of recovery is quite high, especially because the pregnancy motivates the women," he says.

'80s

Seattle's International Community Health Services (ICHS), a federally qualified health center, is one of only about 10 such clinics in the country that primarily serve Asian Pacific Islanders (though all patients are welcome). "We've opened two new clinics this year," says assistant medical director **Kimo Hirayama** (MD '86). He began volunteering there during his internship and residency at Group Health in Seattle, back when ICHS was a small storefront clinic. "Our organization saw 16,000 medical patients for 56,000 visits in 2013." More than half of the health center's patients are below the federal poverty level, and some 75 percent have a language barrier. The clinic bills on a sliding scale, and much of the work is uncompensated. But, he's pleased to report, "With the Affordable Care Act, we see more patients who are able to finally get the care they need."

Hirayama

'90s

In the clinic, **Alexander Norbash** (Diagnostic Radiology Resident '91), professor and chair of Boston University's radiology department, specializes in interventional neuroradiology. In his research, he's focused on creating new ways to improve the patient experience, as well as tools for surgical instruction. "I personally believe that creativity and teaching are two innate drives," he says. He began teaming up with engineers early in his career, designing devices and materials for use in patients with vascular disorders of the brain, spine, head, and neck. Among other inventions, he's developed a treatment for surgically created aneurysms, a nonchemical method for stroke thrombolysis, and a resorbable polymer stent. He also worked with a team that developed endovascular and interventional simulation systems to give new surgeons a safe, hands-on way to practice these delicate techniques.

Jerome Gloster (MD '92) is a man of many hats, including medical director, chief medical officer, and supervising physician of the North Side Christian Health Center in Pittsburgh. And as of this year, he's also an ordained minister. He's a passionate advocate for improving care for underserved populations. "With poorer patients, because they have the worst outcomes with chronic disease, they are really looking at community health centers; and those of us who see these patients strive to become a resource for them." In addition to providing primary care, the center also provides transportation to appointments and helps with the cost of medications. Gloster has grown frustrated with the business-like approach to medicine in this country, he says, and is eager to put the focus back on patients.

'00s

The widely held assumption about rib fractures is that there's nothing you can do for them—besides go home, take some pain meds, and wait for them to heal on their own. However, says **Andrew Doben** (MD '04), assistant professor of surgery at Tufts, "getting better and having a rapid recovery are two very different things." He adds that, given the debilitating pain, risk for opioid addiction, and lost wages that can come with these injuries, "rapid" should be the goal. In 2010, Doben colaunched what's become one of the country's largest programs for rib fixation, as the surgical fix is called, as well as a multidisciplinary effort around it to address these patients' unique pain-management and rehabilitation needs. He says patients are coming in from as far away as Colorado to receive this unique care, though he's doing his best to make it more commonplace. In the June 2013 issue of *General Surgery News*, he coauthored an inter-

national consensus statement on integrating rib fixation into clinical practice.

Once a basic science finding proves worthy of moving to a clinical trial, a whole new hurdle awaits: finding patient volunteers who meet the study's criteria. Usually, researchers rely on their IT departments to create database reports, which can take months. But **Andrew Post** (PhD '06), assistant professor of biomedical informatics and clinical informatics architect at Emory University, has developed a better way, dubbed Eureka! Clinical Analytics. The open-source software cuts out the middle meta-analyzer, allowing scientists to do their own searches. In 2013, his *Journal of Biomedical Informatics* paper on the software, which is now in a test-driving/fine-tuning phase, got a nod in an annual roundup of best articles from the biomedical informatics literature.

You may recall two bioterrorist attacks in the United States since 1945: salmonella in 1984 and anthrax in 2001. Two attacks in all that time isn't bad, you might say. However, "the question is, are you prepared for this? Not how frequently [do] these things happen," says **Amesh Adalja** (Infectious Disease Fellow '09, Critical Care Fellow '10), a senior associate at the UPMC Center for Health Security. It's not just terrorists and pathogen-spread that his office is concerned with, but also natural disasters. In 2010, following Haiti's devastating earthquake, Adalja traveled to that country on behalf of the U.S. National Disaster Medical System to see patients. In his down time, Adalja catches air. He's an avid skateboarder, as well as a heavy metal fan.

