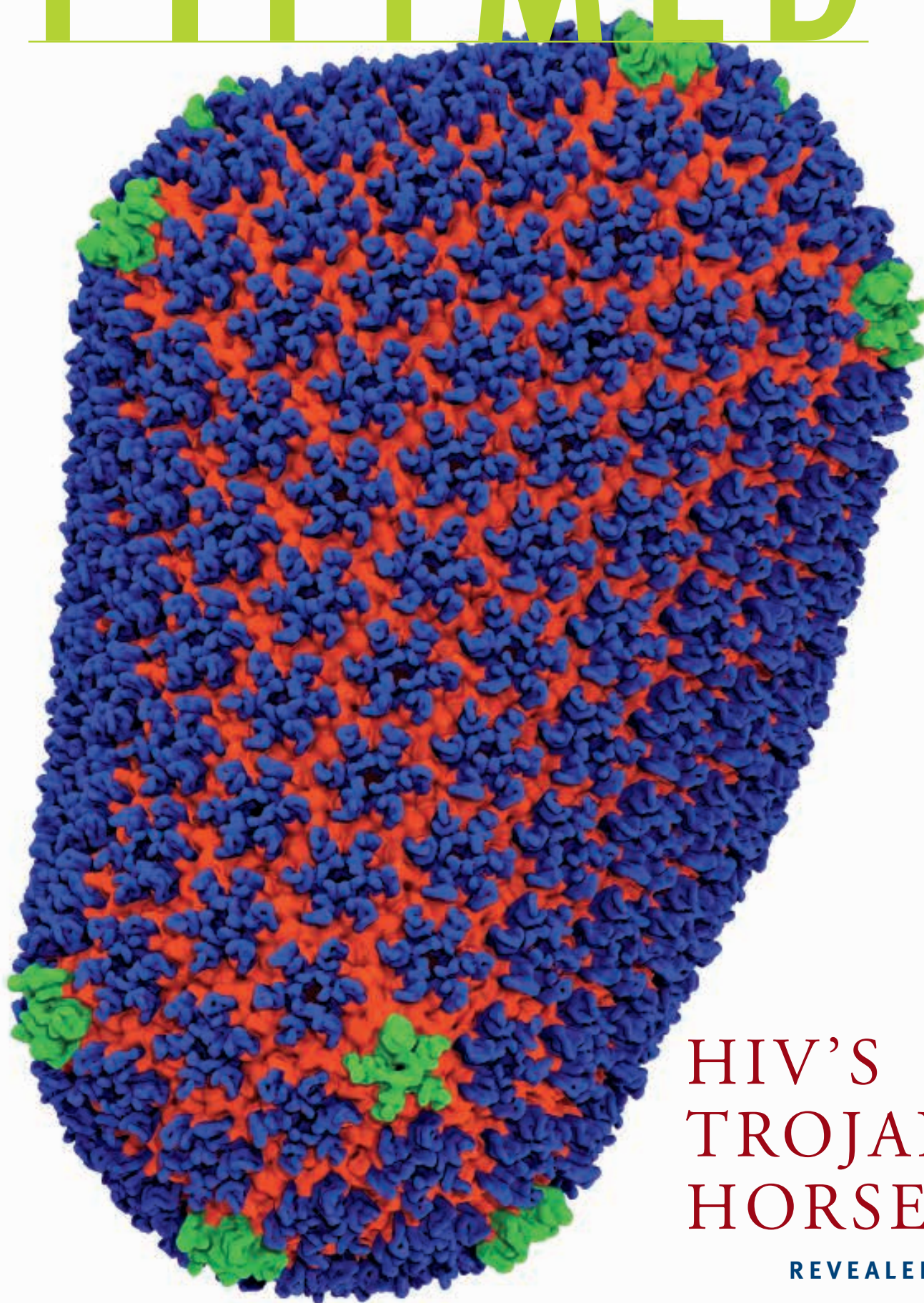
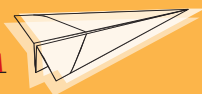


PITTMED



HIV'S
TROJAN
HORSE

REVEALED



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IABC Pittsburgh Golden Triangle
Award of Excellence, Publication Design—
Magazines (E. Cerri)

IABC Pittsburgh Golden Triangle
Award of Excellence, Interactive
Media Design (E. Vitone, “Tinnitus:
A Pitt Medcast”)

IABC Pittsburgh Golden Triangle
Award of Honor, Magazines

2013 Press Club of Western Pennsylvania,
Golden Quill Award, Health/Science/
Environment Article or Series—Magazines
(J. Miksch, “The Meaning of Life,
Told with 13 Polypeptides”)

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for length, style, and clarity).

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MORE WOW!

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PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, WINTER 2013/14
VOL. 15, ISSUE 4



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CONTRIBUTORS

"To your left is the Cathedral of Learning ... Now we're crossing the Roberto Clemente Bridge ... And this is the historic Squirrel Hill." Before coming to *Pitt Med* in the winter of 2005, **JOE MIKSCH** was giving Just Ducky Tours of Pittsburgh. Eight-and-a-half years, more than 30 features, and several science writing awards later, he's on the move again. As the new senior news representative for the sciences at Pitt, Miksch has moved down the hall, but not out of touch. The former senior editor moonlights as a trivia-night champion. And he brings that eye for facts to his writing, along with an unflinching devotion to puns, including our favorite, his Fall 2007 headline for a pioneering orthopaedic surgeon who works with primates: "Monkey Knee, Freddie Fu." Says Miksch: "Everything needs those light moments."

Do what you love and do it well, goes the aphorism. But sometimes you love two things. Case in point: Ithaca, N.Y.-based farmer and writer **SHARON TREGASKIS**. This is her fourth guest-editing stint with *Pitt Med*; when she's not in the fields, where she and her partner raise pigs and hens and tend niche vegetables like purple potatoes and baby ginger, she reports on health care and the environment. Farming was a natural extension, Tregaskis says. "I was reporting on agriculture and the local food movement, and it was time to augment my reporting with *doing*." And do she does. She says you can tell a happy piglet by its curled tail. A happy writer might have a less obvious tell, but she certainly seems to be enjoying the juggling act.

COVER

HIV uses a Trojan horse approach to release its genetic material. Pitt scientists have found a chink in its armor. (Cover: Theoretical and Computational Biophysics Group, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign © 2013.)



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Great Expectations

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For 40 years, Angela Gronenborn has tackled fundamental questions about the proteins that power all biological processes. At Pitt she's built a department of like-minded investigators and equipped them with the tools to drive discovery.

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Associate Professor of psychiatry Margaret McFarland helped establish the Department of Child Development and Childcare at Pitt in the early 1950s. And for 30 years she helped Mister Rogers build his neighborhood.

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Shrinking NIH budgets are putting more talented researchers in troubled waters. Pitt's long-standing intervention puts scientists back on dry ground.

BY JENELLE PIFER

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Our blood is as salty as the sea we used to live in! When we're frightened, the hair on our skin stands up, just like it did when we had fur. We are history! Everything we've ever been on the way to becoming us, we still are." —Terry Pratchett

Knowing of Nathan Clark's work on the influence of evolution on the shared function of genes (on page 8 of this issue), and reading recently about the translucent sea walnut, *Mnemiopsis*

leidy, a comb jellyfish that has populated coastal waters for some 700 million years, my thoughts have turned to the immediate relevance of evolution to medicine. *M. leidy* is known as "combed" because of its long rows of undulating cilia studded with luminescent neurons; when disturbed, it glows blue-green. In December, *Science* published the sequence of the 16,500 genes of this ancient life form; with these data in hand, the authors reconsidered both *M. leidy*'s place on the tree of life and how neurons and muscle cells may have been gained and lost during early evolution. Such insights may well help us to understand human diseases of the nervous system and musculature. In fact, more than half of the known genes that, if mutated, lead to human diseases appear in the comb jelly's genome!

In the quest for insight into the origins of disease, evolutionary biology promises a fresh perspective, and potentially even new approaches to prevention and treatment. Our genomes are remarkably stable, yet changeable enough that mutations occur—both for the good (otherwise we would still be *M. leidy*) and the bad. We must weigh not just the dysfunction conveyed by a particular mutation, but also its benefits and historic origins within a complex system, asking, *What has allowed this mutation to persist? Why has it not been selected against? Is it advantageous under certain environmental conditions?* Imagine posing such questions to reframe our approach to cancer, allergies, autism, chronic inflammation, even depression.

Consider, for example, sickle cell anemia, a brutally painful condition owing to a mutation that reshapes the red blood cells. While a pair of such mutations may impose an early death, a single mutated gene seems to confer natural resistance to malaria, endemic in the same regions of the world in which the sickle cell mutation first emerged. What if insights into the sickle cell and malarial structures were employed to develop a malarial vaccine? Another case in point: Huntington's disease is a devastating genetic condition. *Why does this mutation persist across the generations? Why isn't it selected against?* The answer is simple: Symptoms don't emerge until after the age of reproduction, so this dominant mutation is passed on from one generation to the next. Of an especially immediate relevance to common human ills, consider the rapid evolution of flu viruses (and thus the need for annual changes in the vaccine), HIV (which can evolve rapidly even in one patient), and antibiotic resistance in bacteria—all situations in which our ability to probe evolution, using powerful molecular, structural, computational, and cell biologic technologies, holds great promise. Even cancer may be understood in this way, i.e., realizing that a cancer cell exploits evolvable mechanisms that preexist in us, like cell division and migration. Given these thoughts, perhaps it would be welcome for medical schools to have a greater focus on evolutionary biology and even the fossil record.



JOSHUA FRANZOS

Arthur S. Levine, MD

Senior Vice Chancellor for the Health Sciences

John and Gertrude Petersen Dean, School of Medicine



*Devoted to noteworthy happenings
at the medical school*

SPREADING THE MESSAGE

Jeannette South-Paul, an MD and UPMC Andrew Mathieson Chair in Family Medicine, has long been impressed by the Susan G. Komen organization and its ubiquitous pink. “The publicity has made it so that every woman is screened for what was once a silent killer,” she says.

But the ailments that plague Pittsburgh’s Hill District neighborhood have few such campaigns, South-Paul says. Because of this, she has spoken at a series of community health forums sponsored by the *New Pittsburgh Courier*, the Urban League of Greater Pittsburgh, and Pitt’s Clinical and Translational Science Institute. Her talks highlight not only breast cancer but also other important diseases, including heart disease, cancer, diabetes, and depression.

To make her point, she brings photos of African Americans who died in middle age of common medical issues—among them, Grammy Award-winning musician and arranger Barry White, who died of renal failure. Like many, White’s death was preventable: “The important thing to note is that the issues were not impossible to control. The moral is: Your health is partially in your hands.” —Nick Keppler

FLASHBACK

It was a terrifying time. In 1980, a San Francisco resident was identified as the first American with AIDS. In 1983, HIV was isolated (though the virus wouldn’t be known as HIV for another three years). In 1984, the Graduate School of Public Health responded by launching the Pitt Men’s Study, now one of the longest-running studies of the natural history of AIDS. Pitt’s Charles Rinaldo’s proposal to the NIH was to recruit 7,000–10,000 men ages 18–55 for a “prospective study of AIDS in homosexual men in Pittsburgh.” Now in its 30th year, the ongoing study has contributed to more than 1,000 research papers; it’s also credited with diminishing the impact of AIDS in Pittsburgh.

GETTY IMAGES



Barry White’s deep and silky voice was silenced by renal failure.

BOYS II MEN

Conceived by the Ad Council and the nonprofit Futures Without Violence, Coaching Boys into Men is a program about positive dating habits for high school sports coaches to teach to their players. There are 12 lessons, one for each week of a season.

When she first heard about it, Elizabeth Miller, MD, PhD, suspected the program could be useful. “Coaches are in a unique position compared to phys ed and health teachers,” says Miller, an associate professor of pediatrics at the University of Pittsburgh and chief of the Division of Adolescent Medicine at Children’s Hospital of Pittsburgh of UPMC. For many kids, coaches “are seen as a second dad.”

Miller led a study, published in the *American Journal of Preventive Medicine*, showing CBIM’s effectiveness. The study compared survey results from male athletes in schools that used the program versus a control group that did not. It showed a statistically significant increase in positive attitudes and willingness to intervene in situations of partner abuse among peers.

Miller is now interested in developing a version for middle school athletes and teen cricket players in India. —NK



Overheard Follow the 'script

Medications make such persistent ailments as hypertension, high cholesterol, and many other conditions manageable—if the patient takes the drugs as prescribed. We spoke with Zachary Marcum (shown above), PharmD and Pitt assistant professor of medicine, who contends that non-adherence to prescribed drugs results in preventable deaths and at least \$100 billion in costs to the U.S. economy per annum (some estimates peg that figure at \$300 billion) because of hospitalization and quality-of-life issues. Marcum, along with Steven Handler, MD/PhD Pitt assistant professor of biomedical informatics and of geriatric medicine, authored a thought piece in the May 22 issue of the *Journal of the American Medical Association* that they hope will begin to lay out a plan of cooperation between patients and clinicians to increase medication adherence.

What kinds of patients are at risk for medication nonadherence?

There have been countless studies looking at the risk factors. ... What it really comes down to are complex medication regimens. ... In my mind, from a patient level, for someone who might have a cognitive impairment, [adherence is] very difficult. And, of course, there's cost. The other thing you have to keep in mind ... is [patient] values and beliefs about medication. ... Some people would prefer an herbal supplement or an over-the-counter to a prescription drug. Some people have very strong feelings about the pharmaceutical industry. Some people just think, *I'm on too many pills. I don't care what this next one is. I'm not taking it.*

How much of an impact would greater medication adherence have?

"[Adherence] may have far greater impact on the health of the population than any improvement in specific medical treatment," the World Health Organization says. So, rather than create a new drug, why don't we help people adhere to what we know works? Innovation is important, but let's try to have a quick direct impact and apply what we know.

On how to get the adherence ball rolling.

Why not start screening for it? [A clinician needs to] get a better understanding of what the patient's thinking about before even writing ... a prescription. There are countless instruments you can screen with, but until you start measuring [adherence], you don't know what the problem is in a clinical setting. —Interview by Joe Miksch

Faculty Snapshots

Pitt professor of obstetrics, gynecology, and reproductive sciences and Elsie Hilliard Hillman Chair in Women's and Infants' Health Research Yoel Sadovsky has been elected to the Institute of Medicine, which honors the nation's finest scientists. Sadovsky, scientific director of Magee-Womens Research Institute, is renowned for his research on the placenta and the function of specialized placental cells called trophoblasts. He has elucidated molecular pathways responsible for placental development and the organ's adaptation to stress.

Charleen Chu's work on "eat me" signals in injured cells appeared in *Nature Cell Biology's* October 2013 issue.

Chu, a professor of pathology, and colleagues Hülya Bayir and Valerian Kagan study cardiolipin, a lipid component of the mitochondrion (the cell's energy center), and how its movement from the inside of mitochondria to their surface triggers the breakdown of damaged mitochondria by lysosomes, digestive centers of cells. Chu hopes that understanding the quality control process by which impaired mitochondria are eliminated in neurons could lead to better understanding of Parkinson's and its treatment.



Sadovsky

Bernard Macatangay, assistant director of Pitt's immunology specialty lab and research assistant professor, has discovered that decreased numbers in a subset of CD4 T cells (a white blood cell) associated with HIV may contribute to increased inflammation in affected individuals.

This progress in the understanding of what contributes to inflammation could be helpful in developing new treatments to improve health and increase life expectancy in patients infected with HIV-1. This research was done in cooperation with investigators at Pitt's Graduate School of Public Health, the University of Pittsburgh Cancer Institute, Pitt's Department of Pharmacology and Chemical Biology, and the Pitt Men's Study—part of the Multicenter AIDS Cohort Study. The paper was published in the journal *AIDS*.



Chu



Macatangay

In May 2013, Lisa Grandinetti, associate professor of dermatology, opened UPMC's Gastrointestinal Dermatology Clinic. The clinic's inception was a response to the increasing referrals Grandinetti received from her GI colleagues, highlighting a demand for a specialized care center. The clinic is open the first Monday of every month on the fifth floor of the Falk Medical Building. It offers care for patients with skin-related problems secondary to their GI diseases, such as celiac disease and inflammatory bowel disease, and patients with ostomy-related skin issues. Grandinetti works closely with gastroenterologists, colorectal surgeons, and enterostomal-therapy nurses. As demand increases, she plans to expand clinic hours. —Rachel Puralowski



Grandinetti

Those who can, teach

Cynthia Lance-Jones, a Pitt PhD associate professor of neurobiology and assistant dean for medical student research, is one of four winners of the Association of American Medical College (AAMC) 2013 Alpha Omega Alpha Robert J. Glaser Distinguished Teaching Award.

Her success as a teacher, she thinks, comes from her ability to think like a student: “I’m good at explaining things to them because I spend a lot of time trying to put myself in their heads and trying to figure out what would make [a topic] clearest to them.”

This student-centric thinking led her to develop a combined course in cell biology and pathology and create a computer module on vascular structure, atherosclerosis, and the potential use of non-invasive biomarkers. She also delivers almost all lectures on medical embryology.

“It’s important to give students different ways to learn and to practice what they have learned,” Lance-Jones says of the computer module. “In the lab, they tend to memorize, and this gives them the opportunity to test and enrich themselves.” —JM



RICHARD GREENHOUSE PHOTOGRAPHY

KANTER LAUDED

Steven Kanter speaks quietly but has made a resounding impact on medical education, an achievement recognized by the AAMC, which named him the 2013 recipient of its Merrell Flair Award. As vice dean of the University of Pittsburgh School of Medicine, Kanter oversees all academic programs at Pitt, as well as faculty affairs. The MD and professor of medicine and of neurological surgery has long been involved with the AAMC’s Group on Educational Affairs and served as editor-in-chief of the AAMC’s peer-reviewed journal, *Academic Medicine*. At Pitt, he guided the implementation of a new curriculum for students and a new, and fairer, system for the appointment and promotion of faculty.