—Nick Moffitt, Zach Nichols, and Elaine Vitone

LYNN E. TAYLOR

LET'S ELIMINATE HEP C

Lynn E. Taylor (left) at WaterFire, a World Hepatitis Day event in Providence, in July.

The ever-widening epidemic of hepatitis C virus—the leading cause of liver transplants in the United States—has long been ignored and neglected, says Lynn E. Taylor (MD '97), assistant professor of medicine at Brown. This is partly because of its stigma, and partly because the real weight of it is just beginning to hit. Hep C has a decades-long dormant period before symptoms arise; and in the coming years, that clock will run out on the Baby Boomers, an estimated 1 in 30 of whom have the infection, according to the Centers for Disease Control and Prevention.

Yet Taylor is finding more reasons to be optimistic than at any other time in her 15 years of fighting hep C—both in the clinic, where she specializes in hep C/HIV coinfection, and in her research, where she's working to scale up hep C screening and treatment.

In her own institutions, Taylor has worked to meet the needs of these complex cases by educating students in Brown's med and public health schools about hep C, and by founding and directing the HIV/Viral Hepatitis Coinfection Clinic in Brown's affiliate, Miriam Hospital.

At the state level, in 2013, a grant enabled her to launch a three-year, $300,000 campaign to eliminate the disease in Rhode Island—a lofty goal, she admits. But she stresses it's time to begin framing the discussion in this way. The infection is indeed curable, though many people don't realize it.

In the last two years, the FDA approved the first pills for hep C treatment, which either greatly shorten or eliminate the need for the highly toxic interferon injections that were previously these patients' only hope (many of them can't tolerate interferon). She's now advocating for improved access to these meds, which cost upwards of $80,000 per course. Insurers balk at the price tag, but she's spreading the message that that's small potatoes compared to the alternatives: liver transplants and end-of-life care for 50- and 60-year-olds cut down in their prime.

"I've seen so many advances in the field of HIV," she says, "and to witness [the same progress in hep C] condensed into five years, I just have to pinch myself." *—EV*

MAA SAYS, "VICTORY LAP!"

Geller

David Geller (Surgical Intern '89, Surgical Research Fellow '94, Chief Surgical Resident '96, Transplantation Fellow '98) calls his relationship with Pitt a "25-year love affair," the first 10 years of which he was a trainee and the last 15 as a faculty member. And being named the William S. McEllroy awardee, the Medical Alumni Association's (MAA) annual recognition of a Pitt residency alum, has his heart all aflutter. "I'm very honored," he says.

Geller, Richard L. Simmons Professor of Surgery at Pitt and director of the UPMC Liver Cancer Center, has devoted his career to improving treatments for liver cancer. (Because of the spread of hepatitis C, primary liver cancer is on the rise—see our spotlight on Lynn E. Taylor, above, for more on the epidemic.) Traditionally, this notoriously bleeding-prone organ wasn't considered safe to operate on minimally invasively. But in the early 2000s, after perfecting his techniques on pigs, Geller brought them to the clinic—first for patients with benign liver cysts, then for patients with liver cancer. Today, about a third of UPMC's liver cancer procedures are done laparoscopically.

With this "Band-Aid surgery," patients are healing much faster, with less pain and fewer complications. And, as detailed in Geller's recent paper in *Surgery*, doctors now have long-term survival data to prove that outcomes are just as good with laparoscopic liver procedures as with open liver procedures.

To date, Pitt/UPMC has performed some 800 laparoscopic liver resections—about 10 percent of all cases worldwide. Geller taught the first course in the United States in 2004 and has since trained hundreds of surgeons around the world in these techniques.

Geller has also made notable inroads into the basic science behind liver cancer signalling, including the Wnt/ß-catenin pathway.

On November 5, Geller will give a lecture, lead grand rounds, and receive his honor at the McEllroy Award Dinner. *—EV*

MEDICAL ALUMNI ASSOCIATION WWW.MAA.PITT.EDU

EMMANUEL FARBER

OCT. 19, 1918–AUG. 3, 2014

"If it's not published, it's not data," read a plaque in the late Emmanuel Farber's office. As chair and professor of pathology and professor of biochemistry at Pitt from 1961 to 1970, the MD/PhD prodded colleagues to fundamental oncogenesis discoveries.