“This is a wonderful award and a special honor,” Kanter says. “It’s especially meaningful to me because it comes from colleagues who wake up every day thinking about how to do a better job of educating the next generation of physicians.” —JM



TOM ALTANY / CIDDE

A GOOD REVIEW

John Mahoney, MD, also took home some AAMC hardware. The associate professor of emergency medicine and associate dean for medical education won an AAMC Outstanding Peer Reviewer award. Mahoney ranks in the top 20 of about 550 peer reviewers who examine work submitted to the MedEdPORTAL, the leading organization for publication of peer-reviewed medical educational materials. —JM



TOM ALTANY / CIDDE



COURTESY LIBRARY OF CONGRESS

FLASHBACK

When it comes to the history of Civil War medicine, often the surgeons, physicians, and nurses take the spotlight for their heroism in practicing medicine on the battlefield. The Falk Library of the Health Sciences’ exhibit, *Life and Limb: The Toll of the American Civil War*, swung the spotlight toward “an aspect of the war that has not received the attention it deserves: the experiences of injured soldiers,” says Jeffrey S. Reznick, chief of the History of Medicine Division of the U.S. National Library of Medicine and featured lecturer during the exhibition’s fall run. Advances in weaponry in the Civil War shattered bone, tore skin, and increased infection rates, resulting in a horrific number of amputations, which accounted for 75 percent of the 60,000 surgeries during the war. With little knowledge of sterilization, rampant infections, limited use of anesthesia, and long waits for treatment, surgery was no panacea. Soldiers often viewed doctors as butchers and faced a post-war life full of challenges.



TIM BETLER

Clockwise: A Ryan Clark cardboard cutout with Clark's cleats; the real Clark with Stanley Marks, chair of UPMC CancerCenter; and Steelers center Fernando Velasco (left) with Pitt sickle cell disease researcher Solomon Ofori-Acquah.



Pittsburgh Steelers safety Ryan Clark hits hard on the field. Off the field his Cure League helps tackle sickle cell disease. In November, at the Engine House 25 gallery in Lawrenceville, Clark and teammates watched as their donated, signed, and decorated game-worn cleats were auctioned off to support sickle cell research and patient care in the University of Pittsburgh Vascular Medicine Institute.

"Cleats for a Cure," in its second year, has generated about \$45,000 for sickle cell research over its run. Battling sickle cell disease is personal for Clark. His sister-in-law died from the disease, and Clark himself has the sickle cell trait.

"It's exciting to get the awareness out, but also to raise money for research that gives these people that suffer from this illness a better way of life, a better way to deal with the daily pain ...," Clark says. —JM

Hammering the sickle (cell)

Pitt's **Enrico Novelli**, MD assistant professor of medicine in the Division of Hematology/Oncology and member of the Pittsburgh Heart, Lung, Blood and Vascular Medicine Institute (VMI), has been director of the UPMC Adult Sickle Cell Program since 2007. Over the years, the program has added a physician assistant, a clinical psychologist, and a project manager. In 2013, three more senior faculty members arrived to dramatically expand the program.

"This was a long process because there is a well-recognized dearth of ... hematologists [who work with adults] dedicated to sickle cell in the United States," Novelli says.

Sickle cell disease (SCD) affects about 100,000 Americans. Because of a genetic mutation, the usually donut-shaped red blood cells form into a crescent and become stiff and sticky, tending to block blood flow. The disease causes pain and organ damage. SCD can also raise the risk of infection. There is only one FDA-approved sickle cell drug.

Pitt's new recruits are **Gregory Kato**, an MD formerly of the National Institutes of Health and Johns Hopkins University, **Solomon Ofori-Acquah**, a PhD formerly of Emory University, and **Laura DeCastro**, an MD formerly of Duke University.

Kato, a clinician-scientist, investigates pulmonary hypertension and other ways SCD presents in patients. Ofori-Acquah has published in the *Journal of Clinical Investigation* on a new understanding of acute chest syndrome, a devastating complication of SCD. In addition to her clinical work, DeCastro researches the impact of SCD on end-organ damage and the psychosocial issues relating to SCD.

"It's incredibly special not only to the sickle cell community but also to the national research community to bring three of the brightest minds on this disease together in one place," says **Mark Gladwin**, an MD and director of VMI, home of the UPMC Adult Sickle Cell Program. —JM

PITT ANATOMY SNOOZE

Editors

The Anatomical Staff

Vol. 1, no. 2

June, 1943

Issued

Now and then

The deserted Professor

A tragedy with a moral for all student assistants,
N.Y.A.'ers and other helpers of the past.

In a day that belongs like our tires
To a past that will no more return
We had but to speak our desires
To helpers all eager to learn.

So you who once labored to help us
And got only more jobs for your pains
Know now that we know whose the work was
As well as the brawn and the brains.

Each project was done in a jiffy,
Each reform carried out in a trice.
The skulls were made bright and spiffy
The quizzes were always on ice.

We hope that whenever you get this,
In spring, or in summer or fall,
You will know that for you our thought is
And we're wishing you luck through it all.

Yet that Eden we failed to enjoy:
We profs. were all grouchy and grim;
We felt that all gold was alloy,
That assistants did nothing but swim.

Now our sins have caught up with our footsteps.
Nor assistant nor helpers we see.
We must hoist from the tanks with our boot straps
All we need on the tables. Ah me!

Each lantern slide thumb marked so clearly,
Each bookcase that's scratched on the top,
Each slide-label spelled a bit queerly,
Each tool that is not in the shop

These speak of our helpers so skillful
Now gone where we can't reach their necks
While we are left here with a hill full
Of troubles and are we the wrecks!

Oh, for even one N.Y. Assistant
On whom we could unload a groan
But our cries tho' long and insistent
Are answered by echo - alone.

ALL THE SNOOZE
THAT'S FIT TO PRINT

Davenport Hooker was Pitt's master anatomist. He was also a pack rat. The med school's Falk Library received a raft of his papers in 1997 (along with the whistle he, in the words of Pitt history of medicine librarian Jonathon Erlen, "used to terrorize medical students during tests"). Among the miscellany was the *Pitt Anatomy Snooze*, a typewritten newsletter mailed 'round the world from 1943 to 1949.

The *Snooze* ("Issued Now and Then") was "an effort to keep all former Pitt medical students, not just anatomists, in the information loop," Erlen says. Poems, errata, and news about World War II and the roles of Pitt docs in it, fill the now-yellowed pages.

Humor abounds. Even in wartime. The *Snooze* notes that faculty are no longer bothered by life insurance salesmen because, "one came up here one pay-day and found the place bristling with sub-machine guns." And student griping, in 1943, was 90 percent Army-related and 10 percent faculty-related, compared to the peacetime figure of "110 percent about the faculty."

The *Snoozes*, catalogued in 1999, languished. Until University archivists realized that they hadn't been scanned and digitized. "This material seemed to be of special value since it's so ephemeral," says Ed Galloway, head of the University Library System Archives Service Center. University Archivist Marianne Kasica adds, "We're trying to identify and put online more materials about Pitt and its involvement in the two world wars. Adding the *Snooze* was an easy choice."

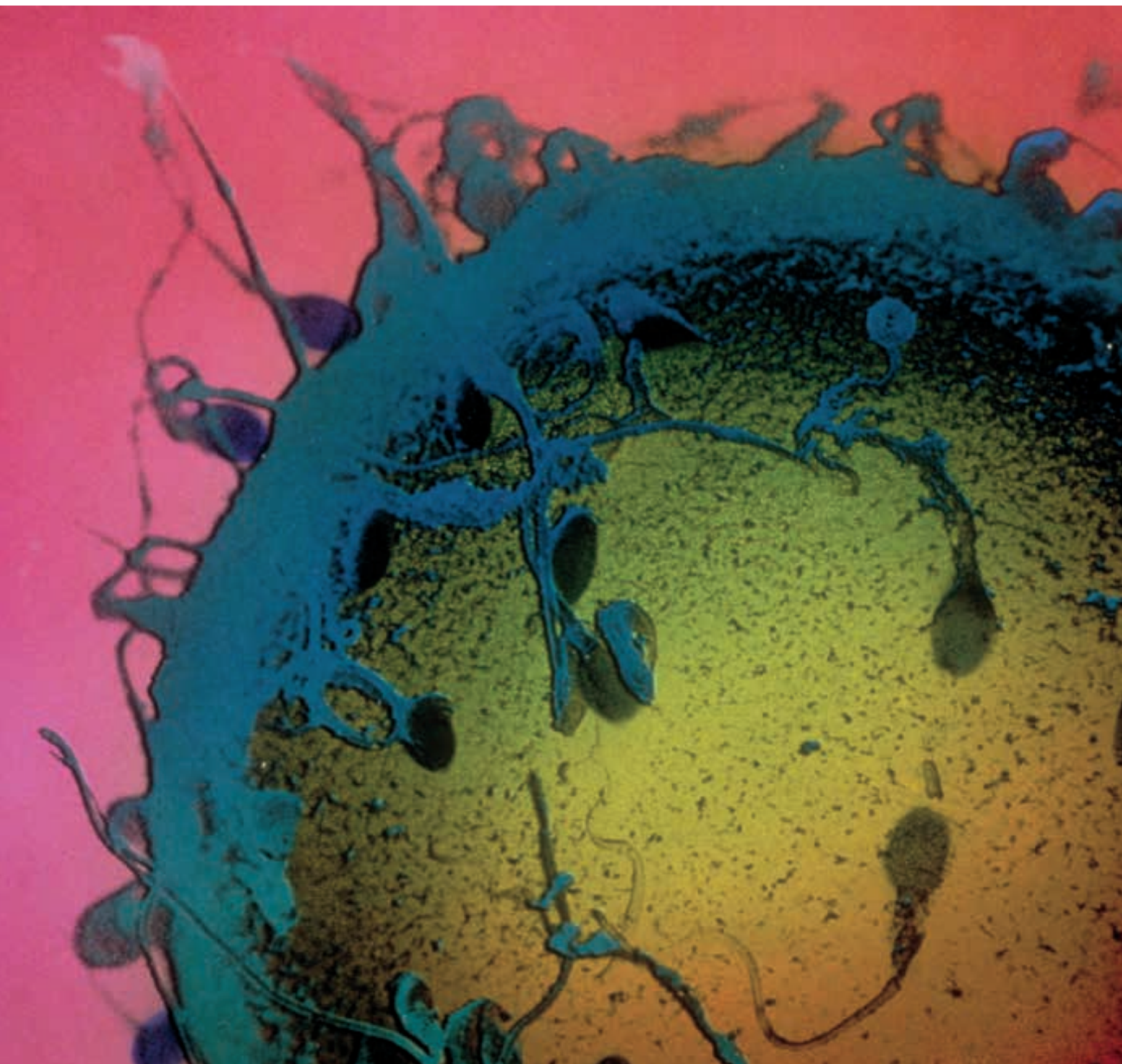
To peruse the *Snooze*, go to documenting.pitt.edu.

—Joe Miksch

—Newsletter courtesy University Archives,
ULS Archives Service Center

INVESTIGATIONS

Explorations and revelations taking place in the medical school



Interacting reproductive proteins, from those of the eggs and sperm in humans (above) to those produced by certain sexually reproducing yeasts, evolve together. Nathan Clark is finding that the patterns of this process, called coevolution, could help scientists identify players in biochemical pathways much faster.



IT TAKES TWO TO COEVOLVE

LIFE LESSONS FROM THE BIRDS
AND THE FLIES

BY ALLISON A. CURLEY

You might expect that millions of years of evolution would have perfected the process of fertilization. Actually, the interacting sperm and egg proteins are still works in progress, says Pitt's Nathan Clark, a PhD assistant professor of computational and systems biology. "As the egg protein changes, the sperm protein that binds to it has to keep up." This process, where one adaptively compensates for changes in the other, is known as coevolution.

Clark's recent insights on proteins and their dance partners could be a boon for biomedicine. He's showing that by studying coevolution patterns, it may be possible to sleuth out previously unknown players in a given biochemical pathway—or perhaps even predict gene function.

In a study published in February 2013 in *Genetics*, Clark compared the rates of evolution between 40 different species (18 yeasts and 22 mammals), concentrating on genes that regulate a process of cell division, called meiosis, which is involved in reproduction.

In some yeast species, reproductive methods have evolved so that meiosis is no longer essential for survival. Clark showed that the evolutionary rates of meiosis-related genes whose proteins had direct physical interactions coevolved, accelerating in a parallel, correlated fashion, leading to a loss of the now-unnecessary meiosis-related DNA sequences. The same was true of the genes for proteins that participated in the same biochemical pathway, even though they didn't directly interact.

Recently, Clark's methods came in handy in a collaboration with Cornell University's Mariana Wolfner, who studies reproductive processes in fruit fly models. Wolfner was interested in studying a protein called "the sex peptide," which gives male *Drosophila melanogaster* an advantage in fertilization. The protein, which is passed from the male to the female along with his sperm, makes her uninterested in mating with other flies for several days.

Seven genes had already been implicated in this behavior. To see whether the team might be able to expand on the list, Clark took a look at the 600 genes expressed in fly reproductive tissue and created a prioritized list of genes whose evolutionary rates changed in parallel with the original seven. A postdoc in the Wolfner lab, Geoff Findlay, then performed a series of experiments to confirm that, of the 18 candidate genes Clark identified, six were indeed part of the pathway. In just two years, the team nearly doubled the number of known genes involved in this behavior.

"A gene's rate of change over time, and who it's changing with, can tell you a lot about its function," says Clark. This approach can be used to discover the function of virtually any protein, so "it's a general recipe we want to try to repeat," he adds. In the future, Clark hopes to create a publicly accessible database into which researchers can input their proteins of interest and receive a list of potential other members of the same pathway.

A related branch of Clark's research examines the process of coevolution experimentally. He's altering the structure of NUP84, a protein that forms a specialized tunnel, or nuclear pore, that allows molecules to be transported in and out of a cell's nucleus. Clark transplanted the NUP84 gene from one yeast species (the donor) into a second, closely related yeast species (the recipient), replacing its native copy of the gene. Even though the change was very small—the protein sequence differs by only 5 percent—the cells containing the foreign NUP84 gene grew much slower than those with the gene from their own species. This stunted growth occurs because the donor NUP84 has not coevolved with the recipient partner proteins, Clark explains. "We've essentially broken this adaptive [coevolution] process," he says. In addition, because the donor and recipient species are each other's closest relatives, the slower growth rate "tells us that the process of coevolution is going on constantly," he adds. ■

SHOW AND TELOMERES

TYPOGRAPHY: ELENA GALAMAS CERRI

ARTHRITIS IN KIDS LINKED TO PREMATURE IMMUNE AGING

BY DANA YATES

A swollen wrist, an inflamed knee, a stiff neck ... these sorts of playground injuries happen to youngsters all the time. But for children and adolescents with juvenile idiopathic arthritis (JIA), painful joints can point to a serious condition. A distinct form of arthritis that strikes people under age 17, JIA is a degenerative disease with no known cause. The most prevalent rheumatic condition in the world, affecting about 50,000 in the United States alone, JIA may involve one or more joints and can limit growth and lead to physical disfigurement.

Arthritis has commonly been seen as an old person's disease. But as one University of Pittsburgh scientist has found, there may be much more to that idea than researchers once thought—even in the case of JIA.

Abbe de Vallejo—associate professor of pediatrics and immunology, as well as a member of the Division of Pediatric Rheumatology at Children's Hospital of Pittsburgh of UPMC, the Cancer Immunology Program at the University of Pittsburgh Cancer Institute, and the Pitt-UPMC McGowan Institute for Regenerative Medicine—is senior author of the first study to show that premature aging is associated with the most common form of chronic inflammatory arthritis in children. In fact, the joints of children with JIA contain

immune cells that look more like those of a 90-year-old than a 9-year-old. The findings, which were discovered by a team of researchers at Children's Hospital of Pittsburgh of UPMC, Pitt, and the Mayo Clinic, were published in the August issue of *Arthritis and Rheumatism*. Funding for the research was provided by the Nancy E. Taylor Foundation for Chronic Diseases, the Arthritis Foundation, and the National Institutes of Health.

Long considered an autoimmune disorder—a case of the body attacking its own tissues and cells—JIA is traditionally treated using broad-spectrum therapies that debilitate the entire immune system. But continued suppression of the body's natural defenses can lead to other health concerns, including infection, lymphoma, and reactivated tuberculosis. That cascade led de Vallejo to wonder whether the conventional, scorched-earth approach to treating JIA might not be optimal.

"The immune system is an army," he says. "Why paralyze the whole army when you may just need to maintain the good soldiers and retire the old ones?"

His previous studies involving young adults with rheumatoid arthritis have shown that some cells in the blood and joint synovial fluid appeared to be undergoing abnormal cell division and premature aging. In the latest project at Children's, de Vallejo was

curious whether the earlier finding would hold true in pediatric arthritis.

The study focused on T cells, a type of immune cell that helps the body fight infection, disease, and other harmful agents. Specifically, the researchers investigated the T cells in the synovial fluid and blood from 98 children with JIA, as well as 46 blood samples from children who didn't have the disease.

One-third of the T cells of the children with JIA were found to be abnormal—and notably, their difference points to premature aging rather than autoimmune activity. Specifically, the T cells had shortened the protective caps on the ends of chromosomes, and thereby lost the ability to multiply. These chromosomal caps, called telomeres, prevent chromosomes from fraying. Every time a cell divides, the telomeres shorten. It's believed that aging happens when telomeres become too short to enable cell division.

Additionally, the T cells had begun to act in unusual ways, and their actions could be stimulated through atypical cell-surface receptors. While more studies are needed to understand why exactly that process occurs, one thing is certain right now, says de Vallejo.

"We need new ways of thinking about JIA. We also need to develop a new generation of selective drugs—ones that target and prevent premature aging of immune cells," he says. ■

A

B

SURPRISE ATTACK

BACTERIA-BUSTER
TAKES CUES FROM HIV

BY DANA YATES

Montelaro's specially engineered peptides, called eCAPs, can kill bacteria that antibiotics are powerless to fight. Here, the bacterium *S. marcescens* (A) is treated with eCAPs (B), which rapidly destroy the bacteria by thinning the inner membranes of the cells, indicated by arrows, and outer membranes, indicated by arrowheads.

Jeff Bezos, the founder of Amazon.com, was likely referring to business empires when he said, “There’ll always be serendipity involved in discovery.” And at the University of Pittsburgh, one researcher is proving that the world of science can still provide sudden and pleasant surprises, too.

Ronald Montelaro, a PhD professor in the Department of Microbiology and Molecular Genetics and codirector of Pitt’s Center for Vaccine Research, is senior author of a study that has found a promising treatment possibility for drug-resistant bacterial infections, particularly those that afflict people with cystic fibrosis. The study, which was supported by the National Institutes of Health, was published in the June issue of *Antimicrobial Agents and Chemotherapy*.

Affecting about 30,000 children and adults in the United States, cystic fibrosis is a genetic disorder that leads to viscous secretions in the lungs and other organs. The continuous production and presence of that mucus creates a hotbed of chronic infection. In fact, after near-constant use of antibiotics, about 80 percent of cystic fibrosis patients have at least one antibiotic-resistant infection in their lungs by age 18.

Simply put, progressively resistant bacteria eventually kill patients by spurring infections that, in turn, block patients’ airways and make breathing increasingly difficult. There is an urgent need to find a way to improve the effica-

cy of antibiotics.

Montelaro has found one potentially life-saving solution. It uses the same tactic to attack infections that the deadly human immunodeficiency virus (HIV) uses to infect cells. The secret weapons in both cases are peptides—compounds that contain two or more amino acids. While studying HIV, Montelaro and his colleagues discovered a sequence of amino acids on the tail of the virus that enabled it to bust through and infect cells. That unexpected discovery led Montelaro to wonder whether the punching action of peptides could instead be used for a life-supporting purpose.

While peptides handle many functions in the body, antimicrobial peptides are a natural defense system against bacteria. Indeed, more than 2,000 antimicrobial peptides have been identified in nature, found in everything from plants to the skin of frogs. However, researchers have long struggled to create effective antimicrobial peptides in the lab.

Montelaro had a realization: When it comes to peptides, one size does not fit all. In nature, each evolved to work only on certain bacteria and in particular environments. “They aren’t generalists,” says Montelaro. “I thought, *If I were Mother Nature, how would I design a peptide for a particular target?*”

After studying the unique qualities of var-

ious peptides, his team developed a synthetic antimicrobial peptide, using an algorithm. Designed as a more efficient version of the amino-acid sequence found on the tail of HIV, this sequence—dubbed engineered cationic antimicrobial peptides, or eCAPs—can quickly kill a broad range of bacteria that standard antibiotics are powerless to fight.

Made from the amino acids arginine and tryptophan, the patented eCAPs are specially manufactured to achieve a uniquely rapid antibiotic effect against diverse types of bacteria—even strains resistant to standard antibiotics. Whereas traditional antibiotics may take hours, or even days, to eradicate an infection, the eCAPs can destroy bacteria in seconds or minutes. They accomplish this by attaching to and disrupting bacterial membranes.

The eCAPs are also effective against biofilms, bacterial networks that are extremely resistant to antibiotics. The eCAPs blast through a biofilm’s exterior to wipe out the whole bacterial community. As a result, says Montelaro, the eCAPs could have numerous important applications in the future.

“I’m passionate about improving cystic fibrosis patients’ quality of life,” he says. “And one day, eCAPs might also be used to help heal burn wounds, attack infections associated with venous catheters, and even save soldiers during a bioterrorism attack.”

INVESTIGATING THE MINUTE
MOLECULES IN BIG BIOLOGY
BY ALLA KATSNELSON

GREAT EXPECTATIONS

Structural biology, a research endeavor that examines the smallest possible scale of biological life, demands some of the most imposing tools in life science. Amble down the aluminum spiral staircase to the basement of the University of Pittsburgh's Biomedical Science Tower 3 and you'll find a massive chamber with sunshine-yellow walls, a concrete floor, and shiny chrome ladders on casters flanking tall white canisters of various sizes. This is the Department of Structural Biology's fleet of nuclear magnetic resonance (NMR) spectrometers. Drop a small tube of your chosen protein into an opening that leads down into the heart of one of the spectrometers, and the magnetic fields it generates—thousands of times stronger than the Earth's—allow researchers to construct three-dimensional images of your or any other macromolecule, down to the last atom. Down a short corridor, three cryogenically cooled electron microscopes detect cellular and subcellular architecture. In a ground floor suite, X-ray generators powered

PHOTOGRAPHY | MARTHA RIAL



Pitt structural biologist Angela Gronenborn, right, has assembled a fleet of nuclear magnetic resonance spectrometers and other tools for three-dimensional protein analysis. Michael Delk, left, manages the lab.



Angela Gronenborn surveys her sandbox—the research space she assembled to fuel the team-based discoveries of Pitt structural biologists.



by a central computer yield high-resolution atomic structures of crystallized proteins in a technique known as X-ray crystallography. In nearby labs, researchers can produce milligrams of pure protein—the functional equivalent to buckets, on the microscale—for any of these studies.

This is the space that Angela Gronenborn, PhD, calls her sandbox—the space she built to give Pitt structural biologists a top-notch place to play. A relatively young field at the junction of chemistry, physics, and molecular biology, structural biology endeavors to determine how the 20 amino acids encoded in the genome take shape to form the proteins that power all biological processes. Gronenborn is a world leader in the effort. Recruited to Pitt in 2004

lar discovery is her role in creating an environment that allows investigators to pursue great science, surrounded by all of the tools they need to do what scientists do: follow their noses. “That approach has been so good to me,” she says.

Gronenborn likes to say she’s been lucky in science. Born in Cologne, Germany, she attended an all-girls boarding school. As graduation neared, the principal and her father dissuaded her from becoming a mathematician. She chose physics and chemistry instead. After completing her undergraduate degree at the University of Cologne in 1975, she stayed on for her PhD in physical chemistry. NMR, a technology used to measure the physical properties of molecules to create atomic-scale

Medical Research Council’s National Institute for Medical Research in Mill Hill, where Feeney’s lab was just beginning to explore the use of NMR in proteins. The group was studying how drugs bind to an enzyme called dihydrofolate reductase, and Gronenborn set out to reveal how ligand and drug binding affect the enzyme. Structural biologists had already solved the structure of a few dozen proteins by X-ray crystallography, but the work provided just a freeze-frame image. To determine the effects of ligands on the enzyme would require repeatedly crystallizing the ligand in complex with the enzyme—a daunting task. NMR offered an easier approach. By measuring the spectral peaks of dihydrofolate reductase in solution, Gronenborn made her first foun-

“[The National Institutes of Health] said, ‘You can work on whatever you want, if you occasionally also look at an HIV protein,’” Gronenborn says.

“Ever since, I’ve been working on HIV or HIV-related proteins.”

to build the Department of Structural Biology and serve as its founding chair, she arrived with a clear vision: Acquire the best instrumentation available and assemble researchers with diverse skills to use it and the compatibility to collaborate. “I’m a strong believer in what I would call ‘team science,’” says Gronenborn, an NMR expert and a member of the National Academy of Sciences, who holds the UPMC-Rosalind Franklin Chair in Structural Biology. “To understand big biological systems, you have to combine different methodologies and perspectives, and then integrate it all to get the final picture.”

The approach is paying off. Under Gronenborn’s leadership, the department has achieved acclaim worldwide and launched a small but growing graduate program. She and her colleagues also established a National Institutes of Health–funded center for structural research on the human immunodeficiency virus (HIV)—one of five such programs nationwide. Last May, *Nature* published the team’s landmark description of the structure of the virus’ capsid, or protein coat, pegged to an unprecedented resolution. Perhaps just as important as Gronenborn’s role in that singu-

lar discovery is her role in creating an environment that allows investigators to pursue great science, surrounded by all of the tools they need to do what scientists do: follow their noses. “That approach has been so good to me,” she says.

Her brother Bruno was a PhD student at the same university, and she would often join him in his lab, where he was studying how proteins regulate gene expression by binding to DNA. The field of molecular biology was in its infancy. Although the structure of DNA had been described by British scientists James Watson, Francis Crick, and Rosalind Franklin in 1953, researchers knew little about how genes were transcribed into proteins, and the ability to sequence DNA was on the cusp of invention. “I found the whole area absolutely fascinating,” Gronenborn says. When she finished her PhD in 1978, she was determined to use NMR spectroscopy to solve the structures of protein complexes—particularly protein interactions with DNA—in order to study how genes are switched on and off.

NMR was a nascent method, and few researchers at the time believed it could be extended to molecules as large as proteins, but Gronenborn was undeterred. She headed off to London for a postdoc with James Feeney at the

dational observation: The protein could exist in different conformations. “That showed us that there were a lot of dynamics going on in proteins—they were not all standing still,” she says. “It also showed that NMR can give information that is not available by other techniques, such as crystallography.”

Gronenborn wasn’t standing still, either. London was a refreshing change after Germany’s highly hierarchical university system. “I was given the freedom to follow my own curiosity, and I was daring enough to do things that were difficult but very interesting,” she says. She met Marius Clore, a student at the institute, and the two of them tackled the topic that had originally captivated her. They spent long hours in the lab, fumbling with early protocols for synthesizing DNA and then running the samples, thrilled with the yield of NMR spectra that had never been seen before. In 1981, Gronenborn was awarded a permanent position at the institute; her reputation in the field was gaining traction. One day in the lab, she got a surprising phone call: On the line was crystallographer Max Perutz, who had shared the 1962 Nobel Prize in Chemistry for determining the structure

of hemoglobin. Now he wanted her to work some NMR magic on a project with which he was struggling. A multiyear collaboration was born. “She was one of the very few people in those days who had the rare combination of biochemical skills and NMR expertise—not to mention her exceptional drive—necessary to develop the fledgling area of biological NMR,” Feeney says.

In her six years at Mill Hill, Gronenborn published more than 50 papers. In 1984, she and Clore, by then married, accepted a joint post at the Max Planck Institute of Biochemistry in Munich. There they headed the biological NMR group and continued refining their use of NMR to study protein structure and function. Klaus Schulten,

physicist and NMR spectroscopist, had just installed a powerful new magnet for the HIV work. NMR uses very strong magnets. Place any molecule—a protein, say—into a magnet, and the nuclei of every atom in the protein interact with the magnetic field. Interject radiofrequency pulses, and the communication among the atoms—known as the exchange of magnetization—can serve as a sort of ruler, allowing researchers to calculate distances and angles among the nuclei and ultimately build a model of the protein. Gronenborn’s and Clore’s expertise lay in expressing and labeling proteins with NMR-active isotopes and developing algorithms to determine their three-dimensional structure. Bax, meanwhile, was a brilliant choreographer, coaxing the spectrom-

the crowded spectra and correctly assign individual peaks to every atom. Their technique has since become routine. “This was a huge breakthrough,” says Tatyana Polenova, a University of Delaware biophysicist and a member of the Pittsburgh Center for HIV Protein Interactions. “Without this seminal work from her lab, we would not be able, today, to solve structures of large proteins.”

The group’s first major achievement with these methods was solving the structure of interleukin-1 beta, a protein with 153 amino acids. Today, a protein that size is relatively easy for a structural biologist to wrangle, but at the time, its size posed a formidable challenge. Other important structures followed: several cytokines and chemokines, a host of HIV-related proteins.

“Angela has this amazing intuition for how to approach things that look risky, yet are very promising questions from the standpoint of general biological insight,” says biophysicist Tatyana Polenova.

a computational biophysicist now at the University of Illinois at Urbana-Champaign, met her there when he was on the faculty at the Technical University of Munich. “When she came back to Germany,” he says, “she was already a very established scientist and she had a very clear and interesting goal.”

In 1988, the National Institutes of Health came knocking with an urgent problem. Researchers had already identified HIV as the virus responsible for a deadly new epidemic ravaging gay men and intravenous drug users, and the agency had launched a clinical trial of a vaccine, but little was known about its modus operandi. Not a single structure for the virus or its associated proteins had been determined. The agency recruited Gronenborn and Clore to Bethesda, Md., where Gronenborn became chief of the structural biology section at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). “They said, ‘You can work on whatever you want, if you occasionally also look at an HIV protein,’” Gronenborn says. “Ever since, I’ve been working on HIV or HIV-related proteins.”

Gronenborn and Clore set up shop in the basement, where Adriaan Bax, PhD, a bio-

eter to deliver sequences of pulses that allow the nuclei to converse. “I would go to Ad and say, ‘Oh, can you do this type of experiment?’” Gronenborn recalls. “And he would always say, ‘Ah, it’s impossible.’ And then, a few hours later, he would say, ‘Oh, let me try this ...’ And he would try it, and it would work!”

In its early days, protein NMR used mainly proton spectra. Unfortunately, all but the smallest proteins had too many overlapping peaks for scientists to resolve. Gronenborn and her colleagues realized that expanding the spectra from two dimensions to three and four could alleviate this problem. As Clore and Gronenborn analogized in 1991, imagine a macromolecule as a large encyclopedia. Arranged in a single line of text, the letters would crowd into an unreadable jumble. Expanded to two dimensions—a page—the overlap would remain too strong to discern more than a few letters here or there. In three dimensions, spaced out into a book, many of the words would be distinct. But only in four dimensions, as a set of tomes, would the entries be fully readable. They combined this methodology with a new way of labeling proteins—on nitrogen and carbon nuclei, as well as the conventional protons—to untangle

The group also solved the structures of several protein-nucleic acid complexes. “Those were things that very early on I had wanted to do but were impossible to do,” Gronenborn says. “So now that we had the technology, we could do it, and that was very gratifying.”

On paper, Gronenborn, Clore, and Bax each had their own research groups, but in practice they collaborated closely; the 30 or so postdocs among them shared a study area, equipment, and resources. “There was tremendous synergy,” says Bax. “Basically, everybody was there 7 days a week, 12 hours a day.” When they weren’t working, he adds, they would be out drinking together or mingling at the frequent parties that Gronenborn organized. Known for their fantastic food and wine, the gatherings were a particular draw for cash-strapped postdocs.

Jun Qin, now a professor of molecular medicine at the Cleveland Clinic, still draws on the collegiality that he experienced as a postdoc in Gronenborn’s lab. Many of his cohort of trainees remain in touch two decades later. “We still exchange ideas and talk about grants and papers,” he says. Like Gronenborn, Qin came to structural biology from a chemistry background, and he was impressed to find Gronenborn herself teaching him how to grow bacterial

cultures and prepare proteins. “Of course, I made some mistakes,” he says, recalling how, early on, he tried labeling a 6-liter batch of cell culture with isotope-labeled glucose. He dumped a few thousand dollars’ worth of the pricey sugar solution into a container and was horrified to find that the cell culture didn’t grow. “I thought it was the end of the world,” Qin says. “But she just said, ‘Okay, sit down and calmly think about what you did and what happened.’” (Happily, together they found the cause of the problem, and his second attempt at labeling worked.) “I learned all the state-of-the-art technology in her lab,” Qin says, “and I also learned how to do science—how to address important questions.”

Gronenborn could have continued on at NIH indefinitely, but she began to feel the tug to leave a legacy larger than her own body of research. She had recently parted ways with Clore when Arthur S. Levine, senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine, reached out to lure her to Pitt in 2004. Medical schools rarely have structural biology departments, but Levine believed that structural, computational, and developmental biology together form the bedrock of contemporary biomedical research. He set out to erect a research building in which structural biology research would serve as a literal and metaphorical foundation. Gronenborn, for her part, was drawn to the challenge of building a new venture. She knew her vision carried a big price tag—more than \$10 million for the NMR instrumentation alone—and was impressed by Levine’s support. “People pay lip service to the need to understand things at the atomic and molecular level, but to really do it as a big enterprise takes a lot of money and commitment,” she says. “And the institution here has been committed—that is what attracted me.”

She was deliberate about faculty recruitment. Rather than assembling researchers based on biological interests, she sought to create a team that was able to innovate methodologically. She began by recruiting people with a wide variety of technical expertise—NMR, crystallography, cryo-electron microscopy (cryo-EM), protein expression—and the ability to collaborate to address big questions.

“It’s very rare that all these techniques can come together in one place, and that’s what I wanted to do here,” Gronenborn says. She also wanted to bring in more than one specialist in each technique. “I’ve learned over the years that you always need to talk to people who are close to you in methodology,” she says.

Gronenborn didn’t explicitly plan to include HIV in her own or the department’s scope, but in 2006 the NIH requested funding proposals for research centers focused on structural elements of the virus. Because she had worked on the virus at NIDDK, she decided to apply and she invited Peijun Zhang, PhD, a new faculty hire and an expert in cryo-EM, to help write the application. “I said, ‘I have no experience with HIV,’ but she said we would pull together all the expertise necessary to carry out the project,” recalls Zhang. “That’s the way she directs the center. She brings the right people together.”

One of the HIV experts Gronenborn engaged was Christopher Aiken, a Vanderbilt University virologist. “I’d seen her name,” he says, “but she wasn’t that central a player in the HIV field.” However, he was impressed with her idea to focus the center on early events in the HIV life cycle, a wide-open topic at the time, and was further hooked by the quality of the draft proposal, which—after years in Europe and at the NIH—was Gronenborn’s first competitive grant application. “I thought, *Wow, this looks like a winning horse.*”

And indeed it was. With the grant awarded in 2007, the center’s researchers—based at Pitt as well as other universities in the U.S. and abroad—embarked on solving the structure of the HIV-1 capsid, the protein shell that carries viral DNA into the cell. That knowledge might point to new ways of thwarting the virus before infection takes hold, a workaround to the drug resistance that occurs with current treatments. “The structural biology of the HIV capsid is extremely challenging,” explains Zhang. That’s because capsids of retroviruses don’t form uniform particles. Structural biology methods, on the other hand, are all based on averaging, and they work best when components are uniform.