Farber

"He made major contributions in understanding the biology of cancer at a time when things like oncogenes … [were] not known or understood," says the current chair and Maud L. Menten Professor of Experimental Pathology, George Michalopoulos, an MD/PhD. Farber recognized similarities between cancer cells and liver regeneration that helped him describe the biochemical origins of tumors. He also served on the Surgeon General's first Advisory Committee on Smoking and Health, contributing to its 1964 report that helped establish the carcinogenic effects of tobacco use.

Called "the philosopher scientist" by colleagues, Farber emphasized a basic understanding of normal cellular processes rather than focusing solely on disease pathogenesis. "Sometimes you didn't agree," says Michalopoulos. "But he did not stifle you with his strong opinions."

Farber received the Rous-Whipple Award, among many other honors. After Pitt, he was director of the Fels Research Institute at Temple University. In 1975 he became pathology chair at the University of Toronto, where he overhauled their curriculum. Says his daughter, Naomi Farber, "My dad had this philosophy: Do something, give it your best, transform it, then move on." *—Robyn K. Coggins*

ALBERT B. FERGUSON JR.

JUNE 10, 1919–AUG. 20, 2014

Albert Ferguson, lovingly referred to as "Ferg," is something of a Pitt legend. "He was really a true gentleman," says mentee Freddie Fu, Distinguished Service Professor and chair of the Department of Orthopaedic Surgery as well as David Silver Professor and chair of the Division of Sports Medicine at Pitt. "He was fantastic to work with. He understood you, allowed you to grow, and was a benevolent leader," he adds.

Ferguson, 95, died in August.

A World War II veteran who graduated first in his class at Harvard Medical School, Ferguson went on to become the founding chair of Pitt's Department of Orthopaedic Surgery in 1954, serving in this role until his retirement in 1986. In his storied career he developed interventions that his colleagues call ingenious—perhaps most notably among them an I-beam nail used to mend hip fractures (still in use today) and a less invasive technique for hip surgery that made it possible to repair hip dislocation in children as young as 2 years old. (A complication of breach delivery, hip dislocation had previously robbed children of their mobility until they were school-aged.)

Ferguson

Ferguson's program at Pitt became so influential that it cultivated upwards of 30 department chairs and leaders of programs throughout the world (including Henry Mankin, profiled on the opposite page).

—Nick Moffitt

See Edwin Kiester Jr.'s 2002 cover story on Albert Ferguson at bit.ly/albertferguson

ROSS H. MUSGRAVE

AUG. 28, 1921–SEPT. 12, 2014

When Ross Musgrave (MD '43) interviewed Kenneth Shestak (Res '85) for a residency position in plastic surgery, what surprised Shestak more than the generous interview were the calls Musgrave fielded during their chat. Musgrave got animated: *No, no, we talked about where those props are going to be.* Shestak later learned of Musgrave's work as a stage actor and director (an interest he continued to foster through his involvement in Scope and Scalpel and the Pittsburgh Academy of Medicine's annual musical).

Musgrave

"Right then and there, it was obvious that he was multidimensional," says Shestak, chief of plastic surgery at Magee-Womens Hospital of UPMC. "He was unceasingly inquisitive," which held true until Musgrave's death in September. He was 93.

Musgrave spent 60 years with Pitt's School of Medicine, from student to resident to Distinguished Clinical Professor of Surgery. He also served as executive director of the Medical Alumni Association for 12 years. Musgrave trained 125 surgeons; he himself was the second resident to graduate from Pitt's plastic surgery program. The school continues to honor Musgrave through the annual Ross H. Musgrave Lectureship, as well as the newly named Ross H. Musgrave Chair in Pediatric Plastic Surgery. (A new namesake award for medical student excellence is also in the works—contact Jennifer Gabler at jag188@pitt.edu for more information.)

Musgrave served on the med school's Board of Visitors and as governor of the American College of Surgeons, president of the American Cleft Palate-Craniofacial Association, president of the American Society of Plastic Surgeons, and director of the American Board of Plastic Surgery.

Throughout his career, Musgrave impressed upon his patients and students the importance of family as an essential component of successful medicine. Musgrave and his wife, Norma Jane, had "an old-time Pittsburgh warmth and graciousness," says Shestak. "[Musgrave] lived a full life. He'd be the first to tell you he had a great life."