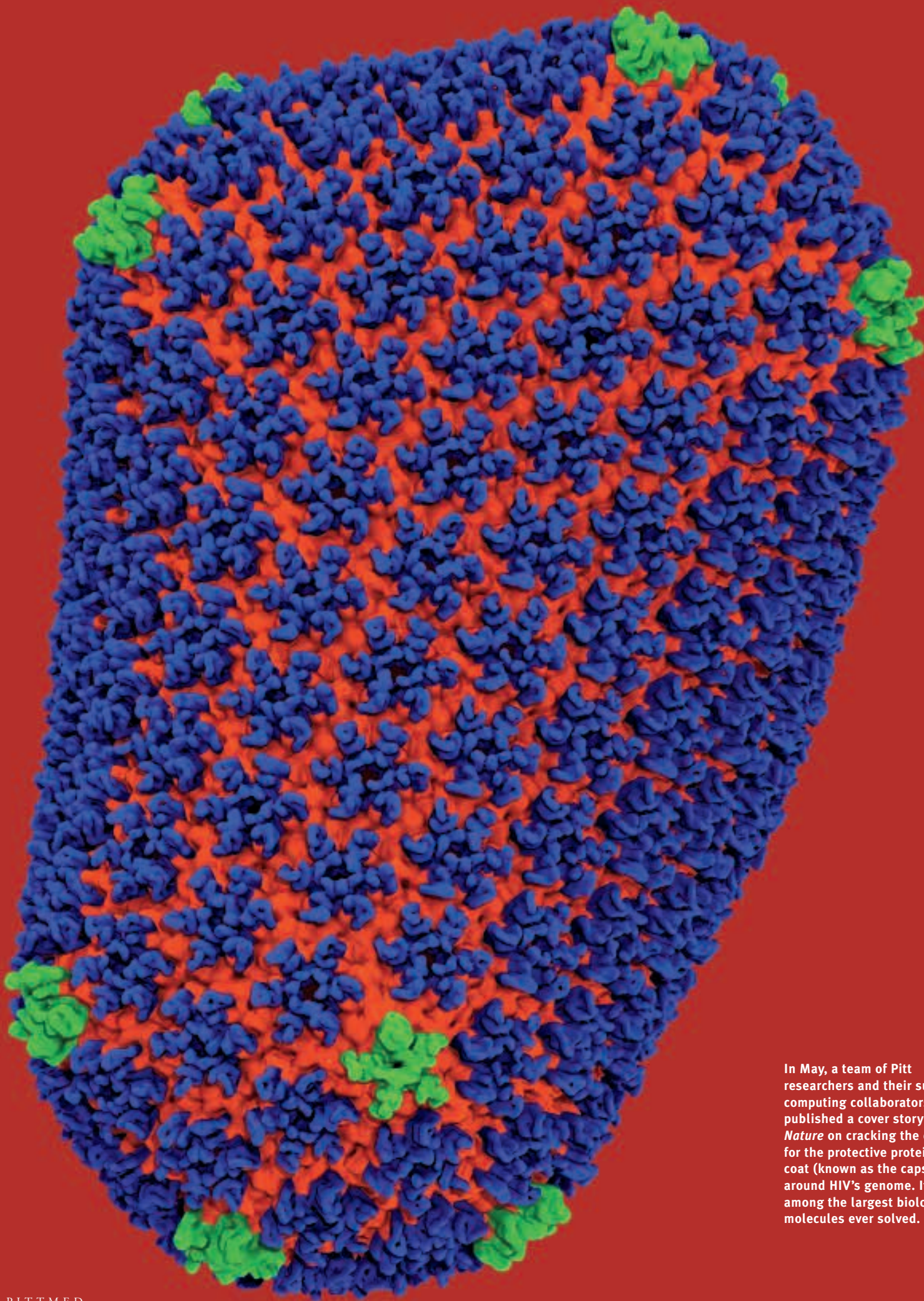
To get around the problem, Zhang and Gronenborn led the center’s efforts to use cryo-EM and NMR to work out an inter-

mediate-resolution structure of an in vitro-assembled capsid. That structure, which *Cell* published in 2009, offered hints on how the capsid forms and dissolves. Other avenues were also pursued. “Angela has this amazing intuition for how to approach things that look risky, yet are very promising questions from the standpoint of general biological insight,” says biophysicist Tatyana Polenova. An expert in a type of NMR conducted in condensed phases rather than on molecules dissolved in solution, Polenova joined the center in 2010, when Gronenborn asked whether her technique might work for studying the HIV capsid. She was happy to give it a shot, but noted that it would be a challenge. “Angela said, ‘Okay, my philosophy is: We may go down in flames, but let’s have fun trying.’”

Meanwhile, Zhang continued to push the HIV-1 capsid structure to high resolution, ultimately combining her findings with computational modeling conducted by Schulten to yield an approach in which individual atoms could be discerned. At 4 million atoms, and 1,300 proteins, the HIV capsid structure is one of the largest ever solved. (See how Zhang and her colleagues solved the puzzle on p. 18.)

As this project moved toward completion, Gronenborn set out on a new quest—one that took her away from the bench. For the past two years, she had held an ongoing discussion with Sandra Mitchell, PhD, chair of Pitt’s Department of History and Philosophy of Science, about success in the scientific process. So she used a sabbatical at Berlin’s Institute for Advanced Studies to try to quantify the value of an idea that has been central to her work: the power of team science. Using data from granting bodies and publication records, she attempted to track whether increasingly interdisciplinary research teams could show measurably higher levels of success.

The answer to Gronenborn’s big question proved more elusive than she expected, though she hopes to return to the problem. Meanwhile, she did learn one thing: If she ever takes another sabbatical, it had better be in a lab. Returning to Pittsburgh this fall, she realized how deprived she had felt. “The initial glimpse of new data that tells you, *hmm, it’s not what you expected,*” she says, “that’s still the most thrilling thing.” ■



In May, a team of Pitt researchers and their super-computing collaborators published a cover story in *Nature* on cracking the code for the protective protein coat (known as the capsid) around HIV's genome. It is among the largest biological molecules ever solved.

COURTESY TCBG

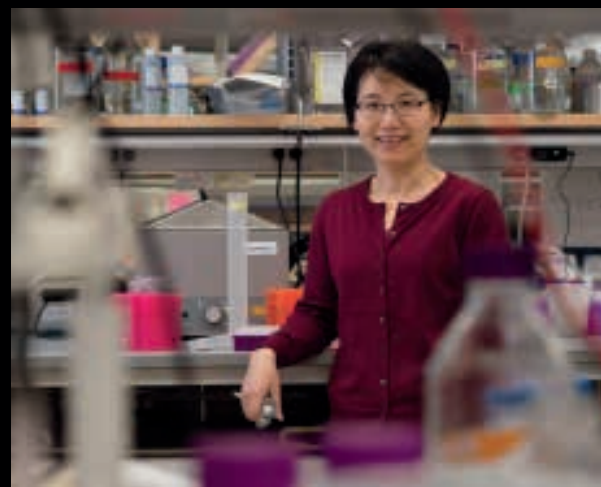
A NEW VIEW OF HIV,
RIGHT OUT OF THE GATE
BY ELAINE VITONE

DON'T SPARE THE HORSES

A Trojan horse full of molecular miscreants rolls into an immune cell—the kind that’s supposed to defend the body against this sort of thing. When the timing is just right, the infiltrators burst out, overtaking the cell and forcing it to build more horses and more armies so they can move on and do this again. Which they do, essentially burning the place down on their way out. In the ensuing years, the body’s would-be outposts, known as CD4 T cells, dwindle, giving free rein to whatever other ne’er-do-wells might come along next.

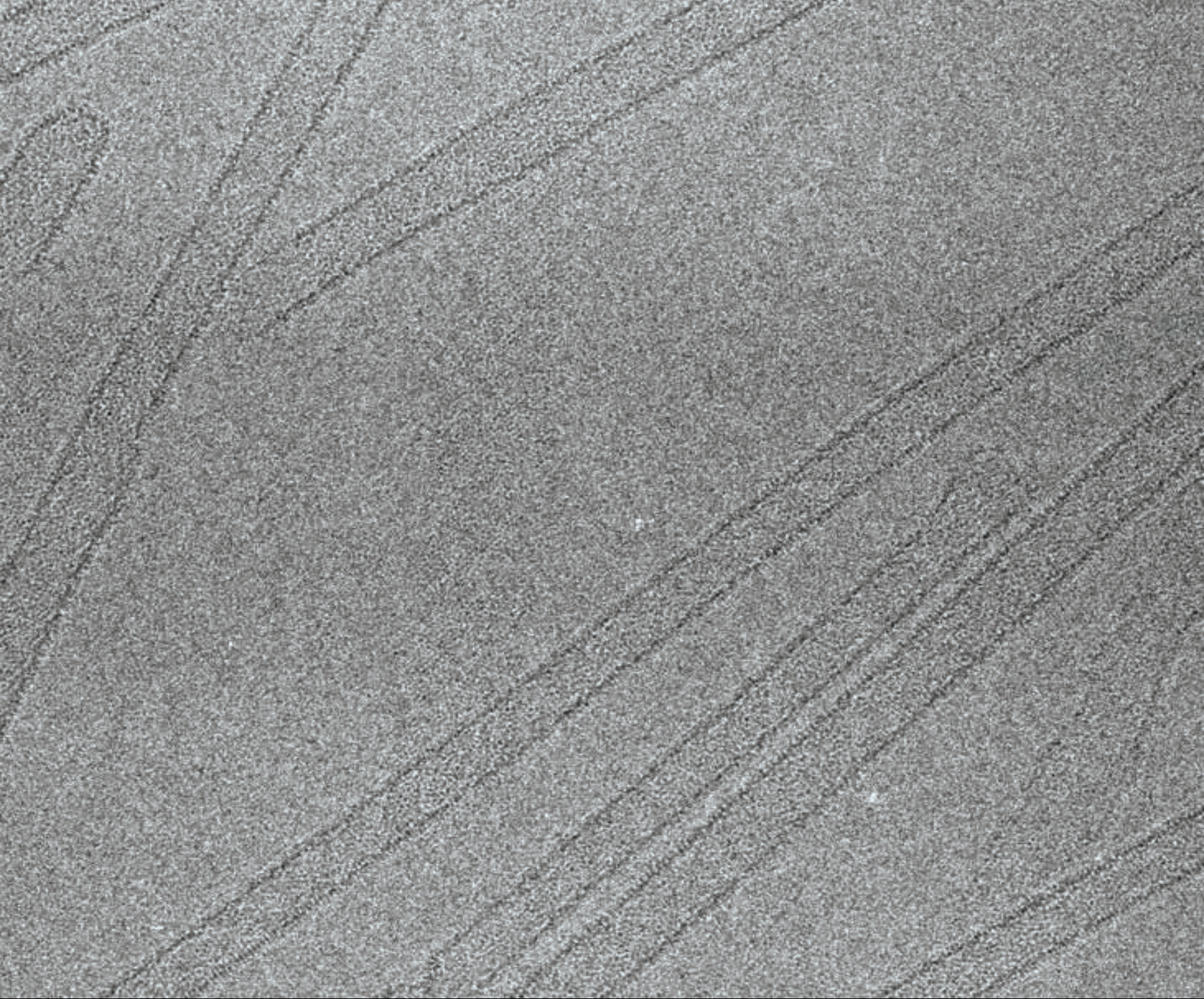
Which they do. In time, the whole empire falls.

The story of the horse is the story of HIV. A retrovirus, it co-opts certain critical white blood cells, putting its own genetic material right into their nuclei. Current treatments target the enzymes that duplicate HIV’s genome and force it into the host cell’s genome. These are the villains within the virion that turn CD4s into HIV’s own munitions plants.



After Peijun Zhang and colleagues figured out the structure of HIV’s protein coat, they pinpointed where it’s vulnerable.

IMAGES COURTESY THE THEORETICAL AND COMPUTATIONAL BIOPHYSICS GROUP (TCBG), BECKMAN INSTITUTE FOR ADVANCED SCIENCE AND TECHNOLOGY, UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN
PEIJUN ZHANG LAB, UNIVERSITY OF PITTSBURGH
PORTRAIT BY MARTHA RIAL



HIV is pretty sloppy about its viral genome duplication processes, but that works out in its favor. Little genetic improvisations churn out new mutants all the time, so this deadly retrovirus—in its perpetual state of reinvention—is a moving target. Drug resistance is a constant threat.

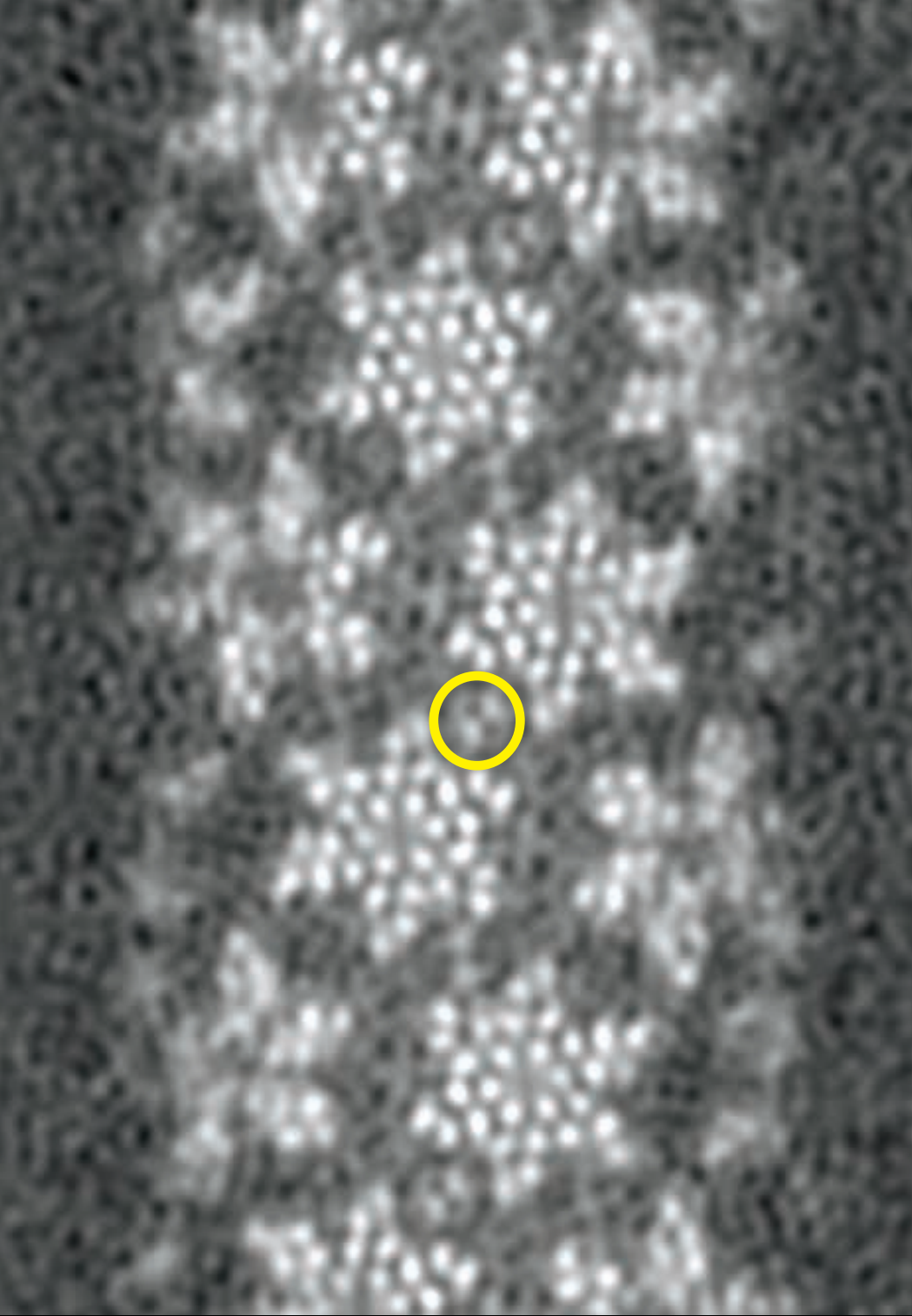
But what if we could stop these dictators before they could even get inside the cell in the first place? What if, instead of trying to take out these individual villains, we could sabotage their Trojan horse, the protective protein coat known as the capsid? It's a target rich with possibilities because, as with Virgil's fabled equine, when it comes to opening the capsid, timing is everything.

"The capsid has to remain intact to protect the HIV genome and get into the human cell," says Peijun Zhang, an associate professor of structural biology at the University of Pittsburgh. "But once inside, it has to come apart to release its contents so that the virus can replicate."

Treatments for many other viruses target capsids. But no one has managed to do this with HIV because, as capsids go, it's a doozy. While other capsids are uniform, soccer-ball-shaped—predictable—HIV's is asymmetrical, cone-shaped, and arranged in a confounding lattice of six-pointed and five-pointed structures—the exact numbers and configurations of which were unclear. No two HIV capsids are exactly alike, so the typical approach of structural biologists—to average together corresponding dimensions from many sample structures—wouldn't fly with HIV.

To make matters worse, the HIV capsid is big. With current imaging tools, you can only get a couple high-resolution images of small sections of the capsid, or low-res images of wide-angle shots.

Then, a few years ago, Zhang decided to apply a hybrid approach, to get the best of both worlds. (With a BA in electrical engineering, an MA in solid state physics, and a PhD in biophysics, Zhang is a bit of a



With all its variety and irregularity, the structure of the conical-shaped HIV capsid has been especially confounding. In a high salt environment, the capsid protein reassembles into long tubes (left). Zhang selected 34,000 among them that shared the same geometry, imaged them in cryo-EM, and created a structural average (right). Circled in yellow is a junction between adjacent hexamers (i.e., six-unit molecules).

Zhang had never worked on HIV before. But she had been working for more than a decade with cryo-electron microscopy (cryo-EM), a method of freezing specimens at liquid-nitrogen temperatures, then magnifying them through a beam of electrons just a fraction of an angstrom wide. It's a favorite tool of structural biologists because it allows them to peek at large protein complexes in their native environments—no chemical treatment, no staining, no worries about compromising the integrity of the structures. (For Zhang's PhD thesis, she solved the structure of a vital calcium pump, involved in muscle contraction, to the 8-angstrom level. This, too, was published in *Nature*.)

In 2008, Zhang began working with HIV capsid protein. She used purified protein, expressed and prepared by PCHPI investigator Jinwoo Ahn, assembled it into highly ordered helical tubes under high-salt conditions, and imaged them using cryo-EM (see opposite page). Cryo-EM is so sensitive it picks up not only the specimen you're studying but also an awful lot of visual "noise" around it. To tune that out, you have to average together a lot of images—the more the better. But given the variability among the HIV capsids, she realized she needed to compare apples to apples, so she selected her tubes carefully, including in her analysis only those that shared the same geometrical organization.

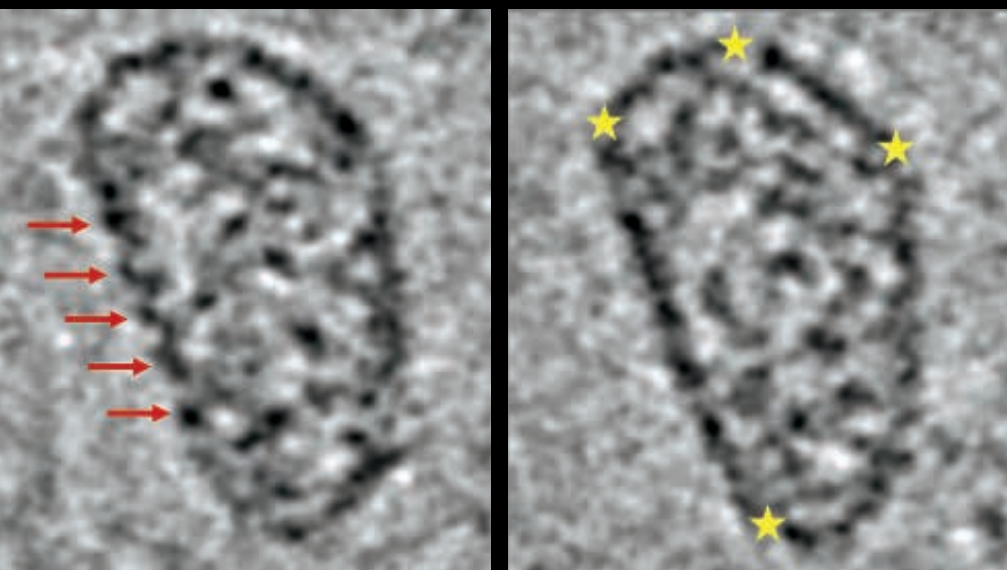
About 18 months and more than 34,000 carefully picked apples later, Zhang's group had an 8-angstrom structural map, which she calls "beautiful hexagonal flower patterns" (shown on this page). The structure revealed critical molecular interactions—previously unrecognized—at the seams of the capsid assembly. PCHPI investigator Christopher Aiken, a professor of pathology, of microbiology, and of immunology at Vanderbilt University, further tested and validated the roles of those interactions in HIV infection.

Map in hand, the PCHPI team decided to push ahead to build a working model of the complete HIV capsid using the structural insights gleaned from the capsid tubes. By converting cryo-EM data on the tubes into high-resolution 3-D images and combining those with results from cryo-electron tomography regarding the shapes of authentic core samples (see page 22) from the Aiken lab, they hoped to calculate the 3-D structures of native authentic HIV-1 cores.

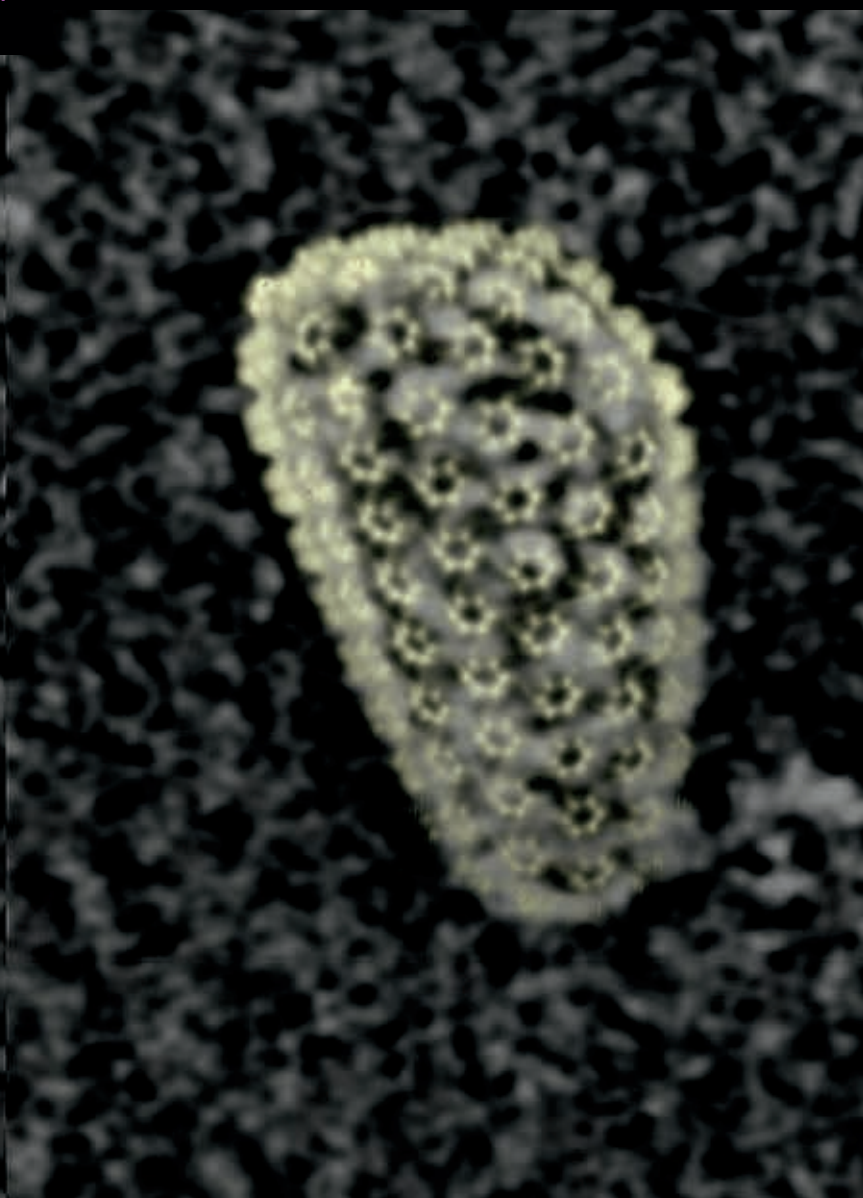
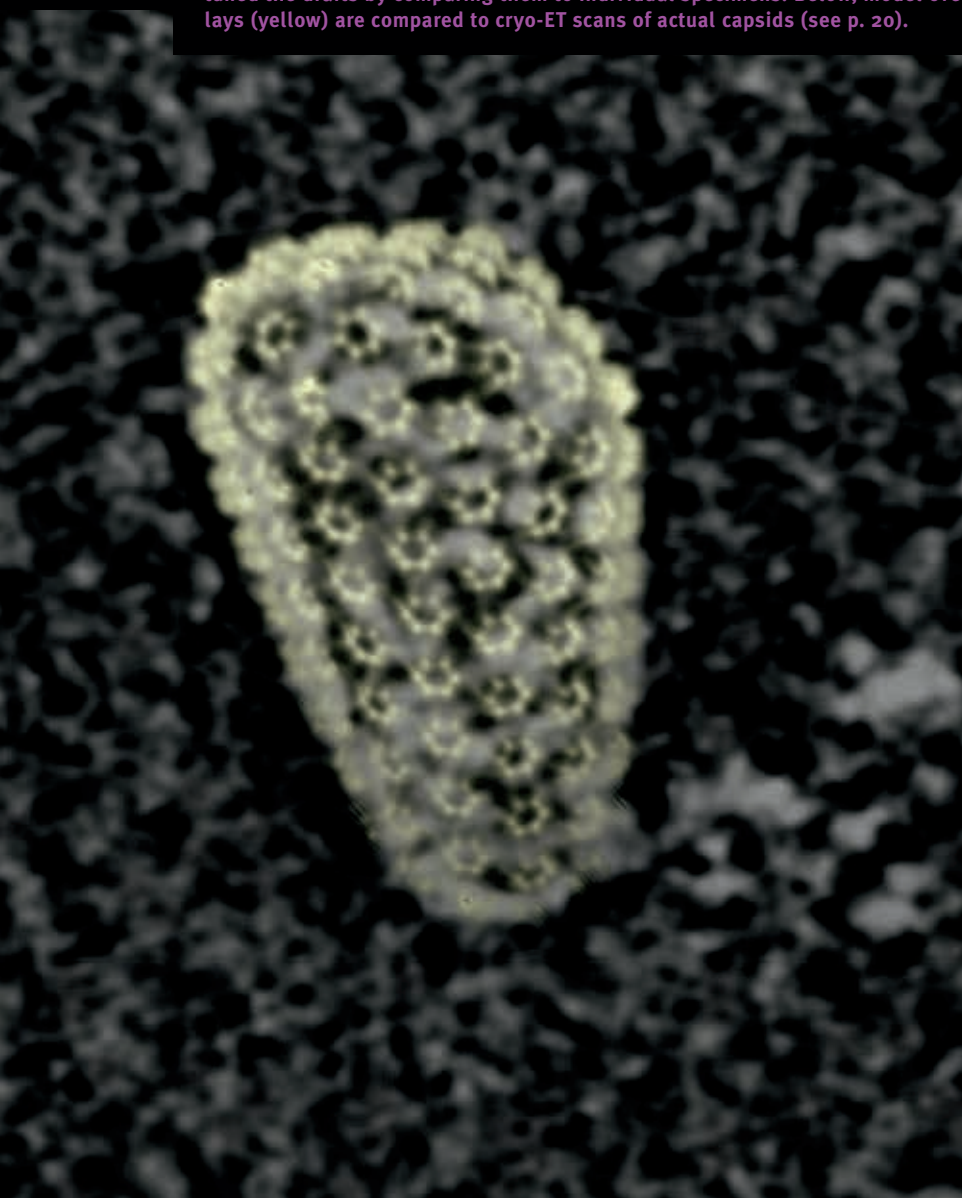
The aspiration would have remained just an untested rough draft if not for another bit of serendipity. Gronenborn called on her colleagues in the Theoretical and Computational Biophysics Group (TCBG) and the NIH Center for Macromolecular Modeling and Bioinformatics at the University of Illinois at Urbana-Champaign (UIUC). Scientists there undertook a heroic effort, investing myriad hours of original work as they applied their own, innovative software (six years in the making) to Zhang's data. Without their collaboration, says

hybrid herself.) In May, her efforts within the multidisciplinary, multi-institutional Pittsburgh Center for HIV Protein Interactions (PCHPI) culminated when the HIV capsid—one of the largest biological molecules ever solved—made the cover of *Nature*.

It all began with one of those right-place-right-time stories. Zhang, a recruit from the National Cancer Institute, happened to arrive at Pitt in the summer of 2006, just before the National Institutes of Health put out a call for applications for a new HIV center grant—which Pitt's Angela Gronenborn, a PhD and UPMC-Rosalind Franklin Professor and Chair of the Department of Structural Biology, decided to go for. And which the Pitt team got, opening the PCHPI in 2007. "The NIH only funded three centers, and we were one of them," says Zhang. "And the other two centers had a long history of studying HIV; we were the new kid on the block." (Pitt was renewed for this five-year grant in 2012.)



To figure out how the molecules fit together, the PCHPI team isolated and froze capsids in their native, conical forms, then built 3-D studies of them, one fraction-of-an-angstrom slice at a time. Above, two adjacent slices show shifts in the configuration. Red arrows indicate rows of molecules. Yellow stars show sharp shifts in the capsid's curvature. The team repeated their process with several different sizes of capsids, drew up a working model for each, and troubleshoot and fine tuned the drafts by comparing them to individual specimens. Below, model overlays (yellow) are compared to cryo-ET scans of actual capsids (see p. 20).



Gronenborn, the project simply wouldn't have progressed.

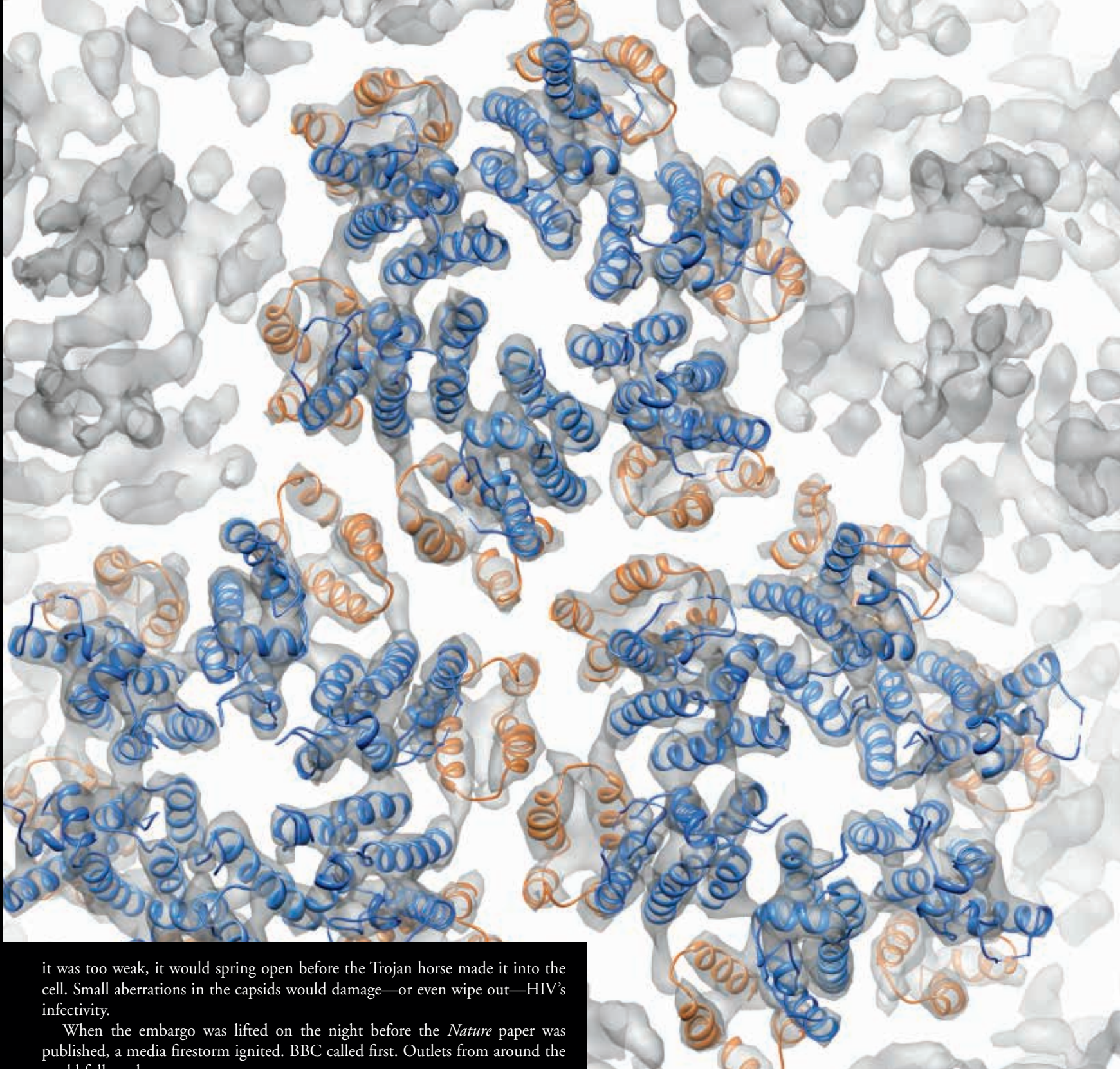
Using their "molecular dynamics flexible fitting" software, the Illinois group created a simulation that integrated the known physical characteristics of atomic structures with Zhang's experimental data. The process took several months.

With each passing day, the excitement grew. "We were periodically checking, 'Oh, is it still good? Still stable? The postdoc at UIUC [Juan Perilla, a PhD who was instrumental to the project] and I talked almost every other day," says Zhang.

In the end, they found it was indeed stable. The capsid was made up of 4 million atoms—216 hexagons and 12 pentagons—consistent with Zhang's experimental data. (See opening spread.)

At specific regions of the proteins, they found critical interactions in the capsid's seams—details no one had ever seen before. These seams are what give the capsid the flexibility it needs to open and close at just the right time.

Further, they found that if they replaced just a few "stitches" in the seams with some small mutation, the virus tripped up. If the seam was too strong, it wouldn't come apart when it needed to. If



it was too weak, it would spring open before the Trojan horse made it into the cell. Small aberrations in the capsids would damage—or even wipe out—HIV’s infectivity.

When the embargo was lifted on the night before the *Nature* paper was published, a media firestorm ignited. BBC called first. Outlets from around the world followed.

This paper represents just one part of the team’s larger effort to understand and unhinge HIV. (Zhang has developed a number of new microscopy technologies for these purposes.) They’re also studying the virus’ process of maturation, as well as host-cell factors that can combat HIV. One host-cell factor the group has already published on, called TRIM5alpha, is found in many mammalian species, but the rhesus monkey version of this protein actually breaks apart the capsid. “So the capsid is really the key for a lot of drug-development targeting stuff,” says Zhang.

Now, the team is also working to develop compounds that target the newfound vulnerabilities in the capsid. We’d love to tell you more about these ongoing, yet-unpublished studies, but that would be putting the cart before the horse. ■

Multiple simulations to calculate the capsid’s structure yielded new targets for HIV drug development. Here, the colorful structural model of the tube is superimposed on a gray density map. Blue represents the N-terminal domain in the illustration above; orange, the C-terminal domain of the capsid protein; gray, the electron density of the capsid assembly.



Fred Rogers looked to his teacher and mentor, Margaret McFarland, for ideas, inspiration, and insight for more than 30 years. Their discussions about children and life were practical as well as deeply philosophical. When they couldn't meet in person or talk over the phone, the discussions continued in their correspondence.

MISTER ROGERS' MENTOR

BY SALLY ANN FLECKER

WHEN FRED MET MARGARET

In the 1950s, before Fred Rogers became Mister Rogers of television fame, he was a theology student who was interested in working with young children. For counseling experience, Rogers was assigned to work under the supervision of child psychologist Margaret B. McFarland, an associate professor in the Department of Psychiatry at the University of Pittsburgh. That, as they say, was the beginning of a beautiful friendship. It was a pivotal professional relationship, as well. For 30-some years, until her death at the age of 83 in 1988, Rogers and McFarland would meet weekly to discuss children, upcoming scripts, props for the show, or song lyrics. They often talked daily. So much of Rogers' thinking about and appreciation for children was shaped and informed by McFarland's work—actually by her very being—that to know and love Mister Rogers is to know and love Margaret McFarland.



PHOTOGRAPHY | JIM JUDKIS

In 1953, a powerhouse triumvirate founded the Arsenal Family & Children's Center, where pediatric students could go for training in normal child development. McFarland, as cofounder and director until 1971, was at the heart of the center. Her partners were pediatrician Benjamin Spock, her then-colleague on the medical school faculty, and psychosocial developmentalist Erik Erikson (a visiting professor in the School of Medicine from 1951 to 1960). McFarland had not achieved the same fame as Spock, author of *The Common Sense Book of Baby and Child Care*, one of the best-selling books of all time, and Erikson, author of *Childhood and Society* and originator of the term "identity crisis." But McFarland, a 1927 alumna of Goucher College who did her doctoral studies at Columbia University, was every bit their equal. Fred Rogers, on the many public occasions when he acknowledged McFarland's significance to his work, frequently passed along Erikson's high praise: "Margaret McFarland," Erikson had said, "knew more than anyone in this world about families with young children."

If Rogers wanted to understand more about the inner life of the child, he had come to the right person. McFarland, a tiny, soft-spoken woman from Oakdale, Pa., had taught kindergarten teachers in Australia for four years and was on the faculty of Mount Holyoke College in Massachusetts before returning to her hometown. She didn't just have deep intellectual prowess in developmental theory. The meanings and textures of the child's emotional landscape were the air she breathed.

One time, Rogers wanted to do a program about fire. He took his ideas to McFarland. "She helped me to realize that it was essential to deal with control of fluids before even introducing anything about fire," Rogers recounted in a conversation published as the prologue to Stuart Omans and Maurice O'Sullivan's book, *Shakespeare Plays the Classroom*. "I learned, for instance, that most children's dreams about fire center around their control of their own body fluids! That's how personal a 'fire' can seem to a child."