—Amy Whipple

See Sally Ann Flecker's 2003 story on Ross Musgrave at bit.ly/rossmusgrave

IN MEMORIAM

'50s

WILLIAM P. LASCHEID
MD '50
SEPT. 19, 2014

JAMES C. FILE
MD '51
SEPT. 3, 2014

ELMER J. MALOY
MD '51
AUG. 3, 2014

EDWARD W. HEINLE JR.
MD '58
AUG. 30, 2014

'60s

ANDREW GERENYI
MD '64
JULY 4, 2014

'70s

MORRIS TURNER
MD' 73
JUNE 30, 2014

JOHN M. KERN JR.
MD '75
SEPT. 15, 2014

FACULTY

EZZAT I. ABOULEISH
FEB. 20, 2014

PAU GOLANÓ
JULY 23, 2014

KEVIN HYUNKYUNG KIM
JULY 18, 2014

HENRY MANKIN
ORTHO ICON

BY NICK KEPPLER

COURTESY K. MANKIN

Father and son orthopods, Henry (MD '53) and Keith Mankin (MD '88), c. 1991.

Orthopaedic surgeon **Henry Mankin** (MD '53) first treated broken bones when he was a U.S. Navy medic during the Korean War, but he didn't pull these wounded soldiers out of the Imjin River or run to them in the streets of Seoul.

"I was called up to spend two years at a Nevada base," says Mankin. "I was the only doctor there, and I tended to broken bones when the Marines and Navy guys went at each other in the bars." (Mankin says his second-most frequent duty was delivering babies because "the guys on the base couldn't stop getting the women in the neighboring town pregnant.") X-raying and setting casts for the country's brasher troops gave Mankin his first deep look at the musculoskeletal system and "set me up for what was to come," he says, adding, "I was so lucky."

After a stint at the University of Chicago, Mankin returned to Pitt. Then, in 1966, he was asked to head the the division of orthopaedics at the Hospital for Joint Diseases in New York City. He told his Pitt mentor, the late Albert Ferguson (see opposite page), that he was happy in Pittsburgh. But "Ferg" wouldn't hear of it. *Go!,* he told Mankin, *This is your chance to become an academic giant!*

Cleaning up after inter-branch scuffles might seem an unlikely basis for an impressive career, but it set a precedent for Mankin: Whatever task presented itself, he'd fully immerse himself in it. Career highlights include 41 years of continuous research funding from the National Institutes of Health and more than two decades (1972 to 1996) as chief of orthopaedic surgery at Massachusetts General Hospital. He is the Edith M. Ashley Professor Emeritus of Orthopaedics at Harvard.

When he started at MGH, several patients came in with Gaucher disease, a genetic condition common to people of Ashkenazi Jewish ancestry. So Mankin became an expert on it. He's published about 20 papers on Gaucher and, in the early '90s, conducted clinical trials that resulted in the first prescription treatment for the ailment (imiglucerase).

When he found that medical records of tumor patients at MGH were expanding past what the old paper filing system could handle, he developed a digital system that now includes information on more than 17,000 patients.

When he struggled to find bone specimens for his research into cartilage, osteoarthritis, tumors, and allografting, Mankin started a bone bank, accessible to orthopaedic surgeons and researchers across the country. He's utilized it for a few of his own 702 published articles and book chapters.

It was Mankin who, in 1972, brought to MGH a new, experimental procedure known in orthopaedics as allografting, the transplant of a bone from a donor cadaver into a patient with life-threatening bone and soft tissue malignancies. "We sometimes took the whole tibia or femur," he says, adding that it's an example of how "everything has changed [since] I started." Though it was a desperate measure that successfully beat cancer recurrence in only a third of cases, allografting brought a new option for terminally ill patients in the era before artificial bone replacements.

He's now attempting to alter the structure of malignant tumors to make them benign. He and his staff have introduced chemical compounds into lab animals, and though they have not neutralized the tumors, they have made them less aggressive.

The paper Mankin is most proud of? One on myeloma, published this year. He's particularly fond of it because it was coauthored with his son Keith, who followed him both to Pitt med (MD '88) and into orthopaedics. ■

WISH YOU WERE HERE

There must be 50 ways to leave your med school. You can go your own way, ride a horse with no name, or take a midnight train to Georgia. Tell us what you've been up to: career advancements, honors, appointments, volunteer work, publications. And we love old Pitt memories. Send us a message in a bottle (or via **medmag@pitt.edu**).