With insight informed, but not dictated, by her psychoanalytical training, McFarland understood just how hard children work at learning to control their bodily fluids. Potty training is no picnic for parents, but imagine it from the point of view of the child. It's a pretty big, anxiety-laced deal. So Rogers created segments where he examined the everyday

flow of water in bathtubs, and he showed films of children damming up streams—a way of manipulating and controlling fluids—and looking at waterfalls (which can be both scary and exciting at the same time). "And then, finally ... a tiny fire—and I mean tiny—in the Neighborhood of Make-Believe," Rogers said. "We didn't show flames, just some smoke; and the fire was put out in half a minute by the make-believe fire people." When the shows aired, Rogers fielded seven complaint calls on behalf of children who had been frightened by the fire. Each of those children was having urinary difficulties. "I was fascinated," Rogers remembered. "If I hadn't had the developmental insight, I wouldn't have been able to

"Margaret McFarland," Erik Erikson said, "knew more than anyone in this world about families with young children."

begin to understand the obvious tie between what was presented on our program and the children's personal developmental concerns dealing with anything related to fire."

The Pittsburgh-born historian David McCullough, in a 2003 interview with the National Endowment for the Humanities, pointed out another of McFarland's great acuties. "What she taught in essence is that attitudes aren't taught, they're caught," he said. "If the attitude of the teacher toward the material is positive, enthusiastic, committed, and excited, the students get that."

Once, McFarland asked a well-known sculptor from Carnegie Mellon University to come to Arsenal, Rogers recalled in the Omans and O'Sullivan book. "Dr. McFarland said to him, 'I don't want you to teach sculpting. All I want you to do is to love clay in front of the children.' And that's what he did. He came once a week for a whole term, sat with the 4- and 5-year-olds as they played, and he 'loved' his clay in front of them. ... The children caught his enthusiasm for it, and that's what mattered. So like most good things, 'teaching' has to do with honesty."

By all accounts, McFarland's performance as a teacher was spellbinding. Rather than rely on textbook descriptions of early development, she would bring in a mother and child for 15-or-so minutes. Then she would spend the next two and a half hours describing what she had noticed about their interactions.

"I've never seen anything like it before or

since," says Margaret Mary Kimmel, a PhD professor emerita of library and information sciences at Pitt. Kimmel, who was also a consultant for Rogers, created a class called Early Childhood and Media, for which McFarland offered to teach the child development segments. "Margaret talked about how the child interacted with the mother. 'Did you see her face and the baby's face? And what about when he started to fuss? How did the mother handle it?' I learned so much from just watching her watch and describe to the class what was going on between the mother and the baby."

Pittsburgh play therapist Carole McNamee was one of McFarland's child development students in the early 1970s. "She could just spot

things. She was phenomenal that way," says McNamee. Was the child exploring? Was the mother encouraging or discouraging? "Mostly she would be aiming for, in development, what that meant."

McNamee remembers telling McFarland a story about her 1-year-old daughter Caitlin, who was terrified of ants. Outside on the patio one day, McNamee showed the little girl how to step on an ant. "That turned out to be a big game," says McNamee. "She went around stomping on bugs for days. Margaret pointed out how handling small things became part of what Caitlin was able to do that gave her control over her life." Throughout the time she worked with children, McNamee says, McFarland's was the voice she could hear in her head.

"Margaret spent her time teaching, and with Fred, and with the children at Arsenal," says Kimmel. McFarland left behind very little written work; this writer unearthed a journal article on the "development of motherliness" and her dissertation, a case study on the relationship between sisters. "It highlights, for an academic, why writing is so important. [Otherwise] your fame is only in your students."

Yet by that token, Margaret McFarland lives on. Her students do not include just the scores of medical school and child development students she taught at Pitt and the many children and families she worked with at Arsenal. Her students also include every child who ever tuned in to *Mister Rogers' Neighborhood*. Quiet fame, perhaps, but nonetheless enduring. ■



At the end of each show, Fred Rogers sang, "It's Such a Good Feeling," punctuated by a snap. The peppy tune and its affirmative lyrics echoed an injunction of his mentor, Margaret McFarland: Attitudes aren't taught. They're caught.

IT'S A BEAUTIFUL, AND WELL-THOUGHT-OUT, NEIGHBORHOOD

Fred Rogers was a lifelong student of childhood and development. Under the exquisite tutelage of the University of Pittsburgh School of Medicine's Margaret McFarland, he honed his intuitive approach toward children with a solid understanding of developmental principles and an appreciation for the actual work of childhood. Not only did he script every moment of his show, but he also approached every storyline, prop, puppet, and lyric—every last detail—from the perspective of how a child would perceive it and incorporate it developmentally.



Entrance

At the start of every show, Mister Rogers enters his house by walking in the door, which is on the left of the viewer's screen, and moving to the right. This is how children's eyes will track when they learn to read.



The shoe change

While Mister Rogers is tying his sneakers and zipping his sweater, children have the opportunity to settle in. As he gets ready to move into the content of the show, so do they.



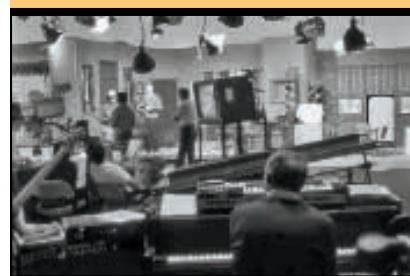
Pace

The show's unhurried pace, in marked distinction from most contemporary children's programs, allows children the chance to process what is being presented, the opportunity to make connections, and the space to concentrate.



Opening and closing moments

Each episode begins with Mister Rogers singing “Won’t You Be My Neighbor?” and ends with “It’s Such a Good Feeling.” Routine gives children a feeling of security.



Music

Piano compositions offer transitions from Mister Rogers’ house to the Neighborhood of Make-Believe through sly key changes that incorporate notes from the old key into the new one. Rogers likens that to a child going to a new school having the opportunity to see mother and teacher together for a moment.



Trolley

The trolley serves as a transition. It brings viewers into the show and ferries them from Mister Rogers’ house to the Neighborhood of Make-Believe and back safely to Mister Rogers again. It also gives young children, who are concerned when parents leave, practice with issues of disappearance and reappearance.



Reality and make-believe

A clear and careful distinction is drawn between what’s imagined and what’s real. Mister Rogers is never present in the Neighborhood of Make-Believe. He does, however, both set up for what will happen in Make-Believe, as well as offer additional commentary when the segment is over. The message to children is that it is they who have control over their pretend worlds.

Unflinching gaze

Mister Rogers often turns to the camera to talk to children—looking right into the television audience for what, to adults, might seem uncomfortably long. For children, though, the eye gaze mimics their earliest interactions with their parents and provides a supportive moment.



You can never go down the drain

Really. But who would have thought before *Mister Rogers’ Neighborhood* aired that young children had very real concerns about those kinds of things?

Text by Sally Ann Flecker
Photography by Jim Judkis

Junior investigators count on the National Institutes of Health to finance their research. Pitt found a way to fuel discovery during the times when political discord leaves scientists unfunded and dangling in the balance.

BRIDGES TO SOMETHING

HOW PITT SPANS THE FUNDING CHASM

BY JENELLE PIFER

In the winter of 2009, Lisa Borghesi was primed to decipher a fundamental question of longevity. She wanted to know how immune cells develop—in particular a variety called hematopoietic stem cells. Accounting for just 1 in 100,000 blood cells, they are solely responsible for regenerating blood throughout life.

“Part of our longevity is determined by how long these stem cells can continue to repopulate,” says Borghesi. “This is a question about life, about vitality.”

Borghesi was still relatively new at the University of Pittsburgh, having joined the faculty as a PhD assistant professor of immunology in 2004. With start-up money—which the University provides to new hires—and several small federal and private grants, her five-person lab team had studied cells in the immune system that produce antibodies, working to understand how they fight infection. It was only in 2009 that their interests began to swim “upstream,” Borghesi says, from the function of mature cells to the complex ways in which they develop. “How are these cells replenished every day?” they wondered.

ILLUSTRATION | MICHAEL LOTENERO

The team was eager to investigate. Specifically, they wanted to understand an underlying transcription factor in hematopoietic stem cells called E47, essential to the regulation of immune cell formation and function. The work had special promise to help patients with compromised immune systems, including those who'd undergone transplants or chemotherapy, says Borghesi. But the proj-

allocated by Arthur S. Levine, an MD senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of the School of Medicine. The other half is allocated by the investigator's department. Funding is based on availability and totals an average of between \$1.5 and \$2 million per year.

"[The program] was created in response to increased difficulty in acquiring external fund-

wide. Of the 74 institutions that responded, 91 percent had formal bridge funding policies in place, according to an analysis published by the AAMC in February.

The Pitt program, then, isn't novel. But it is one of the longest running, administrators having been quick to recognize the power of such a mechanism to help researchers. "Ours was one of the first if not *the* first," says Broido of the program, which began in 2006.

Already, nearly \$8 million in bridge funding has supported Pitt investigators in maintaining the groundwork that

sometimes takes years of labor and significant funding to develop, even before the innovative work can be begun. Costs might involve keeping trained staff on the payroll, making sure selectively bred mice stay alive, and procuring the necessary supplies for day-to-day lab work.

For researchers interested in applying, Broido is the gatekeeper. She is the first person prospective applicants speak with about whether or not they are a good fit and likely to qualify. She also oversees the review committee, made up of faculty within the schools of the health sciences. In three application periods per year, this anonymous group of established investigators considers which researchers deserve bridge funding and how much they should receive. Applicants are considered in five separate categories, each with distinct criteria. There's no set minimum or maximum monetary amount for the award, Broido says, but rather a constant consideration of the question: "Are these the monies really needed to prevent things from falling apart?"

Derek Molliver, a PhD and assistant professor of medicine, joined Pitt as a research associate in 2002 and was able to secure his first R01 relatively quickly. The young scientist led a small team studying the role of the peripheral nervous system in chronic pain. Early on, they discovered a new class of receptors in sensory neurons—called the P2Y family—that Molliver felt could be important in sensing and transmitting pain. The team wanted to characterize the receptors' function. If they could figure out how the receptors were involved, perhaps they could disrupt function and ease pain. But there was a great deal of digging to be done.

Throughout the course of a multiyear grant, the team amassed data, published papers, and

"The idea that the school offers bridge funding says that it cares enough to keep its faculty, even when they're down on their luck a little bit."

ect was big. "And we couldn't begin without knowing we had stable funding," she says. At that point, they didn't.

That winter, Borghesi had narrowly failed to attain an R01, a five-year grant from the National Institutes of Health that she calls "the benchmark for promotion and tenure at most U.S. universities." She was keenly aware that she needed the award—to benefit her research, her lab, and her career. Without it, the salaries of her staff were on the line. She had scored highly, within the top 14 percent. But she was still denied the resources she needed, largely because the U.S. Congress was in the midst of a budget standstill that had left the resources of the NIH undefined, and dwindling. She watched her students' enthusiasm deflate.

"When they see their mentors who are just a few years ahead of them struggling, it is a disincentive for our brightest young people to continue," says Borghesi. Some of the graduate students in her classroom—as well as the postdocs in her lab—began to wonder whether a career in academic research was realistic, she says, or whether the bar was set just a little too high.

"To that point I had only understood the significance of budget impasse in theoretical terms," she says. "It was the first time a congressional situation became very personal." That winter *Nature* published her op-ed on the subject. "What makes the crucial difference for me," she wrote, "is tremendous support from my department and colleagues."

In those early months of 2009, Borghesi, now associate professor of immunology at Pitt, was among a handful of researchers chosen to receive bridge funding—a short-term grant from Pitt meant to "bridge" lapses in funding from external sources. Half of each award is

ing," says Michelle Broido, a PhD and associate vice chancellor for biomedical research for the health sciences. "In particular, applications that did very well in peer review, that in previous years would likely have been funded, were not being funded."

Here's how it works: NIH money goes to applicants who score within a certain top percentile after peer review. The exact percentage of funded applications—called "the payline"—is determined by budget. When the budget dips, the payline gets lower. In the 2013 fiscal year, the payline at many of the institutes hovered just above or in the single digits. In this way, budgetary decision making at the federal level always affects the greater scientific community. But current politics are unprecedented, forcing a funding scarcity and leaving the careers of both junior and established researchers victims of bad timing.

For the past decade, the NIH's budget has been shrinking. Since it peaked in 2004, small increases in funding have failed to meet the pace of inflation. This alone shriveled the agency's spending power by some 20 percent. Then the 2013 sequester took hold, slashing an additional \$1.55 billion—or 5 percent at each of the 27 institutes. The NIH turned away patients from its own clinical trials and shelved projects exploring ways to use stem cells to cure Parkinson's disease, manage pain in sickle cell disease, and diagnose autism sooner.

In such a funding climate, bridge funding is popping up at more research universities across the country as one of the best, if most temporary, options for helping investigators make do. In 2013, the Association of American Medical Colleges surveyed 123 medical schools nation-

succeeded in expanding the basic knowledge of the subject. “But then my renewal didn’t go through,” says Molliver. In 2012, he had a lapse in funding. “The application got a fairly low impact score, which is sort of the kiss of death,” he says.

One of the key discussions Broido has with researchers interested in bridge funding explores why the application wasn’t funded in the first place. “Consider this,” says Broido. “Somebody proposes something. It’s a good question. The person has the expertise to do it and the facilities to do it, but one experimental component is fatally flawed. The reviewer is going to think, *No*, and the score will not be good.” Contrast this with the case in which reviewers judge the potential impact of the work to be low. The study is sound experimentally, but is it really the best use of money? The reviewer is going to think, *No*, and the score will not be good.

“You can have the same poor score with two different meanings,” says Broido. “In determining whether or not to apply for bridge funding, the difference between the two is important.” Bridge funding is only awarded to those projects that have a reasonable expectation of receiving external funding within two years. “Otherwise there’s no point,” says Broido, “because you’d be building a bridge to nowhere.”

Molliver’s application, with its low impact score, was not eligible for bridge funds.

But he bounced back quickly. “Once we got those criticisms, we retooled,” he says. During the course of their previous research, Molliver and his team had uncovered something exciting. “There was a related family of receptors that were potentially analgesic,” he says. The receptors they studied initially were helping to transmit pain signals, but this related subset actually seemed to be blocking them. “So we started looking at how we could harness those potentially analgesic receptors to treat persistent pain.”

He resubmitted a brand new R01—“a much stronger application,” he says—and though the application still fell outside the payroll on first attempt, the impact score was higher. This time, he qualified for bridge funding and received \$32,000 to support the lab while he revised the application to include additional preliminary data. He subsequently

garnered a \$750,000 R01 to fund his lab through 2017.

Young researchers, historically, compete not only with one another but also against long-standing labs and investigators with established track records. In her op-ed in *Nature*, Borghesi wrote about “the trend that has raised the average age of first funding from 37 in 1980 to 42 in 2007.” To combat the numbers, the NIH in recent years began funding a slightly wider payroll for “new investigators”—those who have not previously achieved federal funding as principal investigator or program director on a project—and asked that review committees put less emphasis on their track records and preliminary data in favor of their overall approaches. Consequently, from 2006 to 2010, the number of new investigators receiving competing R01s increased. Still, the average age at first award has not lowered. In 2009, just before receiving her first R01, Borghesi wrote, “My age? 39. My optimism? High, reflecting a supportive university environment.”

Both Borghesi’s and Molliver’s cases involved awards that helped preserve the career

medicine, was among them. She uses an animal model to study mechanisms related to injury and repair in the lungs.

“We actually don’t know a lot about lung injury. We know when it happens to patients, but we don’t exactly understand the process,” she says, noting that the work is important for treating a number of conditions, including pneumonia, pancreatitis, sepsis from aspiration, and even fibrosis.

In 2011 she was several years into a five-year R01. “I remember trying to prepare for the worst,” she says of the period before her renewal was due. She watched the NIH payroll tick up and down, dipping as low as 6 percent at her funding organization, the National Heart, Lung, and Blood Institute. She looked at what she was spending and proactively made adjustments, creating for herself what’s called a “no-cost extension,” which essentially allowed her additional time to use the funding she saved by operating frugally. She bred fewer lines of mice, purchased only essential reagents, and left a lab staff position unfilled.

“I wanted to calibrate my spending so that I knew I had enough money to keep going for a while. Not forever.”

It was a prescient move. Lee’s renewal fell

“People who have had 20 years of continuous funding are having problems, and that’s a direct function of money being cut.”

paths for tenure-track investigators who experience a delay or lapse in funding.

Although bridge funding has surely been a strong source of support for young researchers at Pitt, this was never the sole intention of the program. “No, in many ways the original focus of bridge funding was for people who had funded projects, who applied for renewal funding and, as they say, came close but didn’t get the cigar,” says Broido. “People who have had 20 years of continuous funding are having problems, and that’s a direct function of money being cut.”

Enter Pitt’s Category Two, wherein established tenured or tenure-track investigators can apply for funding to continue projects that have been ongoing for years, or even decades. Near the close of one funding period, several applicants’ renewals were unexpectedly denied.

Janet Lee, an MD associate professor of

below the NIH payroll, yet her score was close enough to qualify for \$50,000 in bridge funding from Dean Levine and an equal amount from her department. Combined with her own frugality, it was enough to support key personnel and maintain animals until her R01 was successfully renewed in the following cycle.

While Lee’s effort to calibrate spending is perhaps a useful exercise, it’s also emblematic of a time-consuming—and some might say all-consuming—new pressure that diverts scientists’ attention away from their work and toward the bottom line.

“It’s a second job to look for research money,” says Bruce Rollman, a tenured MD professor of medicine and 2011 bridge fund recipient. Rollman has conducted NIH-funded clinical trials for treating mood and anxiety disorders in primary care and cardiac settings for more than two decades. Yet in

2010, while successfully completing two trials—including one published in the *Journal of the American Medical Association* in 2009—he found himself suddenly unable to secure new NIH grants.

As a result, Rollman had to lay off most of his staff, some of whom had worked with him for a decade or longer. “I was able to network with colleagues to find everyone new positions,” he says. Nobody was left unemployed, but Rollman found himself “in a near-death experience as a clinical investigator.” Since then, he has won nearly \$10 million for two new R01 trials—one testing the effectiveness of an Internet support group to treat depression and anxiety in primary care and another testing the efficacy of a “blended” model for treating depression and heart failure together. Yet climbing out of the deep hole wasn’t easy.

What really helped Rollman continue—he insists—was a small but critical boost he received through Pitt’s bridge funding program. Those funds allowed him to retain his project coordinator (who had been with him for 11 years) as well as a statistician and a graduate student data analyst. This small team continued to write and publish data from completed trials while Rollman focused on new grant applications.

His clinical research team is now eight people strong, he says, and will double in 2014.

Perhaps the most basic idea underlying the power of bridge funding is that a small investment today can lead to a bigger award in the future. At Pitt, it’s estimated that at least 70 percent of bridge awards lead to subsequent funding, says Broido, who notes that this figure doesn’t include funds received through private foundations and other non-NIH sources and is likely low. The AAMC analysis also underscores the amplification effect. For the several schools that made data available, bridge funding led, on average, to nearly 12 times the amount in external funding.

Take, for instance, the experience of Pitt’s Gregg Homanics, PhD professor of anesthesiology, who in the winter of 2009 was getting the sinking feeling that he was living a researcher’s version of *Groundhog Day*.

“I was really frustrated,” he says, “I had a grant that we made a lot of progress on a few years prior. It was a long-standing grant, it didn’t get renewed, and I had to give up the work. I was afraid the same thing was going to happen with this project.” In 2009 he failed to

renew a second R01 on a project he’d pursued for 14 years.

The work sought to study the molecular effects of alcohol in the brain. Despite alcohol being the most widely used and abused drug, the mechanisms underlying alcohol-induced behavioral changes remain largely unknown, says Homanics. His project uses two approaches in genetically altered mice. One investigates the role of a common type of brain receptor called GABAA in affecting behavioral change through alcohol use. The other explores epigenetic effects—those that are genetically inheritable that affect gene expression—in the presence of alcohol in the brain.

Through a total of \$20,000 in Category Two bridge funding—“a small drop in the bucket,” says Homanics—he leveraged approximately \$4.7 million in research dollars over 10 years in the form of a prestigious NIH MERIT (Method to Extend Research in Time) Award. “We asked for five years of funding, but they said, ‘We like this so much, we’re going to give you ten years of funding,’” says Homanics, who is funded through the National Institute on Alcohol Abuse and Alcoholism.

In a passage on its Web site, the NIH characterizes the MERIT Award for researchers as intended “to foster their continued creativity” and “spare them some of the administrative burdens” of grant applications.

For the bulk of his career, Greg Siegle, a PhD associate professor of psychiatry, accepted that when people get depressed or anxious, they become very reactive. “Their brains react strongly to emotional information, and they keep reacting,” he says.

But three years ago, he and collaborator Wendy D’Andrea at the New School in New York City began wondering about the opposite end of the spectrum—whether people with various psychiatric disorders might shut down or stop processing emotional information altogether. Once they opened their eyes to the possibility, it was everywhere they looked.

“It was like realizing I was looking at only half an elephant for the past 20 years,” Siegle says. “It was not just a slightly broader perspective as much as an entire retrenching of my theoretical, methodological, and analytical platform.”

While the other bridge-funding groupings support scientists at career stages either early or advanced, Category Three bolsters investi-

gators who, in some way, find themselves at the nexus of both. “We recognized that there were established investigators who wanted to change their research direction,” says Broido.

Siegle and D’Andrea launched an R01 project to scan the brains of people in various diagnostic categories—including PTSD, anxiety, depression, and borderline personality disorder—and characterize the results. When the grant was not funded initially, strong support from his department—including chair David Lewis and assistant director of research Hermi Woodward—helped Siegle secure \$60,000 in bridge funding and ultimately find R01 funding success.

Departmental support and a letter from the chair are must-haves in any bridge application, as the department funds half of any award that is made. For Siegle, it underscored the idea that being a medical researcher is not at all like having a job without a net. “The idea that the school offers bridge funding says that it cares enough to keep its faculty, even when they’re down on their luck a little bit,” he says. “And that conceptual support is huge.”

Bridge funding is a support system that continues to evolve. Broido and her colleagues create new categories as they watch needs arise. There is a fourth grouping for scientists who officially earned funding but experience delays getting the money. And a fifth that’s investigator-based and awarded, albeit rarely, on the basis of track record.

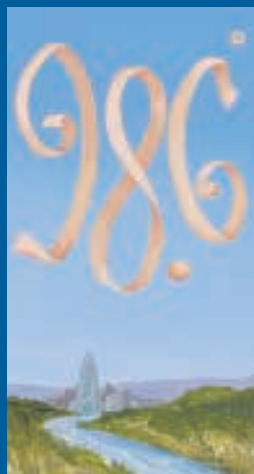
This fall, Broido and her team explored how Pitt scientists were affected by the 16-day government shutdown, asking, *How might bridge awards accommodate them?* Happily, they found that Pitt scientists had survived the shutdown—which occurred just after the September application period closed—unscathed, though they remain on the lookout for less positive scenarios.

Borghesi herself is unsure how things will go for her lab this time.

She has a second grant in the works—a smaller R21 that received promising initial scores from reviewers. But no matter where the payroll falls, she knows how she’ll react.

“The difference is I don’t take it personally. Before, I took it as a reflection on my scientific competence. Now, I understand that this is the status quo.” It’s happening to everyone, she says. And the best thing investigators can do for themselves, their students, and their universities is to maintain enthusiasm for the work itself, to “keep focus and try to drive good science.” ■

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



COURTESY OF THE WOOD LIBRARY-MUSEUM
OF ANESTHESIOLOGY, PARK RIDGE, ILLINOIS



**Anesthesiologist Ephraim Siker
extended his passion for innovation
to the professional societies he led.**

A NEW AGE IN ANESTHESIOLOGY

PROFESSORSHIP ENDOWED

BY NICK KEPPLER

Jan Ehrenwerth (MD '73) was a young medical student unsure what specialty to pursue when he entered a summer program to shadow a doctor at Mercy Hospital (now UPMC). He was paired with Ephraim Siker, MD, chair of the Department of Anesthesiology.

"He was always pulling out new pieces of equipment for monitoring patients and getting excited over them," recalls Ehrenwerth. "It was like Christmas morning all the time in our department." He says that Siker, who died in June at the age of 87, "always stressed that we were on the verge of a new age in anesthesiology." Ehrenwerth, now a professor of anesthesiology at Yale School of Medicine, was one of many students whom Siker recruited into the field during his 34 years as chair.

Always enthusiastic about discovery and travel, Siker leapt at the Nixon administration's call for doctors to go to China after the reestablishment of diplomatic relations in 1973. He was one of eight American physicians chosen for the mission, on which his interest in pain management, pain pathways, narcotics, and narcotic management dovetailed with the study of holistic Eastern medicine and an investigation of the efficacy of acupuncture.

To honor Siker's legacy, the University of Pittsburgh Physicians and UPMC Mercy's Department of Anesthesiology are creating

in the area of patient safety.

Siker was enamored by his field from the start, says Eileen Bohnel Siker, his wife of 62 years. "He did a brief rotation in surgery as a resident [at Westchester County Hospital], and he didn't care for that at all; but once he did an internship in anesthesiology, he was captivated by it because it was at a pioneer stage."

Siker served in the U.S. Navy and in a MASH unit during the Korean war. In 1952, he moved to Pittsburgh to finish his residency at Mercy. In 1955, he held a one-year teaching position as a consultant in the British National Health Service at the Welsh National School of Medicine. In 1960, he was appointed chair of anesthesiology at Pitt.

Over the years, Siker held myriad leadership roles in his field. He was a founding member and first executive director of the Anesthesia Patient Safety Foundation, president of the American Board of Anesthesiology, and president of the American Society of Anesthesiologists. He also wrote the section on narcotics for the *Encyclopedia Britannica*.

A voracious reader, enthusiastic gardener, and accomplished pianist, Siker had a knack for magic tricks and a reputation as a true gentleman. "He and his colleagues had a high level of congeniality," says David Siker, MD, his son and a neuroradiologist in Portland, Ore. "That kind of stuff gets lost these days."

Those wishing to contribute to the chair established in honor of Siker can send checks to: *Siker Fund in Anesthesiology and Patient Safety, Development Office of UPMC Mercy, 1400 Locust St., Pittsburgh, PA 15219.* ■

BOOSTER SHOTS

There is no shortage of child-centric charities founded by major league ball players, from Derek Jeter's Turn 2 Foundation to the David Ortiz Children's Fund. **Elliot Mast** of Altoona did not wait for big-league fame to start his own nonprofit effort. Nor did he wait until he turned 12.

Four years ago, he and his family started organizing an annual auction, a sale of sports memorabilia to benefit the Child Life Department at Children's Hospital of Pittsburgh of UPMC.

Elliot was born with club foot. Though UPMC surgeons corrected it, the ailment stays on his mind. "I'm always aware if it weren't for them, I wouldn't be able to play ball like I do," says Elliot, now 15 and a starter on Altoona High School's junior varsity team.

The family got out the word through social networking—including Elliot's Web site, elliotmast.blogspot.com—and dozens of sports stars have stepped up with donations. Countless signed baseballs, jerseys, photos, and Topps cards have been auctioned. This year's hot-ticket item, donated by former NFL running back Rocky Bleier, was a set of Steelers Legends tickets, which allowed the holders to attend the 2013 opening game with Bleier and other Steelers alumni.

Four auctions—the most recent during the minor-league action at Peoples Natural Gas Field in Altoona in August—have raised more than \$15,000. Not bad for someone not yet old enough to drive.

—NK



CLASS NOTES

'50s

After 40 years in the Air Force—as a combat veteran of WWII, an MD in the Korean and Vietnam wars, and as chief of ophthalmology at USAF School of Aerospace Medicine—Colonel **Tom Tredici** (MD '52, Ophthalmology Resident '56) finally retired from active duty in 1987. But it didn't stick. He stayed on as a civilian senior scientist with the Aerospace Ophthalmology Branch until 2011. It was Tredici who first formalized the ophthalmology curriculum for flight surgeons, as well as certification for ophthalmologic technicians. In his decades of research, he developed UV-radiation-proof visors for astronauts and contact lens safety standards for aviators. He also showed that intraocular lens implants were safe for pilots who'd been grounded by cataracts—even jet pilots. “That, I think, is kind of a miracle,” Tredici says of the latter accomplishment, which has put some 150 aviators (from the 40-plus set) back into the cockpit. “They're good, quality fliers, and their careers have been salvaged.”

'70s

William Young (MD '70) began his global-health journey in 1970, traveling to El Salvador with a group from what is now Magee-Womens Hospital of UPMC. Later, as an ob/gyn professor at Dartmouth, he served as a clinician and faculty member on medical-volunteer trips to Kosovo (which he still coordinates now as an emeritus professor). In 2001, while on a similar trip to Nicaragua, he met a Dartmouth med student from western Kenya, Milton Ochieng', orphaned by AIDS. Like his brother, Fred Ochieng', Milton would come under Young's wing as a physician-in-training. In 2007, the three MDs realized a shared dream with the

opening of Lwala Community Alliance, which provides medical care, health education, and potable water systems in the rural village where the brothers grew up. “It all started as a grassroots effort, two bright young people being the inspiration,” Young says. “They charge up the rest of us.”

'90s

As the chief physician safety and quality officer (PSQO) at Froedtert Hospital and the Medical College of Wisconsin, **Timothy Klatt** (MD '92) helps colleagues unlearn their automatic reaction when things go wrong—namely, to point fingers. Blame culture is all too prevalent in health care. “The things I really love are the near-misses,” he says. “When there's a bad outcome, people get defensive. But after a near-miss, people will talk, and there's a clear urgency for the need to improve.” Klatt, an ob/gyn, served a one-year trial as Froedtert's first PSQO in 2010. The results of his various quality and safety projects (to lower birth trauma rates, for example) were so encouraging that he was asked to lead the efforts of all 19 departments.

For a tumor to show up in an MRI or CT scan, it has to be almost a cubic centimeter. When cancer spreads from primary to secondary sites, the new seedlings begin much smaller than that. The only way to see these secondary masses is to operate. This is exactly the scenario **Charles Staley** (General Surgery Resident '92), chief of the division of surgical oncology at Emory University, finds in about a fifth of his patients who have pancreatic cancer. “You want to be able to stage people accurately so you can decide what the best treatment is,” he says. Staley is working to develop nanoparticles that will make cancer easier to detect, stage, and treat. In his team's animal studies, they've found that these new tools can detect tumors as tiny as 1 millimeter and deliver chemotherapy to even the pancreas—a notoriously difficult feat. “[Pancreatic] tumors have this almost impenetrable force field around them. They create dense

stroma—connective tissue. But these nanoparticles seem to be able to get through it.”

When she joined the staff of UPMC Presbyterian in 1996, it was a mentor—Anthony O. Udekwe—who first interested **Anita Courcoulas** (MPH '93, Surgical Res '95, Pediatric Surgery Research Fellow '96, Minimally Invasive Surgery Fellow '00), chief of minimally invasive bariatric and general surgery at Pitt, in surgically treating obesity. Now she performs and advocates for bariatric laparoscopic procedures suitable for treating morbidly obese patients. Shown to be one of the most effective ways to help these patients lose weight and keep it off, bariatric surgery also lowers cardiovascular and diabetes risk. Her research on long-term effects of bariatric surgery across the United States in the NIH-funded Longitudinal Assessment of Bariatric Surgery was published in December 2013 in the *Journal of the American Medical Association*.

In the '90s, emerging technology and pressure from insurance companies to improve patient recovery and shorten hospital stays inspired **Brian Williams** (Res '95, Anesthesiology Fellow '96, Katz MBA '96), professor of anesthesiology and director of ambulatory anesthesia, to bring regional anesthesia to UPMC sports medicine orthopaedic surgery. This technique uses drugs to numb and immobilize an area of the body and provide sustained pain relief after surgery. Surgical patients undergoing regional anesthesia are often out of the hospital on the same day, bypassing the recovery room entirely. Since late 2010, Williams has worked on sustained pain relief after nerve block injections for surgery. In a yet-unpublished study, this strategy has yielded 40 hours of pain relief for patients undergoing total knee and total hip replacements, reducing mortality and morbidity rates. In May, Williams received a Distinguished Alumni Award from Northeast Ohio Medical University.

'00s

Pitt assistant professor of psychiatry **James Tew Jr.** (MD '01) is, in his own words, a “pretty good teacher,” but his students give him more credit. Three years in a row, Pitt med first-years have given him the Excellence in Education Award. And for the past two years, as medical director for care management at Western Psychiatric Institute and Clinic (WPIC), Tew has applied his instructional savvy to improving clinical efficiency at the hospital. In a 45-minute talk, delivered in his trademark charismatic style, he's educating docs on essential principles of the Affordable Care Act—i.e., how to deliver the high-quality services they always have, but in less time. “Especially with an aging population,” he says, “we need to create more capacity. We have to be more efficient.” So far, Tew's efforts are working. In 2011–12, his geriatrics unit went from serving 465 patients to 681, dropped the average length of hospital stay from 33 days to 20, and significantly reduced 30-day readmission rates.

After working during medical school with J.B. McGee, MD director of Pitt's Laboratory for Educational Technology, and



Courcoulas



Williams (center) and colleagues at Northeast Ohio Medical University's 2013 commencement ceremony.

during his residency with the late James Levin, then-chief medical informatics officer of Children's Hospital of Pittsburgh of UPMC, **Jonathan Bickel** (MD '04, Pediatrics Resident '07, Biomedical Informatics MA '10) discovered his passion for biomedical informatics. Now, as director of clinical research informatics and director of business intelligence at Boston Children's Hospital, he acts as "a translator between the clinical and the technical," working with algorithmic, clinical, and biological models. For example, certain patterns of ER visits can be used to identify a person who may be suffering from domestic abuse. Bickel hopes that algorithms like this can be used to help doctors provide better care for their patients.

'10s

Michelle Moniz's (Ob/gyn Resident '12) quest for a practice that was "patient centered and population aware" led her to a fellowship at the University of Michigan as a Robert Wood Johnson Foundation Clinical Scholar. This prestigious program allows Moniz to pursue her own research—a project focusing on how social marketing can prevent excessive weight gain in pregnancy—while rubbing elbows with experts in such fields as business, communication, and behavioral therapy. The interdisciplinary approach feeds Moniz's desire for more global perspectives in treating patients and doing research, all while she pursues her master's degree in health and health care research.

—Rachel Puralewski and Elaine Vitone

AMY GOLDSTEIN

MITO DETECTIVE

During Amy Goldstein's (MD '96, Res '99) intern year, a 2-year-old who had been repeatedly admitted for failing to thrive arrived at UPMC Mercy in a coma. Her case had confounded doctors for a year. But that day, when the child's lactate test results came back high, pediatric neurologist Rajiv Varma walked into the room and said, simply, "This child has mitochondrial disease." And walked right back out.

Goldstein was flummoxed. "What just happened? What is mitochondrial disease?" she asked. Such diagnostic skill was "the coolest thing" she'd ever seen. "I thought, *If I could be that smart one day, that would be awesome.*"

In 2007, Goldstein, who is now both a pediatric neurologist and that smart, founded Children's Hospital of Pittsburgh of UPMC's multidisciplinary mitochondrial disease clinic. It's one of a few of its kind in the country.

Inside every human cell (except red blood cells), mitochondria create adenosine-5'-triphosphate (ATP), the molecules that supply 90 percent of the body's energy. When mitochondria fail, things fall apart—hearing, vision, the endocrine system, the central nervous system, skeletal muscle, the heart, the liver, the GI tract.

And with symptoms varying so widely, the disease can be hard to spot.

"For instance, they'll come in with their first stroke when they're a teenager," says Goldstein. Then, in talking with the parents, more red flags pop up: failure to thrive, short stature, migraines, diabetes, and deafness running in the family. "Before you know it, we've diagnosed six family members. ... People didn't realize it's the same disease, just at different levels."

There's no cure—or even treatment—available for these patients. In her research, Goldstein is working to change that. She gives patients a vitamin cocktail that she's developing to facilitate ATP creation, then measures its effect using exercise treadmills and MRI scans.

"There's mitochondrial dysfunction in every degenerative disease you can name," says Goldstein. Thus, she is active in the Mitochondrial and Metabolism Working Group at Pitt, the Mitochondrial Medicine Society, and the North American Mitochondrial Disease Consortium, among others. Someone's insights into Alzheimer's could benefit Goldstein's patients, and vice versa, she says. That would be awesome, indeed.

—Amy Whipple



Amy Goldstein (right) with her patient, Lindsey Meyer (center), and Lindsey's mom, Heather Meyer.

MAA SAYS, "GO TEAM"

Gloria (née Kohl) and **Robert Wilkins** (MD '59) are one of those duos who do everything together. One year, during Robert's nine-year residency in surgery and neurosurgery, he had no funding for a lab assistant. Gloria (BA School of Education '58) volunteered, even though she had no background in biology; they went on to publish their results together. The Wilkinses also teamed up to found the journal *Neurosurgery* in 1977, edit the textbook *Neurosurgery* in 1985 and 1996, and publish *Neurosurgical Classics II* in 2000. And early in his tenure as chair of neurosurgery at Duke (1976–96), when Robert found himself without an administrative assistant, he asked Gloria to fill in for a couple of weeks. She stayed on for 18 years.