ROCK ON, SISTERS

Eight-year-old singer Isabel and her bandmates, the Lightning Girls, shook the speakers during the Girls Rock! Pittsburgh concert in August. But these budding rockers hadn't always been so boisterous. Isabel arrived at the organization's weeklong camp shy and quiet, says Vanessa Veltre, one of the program's volunteers.

"Throughout the week, it was so inspiring to see her open up," Veltre says.

The program's campers, ages 8–18, often began as strangers with little or no musical experience. Before they knew it, they were rocking out with new friends, writing songs, talking about body image, and learning self-defense and zine-making. Some goals for the campers: Be empowered. And be loud.

This spirit is exactly why WolfePack Goods—a community of artists and others who came together in memory of Sarah and Susan Wolfe—donated about $9,500 in scholarship funds to Girls Rock! Pittsburgh this year.

The Wolfe sisters, who were murdered in their Morningside home in February, were beloved by many. Sarah, a pediatrician and psychiatrist (Res '12), was an assistant professor in the University of Pittsburgh's Department of Psychiatry; she was on the faculty at Western Psychiatric Institute and Clinic, as well as Children's Hospital of Pittsburgh of UPMC. Susan worked at the Hillel Academy of Pittsburgh in Squirrel Hill.

To honor the sisters' love of kids, animals, and music (Sarah was involved in the Riot Grrrl movement in the '90s), WolfePack Goods began selling artwork to fund scholarships for Girls Rock! Pittsburgh.

"[Girls Rock! is] helping young girls to believe in themselves while also making music and being LOUD," writes Sarah's boyfriend Matt Buchholz, who helped form WolfePack Goods.

"It's a great way to focus not on this senseless tragedy but on bringing something positive into the world," he adds. *—Emily DeMarco, Photos by Matt Dayak*

Learn more about the ongoing project at **www.wolfepackgoods.com**

CALENDAR

FOR ALUMNI & FRIENDS

MEDICAL ALUMNI ASSOCIATION WILLIAM S. MCELLROY AWARD LECTURE
NOVEMBER 5
3 p.m.
Recipient—David Geller, MD
For information:
Jen Moritz at 412-648-9059
jlm337@pitt.edu

MEDICAL ALUMNI ASSOCIATION SCHOOL OF MEDICINE PHONE-A-THON
NOVEMBER 11, 12, AND 13
Evening hours
Forbes Tower, 8th Floor
For information:
Andre Burton at 412-648-9090
aab86@pitt.edu

HEALTH SCIENCES ALUMNI RECEPTIONS
FLORIDA
MARCH 11, 2015
Winter Academy Palm Beach
MARCH 13, 2015
Winter Academy Naples
For information:
Pat Carver at 412-648-9741
cpat@pitt.edu