The couple plays together, too. They've watched Pittsburgh Steelers games from the sidelines (pictured above)—their son Mike Wilkins is part-owner of the franchise. The family has kicked off a Pitt med scholarship in honor of its esteemed alumnus; naturally, the Robert H. and Gloria Kohl Wilkins Student Resource Fund celebrates both halves of the husband-and-wife dream team. "Both of us owe Pitt a lot," says Robert.

In November, the **Medical Alumni Association (MAA)** enlisted Pitt med alums to put quite a few pennies into students' purses as well, raising \$15,000 in the annual phonathon. These gifts help tackle the cost of tuition, as well as travel expenses for conferences and for clinical or research experiences in underserved areas.

MAA will welcome alums—including Robert Wilkins' Class of '59, which is celebrating its 55th reunion—and other assorted Pitt med boosters back home for Medical Alumni Weekend, May 16–20. Join in to take a tour of WISER, celebrating its 20th anniversary (and pick up CME credit while you're at it); hobnob at the Reunion Gala; and take in this year's installment of *Scope & Scalpel*, starring the Class of '14. See p. 40 for the full calendar. For more details, contact Pat Carver at cpat@pitt.edu. —EV



Gloria and Robert Wilkins at a recent Steelers game

ANDREW S. FISHER

APRIL 3, 1978–DEC. 8, 2013



Fisher

The memorial service for Andrew Fisher (MD '08, Internal Medicine Resident '11) was held on a snowy Saturday in Pittsburgh within the elegant stone-and-wood confines of a 110-year-old church in Shadyside. Through eloquent testimonials and a few sing-alongs, the service paid tribute to a man who was said to bring out the best in everyone he met, built community around him, was full of love for

his young family, and never hesitated to go barefoot, sing karaoke, bike to work in bad weather, or dress in costume.

Fisher, an internal medicine physician with UPMC's Solano & Kokales Internal Medicine Associates, died on December 8 in an accident on the Pennsylvania Turnpike following a chain-reaction crash. He had left his car to assist others and was hit by a vehicle that slid off the road.

Fisher's colleague Amy Soni, MD, addressed him directly on a Facebook page that became a memorial as the news of Fisher's death spread. *The last time I saw you, she wrote, you had biked to the hospital. It was so cold that your bike lock was frozen shut, but you came in to help on your day off since folks had been slammed with admissions the night before.*

As a U.S. Peace Corps volunteer in Jamaica, Fisher educated health care workers on HIV/AIDS, taught classes, and came to the realization that he could best serve others as a physician. In 2005, after his first year of med school, he married his Peace Corps sweetheart. Elly and Andy Fisher have two children, Peter, age 5, and Estelle, age 3. The family invites contributions to the Andrew Fisher Memorial Fund through the Pittsburgh Foundation (pittsburghfoundation.org/give_a_donation) so that the children may annually celebrate their father's giving spirit through the foundation's work. —Chuck Staresinic

GEORGE J. MAGOVERN

NOV. 17, 1923–NOV. 4, 2013

George Magovern Sr. joined the staff at Allegheny General Hospital in 1959, in an era when the staff regularly collaborated with UPMC doctors. After performing the first successful heart valve replacement at AGH, Magovern, an MD, joined his colleagues at UPMC Presbyterian to perform the world's second lung transplant.

"Most thoracic surgery in the early '60s was pulmonary surgery, because heart surgery was in its infancy," says his son George Magovern Jr. (MD '78). He adds that his father and Hank Bahnson, Pitt chair of surgery 1963–1987, "were competitive, but remained friends and collaborators for their entire careers."



Magovern

Always innovative, Magovern became known by colleagues as "The King of Hearts." He sought a way to reduce surgery time—nearly half of open-heart surgery patients died on the operating table in the '60s—and conceived of a valve that could be attached with clips instead of sutures. Magovern popped into a machine shop he passed on his way home from work to see if the machinist could build a prototype. The resulting Magovern-Cromie valve improved patient outcomes to 90 percent.

Magovern's teenage sons became curious about their father's occupation, and the elder Magovern invited George Jr. and James (MD, '80) to the observation tower above Presby's operating theater. The boys peered down to watch, fascinated as much by the heart-lung machine as George Sr.'s apparent skill. "We looked at our dad doing something obviously very satisfying and intellectual. He was head of the team and very well regarded, and we wanted to follow in those footsteps," says George Jr. Both sons went on to study medicine at Pitt, following their father into careers as cardiothoracic surgeons at AGH.

By the time Magovern Sr. was appointed chair of surgery in 1970 (a title he held for 24 years), he had performed AGH's first heart

transplant. He developed the largest open-heart program in Pennsylvania and the 10th largest in the United States. He built the first trauma center in the tri-state region and was named director of the American Board of Thoracic Surgery (ABTS). Upon retirement, George Sr. handed the reins to George Jr., who is now chair of thoracic and cardiovascular surgery at AGH and director of ABTS.

—Katy Rank Lev

DAWN A. MARCUS

JULY 13, 1961–OCT. 19, 2013



Marcus

Keep the introduction short, Dawn Marcus (Neurology Resident '90) told her colleague and friend Cheryl Bernstein (Fellow '02) before a presentation: *Dr.*

Marcus is a neurologist who treats fibromyalgia and headaches.

"She had this long list of accomplishments, and that's all she wanted me to say about her," says Bernstein, associate professor of anesthesiology and neurology. "She was very modest."

Marcus died October 19 from a heart attack while on a bike ride with her husband. She was 52.

There was more to Marcus, of course, than her requested short introduction: staff neurologist and coordinator for Pitt's Pain Evaluation and Treatment Institute, professor of anesthesiology at the University of Pittsburgh, Animal Friends volunteer, and author of 17 books.

Marcus took a multidisciplinary approach to the treatment of chronic pain, from medication to meditation. Her more recent research and practice focused on the therapeutic effects of dogs. She even had her own dogs trained and certified as therapy animals so she could bring them to her clinic.

Marcus was patient and compassionate both in and out of her exam room, says Bernstein. As a mentor, Marcus pushed her students and mentees to work harder, reach higher. She could field just about any question from patients with chronic pain and provide thorough answers, complete with research citations.

"She brought a light with her," says Bernstein. "There isn't a day that goes by that I'm not sad she's gone." —Amy Whipple

IN MEMORIAM

'40s

ROBERT HOOD
MD '44
NOV. 4, 2013

'50s

ARTHUR J. PASACH
MD '54
OCT. 29, 2013

WILLIAM A. FREY
MD '49
NOV. 19, 2013

RACHEL EASH-SCOTT ON THE FRONT LINES OF COMMUNITY CARE

BY LILY DAYTON

One of **Rachel Eash-Scott's** (MD '03) first patients was a missionary who came to her 38 weeks pregnant and searching for a doctor. After being out of the country for most of her pregnancy, she'd recently returned to the United States—where she spent several weeks calling medical offices, to no avail.

"She was one of those people who get ignored by our system, one of the people you don't hear about on TV," says Eash-Scott. With an income too high to qualify for social services—but too low to afford health insurance—the soon-to-be mother couldn't find anyone to care for her. And then she called SouthEast Lancaster Health Services, a Federally Qualified Health Center (FQHC) in Lancaster, Pa., where Eash-Scott worked.

"We said, 'Of course we can help you,'" Eash-Scott remembers. She cared for the patient, who gave birth to a healthy baby. From that moment, the desire to dedicate her career to FQHCs was cemented in Eash-Scott.

With roots in the community health centers of the 1960s, FQHCs grew from the Civil Rights Movement and President Johnson's "War on Poverty." In the 1990s, Medicaid and Medicare benefits were expanded to include FQHCs. Today, they act as the sole "safety net" providers in many communities, offering a sliding fee scale—no one is turned away for inability to pay. More than

22 million people were served by FQHCs in 2012, a doubling since 2002.

In July 2013, Eash-Scott became medical director at Health Ministries Clinic, an FQHC in Newton, Kan. Sixty percent of the clinic's patients are uninsured, with most others on Medicare or Medicaid. She points out that at least three fellow Pitt med grads—**Michelle Dorsten Catanzarite** (MD '03), **Jonathan Weinkle** (MD '03), and **Kristen Cotter** (MD '04)—also work in FQHCs.

"These patients really need our help—and that feels good," says Catanzarite, who has served as medical director of Community Health Centers of Greater Dayton since 2009.

Like Eash-Scott, she not only practices medicine, but also uses her expertise to help patients navigate the health care system within their social and economic constraints.

Increasingly, people *with* choices are also coming to her clinic, says Eash-Scott, for a couple of reasons. For one, evidence-based care, which is the best way to prevent disease and larger problems, is built into the guidelines for FQHCs (they're now one of the nation's largest data repositories). For example, Eash-Scott's clinic tracks patients with diabetes to ensure that they receive eye exams and foot checks and manage their blood sugar levels—practices that have been shown to result in fewer complications, as well as reduced health care costs from diabetes-related illness.

Another reason patients choose her clinic is its user-friendliness. "We're one of a handful of places that I know of in Kansas that are truly doing integrated mental health care with our medical care," she says. Offering the gamut—mental health, dental health, and medical care—in the same building allows Eash-Scott to pull a counselor into the exam room at any time to help a patient as soon as she identifies a problem—such as depression or anxiety—or to support lifestyle changes—such as quitting smoking or starting an exercise regimen. There's no need for a patient to return for a second visit.

"All these things really affect health care," Eash-Scott says. "It's exciting to give patients the care they need in that moment." ■

COURTESY EASH-SCOTT



Eash-Scott, who received a National Health Service Corps scholarship as a Pitt med student, is now medical director of Health Ministries Clinic, a Federally Qualified Health Center in Newton, Kan.

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, like: What's going on with this scene we found in Pitt's 1975 edition of *The Owl*? Send us a message in a bottle (or via medmag@pitt.edu).





I DO. AGAIN.

As part of the Heinz Memorial Chapel's 75th anniversary celebration, 184 couples—including 11 MD alumni—renewed their wedding vows on November 23. Max Baer (BA '71), a justice of the Pennsylvania Supreme Court, officiated. A pipe organ medley of processional set the mood, and Baer gave a brief sermon. Some 200 couples affirm their romantic love at the nondenominational chapel each year, he noted, yet it is friendship that sustains them through the subsequent years.

Then Baer asked the couples to rise from their pews and face one another. With hands clasped so their entwined fingers touched each other's wedding bands—and as children and grandchildren squirmed nearby—each again declared, "I do."

Couples traveled from as far as California. Some had been married 50 years (to the day). Others, not yet six months. For one pair, the day marked their 17th renewal.

Toni Robinson-Smith (BS '81, MD '86) was ill in the hospital when she received an invitation to the event. As a student, she visited the chapel for solace. In 1998, she and her husband were married there. Returning to renew her vows was poignant, she says. "I was happy to be well enough to be a part of it."

Nicholas J. Feduska (BS '63, MD '67), too, visited the chapel whenever possible during his student years. He celebrated his entry into the world of medicine there on May 31, 1967, and three days later returned to the Gothic structure to marry fiancée Katharine Wong. "The chapel has always meant so much to us," he says. "So many happy memories."

Plastic surgeon Robert Bragdon (MD '73) and nurse Theresa "Bunny" Clements married in the chapel in 1968. Over the intervening 45 years they've brought up four daughters and worked together for three decades. For them, says Bragdon, the renewal was "our time to be together and focus on each other."

—Amy Whipple

—Photograph by Tom Altany

CALENDAR

FOR ALUMNI & FRIENDS

ALUMNI RECEPTION

FEBRUARY 19

Palm Beach, Fla.

WINTER ACADEMY

FEBRUARY 21

Naples, Fla.

www.winteracademy.pitt.edu

MEDICAL ALUMNI WEEKEND 2014

MAY 16–20

Reunion Classes:

2004, 1999, 1994, 1989, 1984,
1979, 1974, 1969, 1964, 1959, 1954

SENIOR CLASS LUNCHEON

(ALUMNI WELCOME)

MAY 16, 11 a.m.

Campus View Club, Peterson Events Center

OPENING RECEPTION

MAY 16, 6 p.m.

Heinz History Center

SCOPE AND SCALPEL PRODUCTION

MAY 16, 7:30 p.m.

MAY 18, 2 p.m.

Venue TBA

For information:

www.scopeandscalpel.org

CHAMPAGNE BREAKFAST WITH THE DEAN AND PHILIP S. HENCH DISTINGUISHED ALUMNUS AWARD PRESENTATION

MAY 17, 9 a.m.

11th Floor Conference Center, Scaife Hall

WISER 20TH ANNIVERSARY TOUR

MAY 17, 12 p.m.

WISER, 230 McKee Place

REUNION DINNER GALA

MAY 17, 6 p.m.

Fox Chapel Golf Club, 426 Fox Chapel Road

CLASS OF 2014 COMMENCEMENT

MAY 19, 4 p.m.

Soldiers & Sailors Memorial Hall & Museum

Unless otherwise noted, for more information:

Pat Carver 412-648-9059, cpat@pitt.edu.

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



CORBIS

KIDS' STUFF!



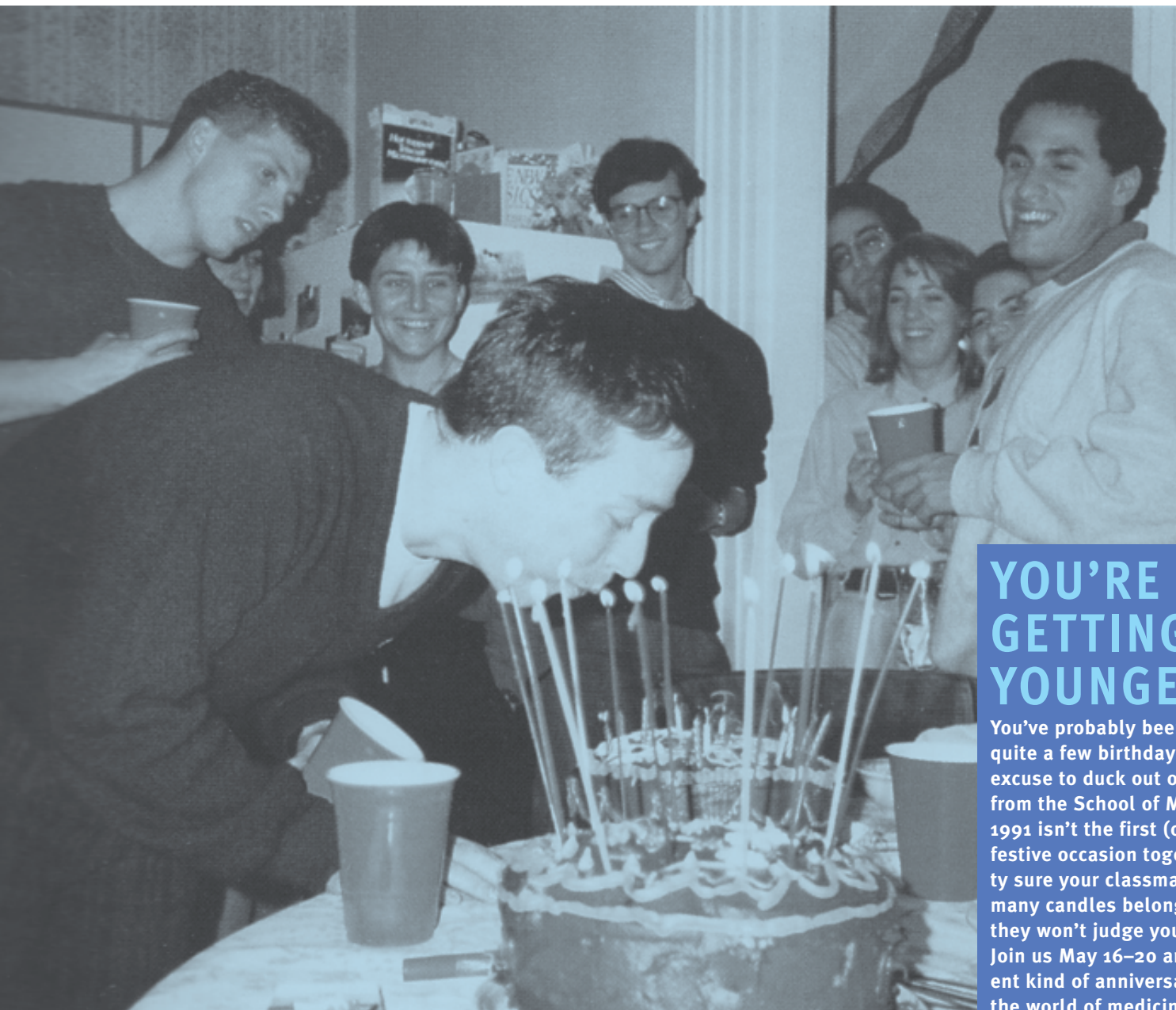
FOR REAL! TWEEN SCIENCE.

Kids and dogs have a lot in common: they're cute, like to play, and have better hearing than adult humans. Teens and younger kids can hear frequencies up to about 20 kHz.

But by the time we are 30 or so, most humans can't hear frequencies much above 14 kHz. In fact, some crafty kids have found a way to stealth-text by using high-frequency ring tones that adults can't hear! Why the difference? We actually start to lose our ability to hear higher frequencies during adolescence. Inside our ears are tiny sound sensors called hair cells (so named because they are long and thin, like hairs). Sound waves cause air pressure to change inside our ears, bending the hair cells, which transmit the sensation to the brain. If the sound is too loud, the drastic change in air pressure can bend the hair cells too far and kill them. Different hair cells are sensitive to different frequencies. Once hair cells die, you lose the ability to hear that frequency forever—mammal hair cells cannot regenerate. For some reason, hair cells that detect higher frequencies seem to die young. It's not clear why this is, but perhaps they are more fragile than hair cells that detect lower frequencies. Hearing loss may be inevitable, but to prolong your high-frequency advantage over the geezers, consider keeping the volume below a dull roar.

—Jenifer Lienau Thompson

Kudos to Pitt med prof Karl Kandler (tuned in to all things auditory) for bending our ears about hair cells. For more kid-friendly science, visit How Science Works at www.howscienceworks.pitt.edu



1991 HIPPOCRATEAN

YOU'RE NOT GETTING ANY YOUNGER

You've probably been "turning 30" for quite a few birthdays now, but that's no excuse to duck out on reunion. This group from the School of Medicine's Class of 1991 isn't the first (or last) to mark a festive occasion together. And we're pretty sure your classmates know just how many candles belong on your cake. But they won't judge you. So don't blow it! Join us May 16–20 and celebrate a different kind of anniversary—your entry into the world of medicine.

2004 10th Reunion
1999 15th Reunion
1994 20th Reunion
1989 25th Reunion
1984 30th Reunion
1979 35th Reunion
1974 40th Reunion
1969 45th Reunion
1964 50th Reunion
1959 55th Reunion
1954 60th Reunion

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