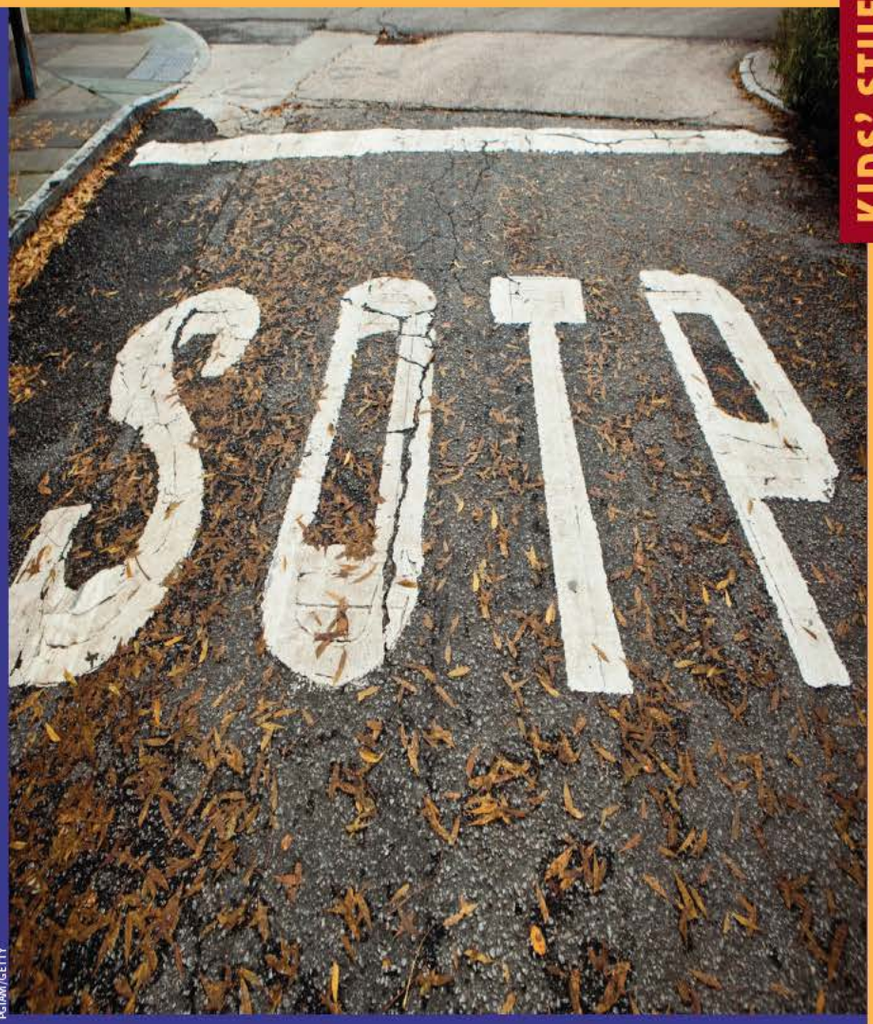
MEDICAL ALUMNI ASSOCIATION REUNION WEEKEND
MAY 14–18, 2015

CLASSES:

1955 60th Reunion	1960 55th Reunion
1965 50th Reunion	1970 45th Reunion
1975 40th Reunion	1980 35th Reunion
1985 30th Reunion	1990 25th Reunion
1995 20th Reunion	2000 15th Reunion
2005 10th Reunion	

For information:
Jen Moritz at 412-648-9059
jlm337@pitt.edu

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



PGIAM/GETTY

FOR REAL! TWEEN SCIENCE

Reading is a skill that many of us take for granted. Of course, we aren't born knowing how to do it. Just like learning to play a musical instrument or program a video game—it usually takes years of concentrated practice before we get really good at it. And the biology of reading is more complicated than you might think. In fact, scientists don't yet fully understand all that is happening in your brain as you read these words. This makes it hard to figure out what's happening in the brains of people who have dyslexia (that is, trouble deciphering, pronouncing, or reading words). Studies have shown that it takes more than visual decoding of groups of letters to understand the meanings of written words—we actually need to hear the words pronounced to really "get it." As you read these words, think about what's going on in your head. Do you hear a voice? When we read silently, an inner voice talks to us. It turns out that our brains process the combinations of letters we see into sounds that the inner voice pronounces. The brains of people with dyslexia have trouble recognizing letter combinations that make certain sounds, and their inner voice stumbles on pronunciation, making reading slow and difficult. But just like other learned skills, reading is easier for some people than others. And with practice, pretty much anyone can do it. *—Jenifer Lienau Thompson*

Many thanks to Julie Fiez at Pitt's Learning Research and Development Center for clearly pronouncing the details of dyslexia. For more kid-friendly science, visit the Office of Science Education Outreach, Health Sciences' Web site, How Science Works, **www.howscienceworks.pitt.edu**.

UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE
SUITE 401 SCAIFE HALL
PITTSBURGH, PA 15261

CHANGE SERVICE REQUESTED

NONPROFIT ORG.
U.S. POSTAGE
PAID
PITTSBURGH, PA
PERMIT NO. 511

WHEN MAA CALLS,

you should answer. The Medical Alumni Association's Phone-A-Thon to support medical students is happening this November 11–13. Pick up your phone and help fund programs like the MAA Scholarship Fund, the MAA Summer Enrichment Fund, and the White Coat Ceremony. Every bit you can give helps!

Miss the call? You can phone MAA at 1-800-817-8943 or go to maa.pitt.edu/donate/ways-to-give.php