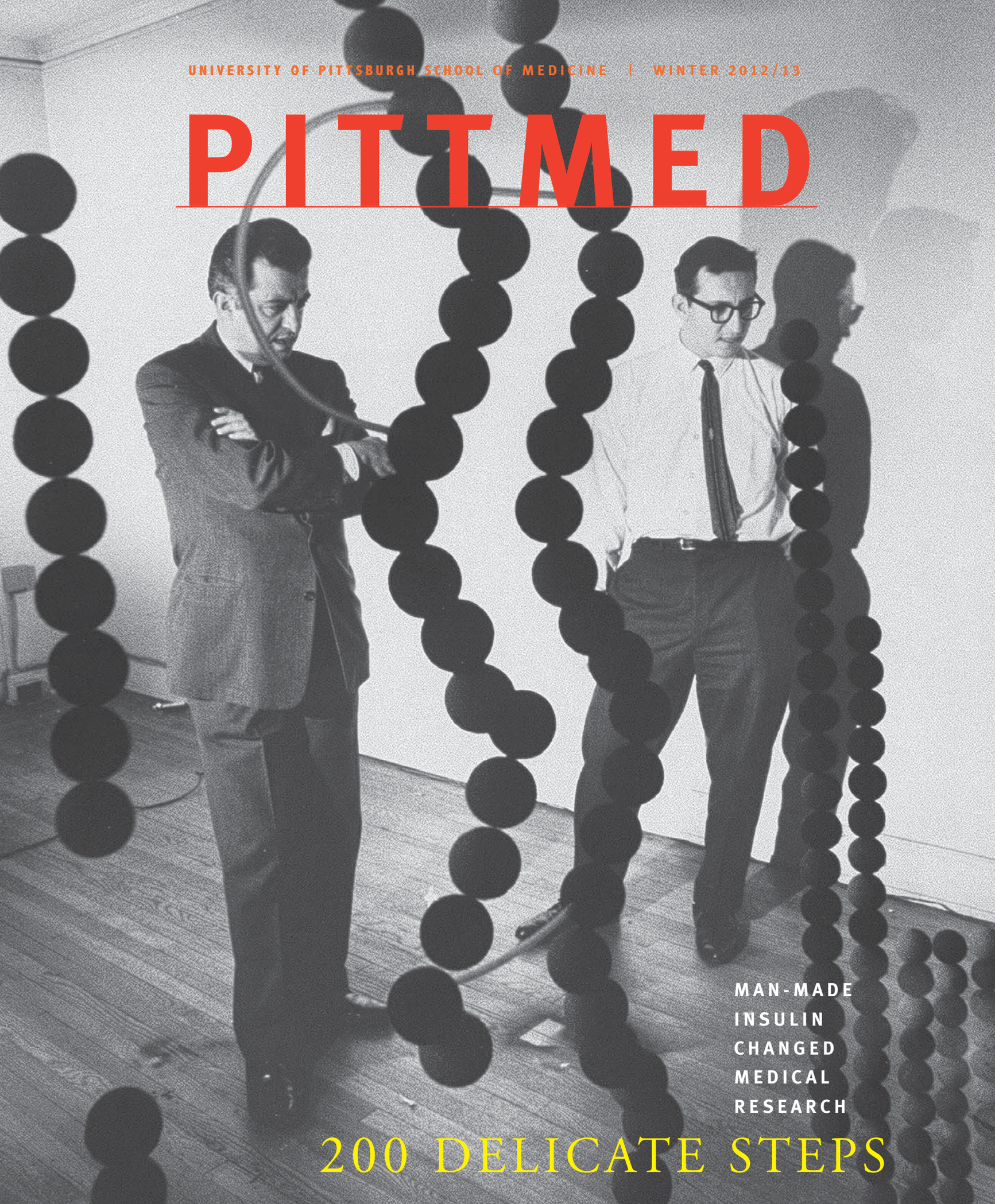
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | WINTER 2012/13

PITTMED



MAN-MADE INSULIN CHANGED MEDICAL RESEARCH

200 DELICATE STEPS

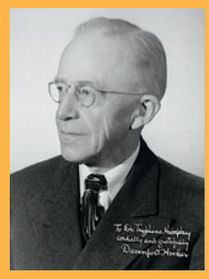
MAJOR ADVANCE FOR PREMATURE BABIES

Congratulations to Jenelle Pifer for her excellent article about Charles Cochrane and the Pittsburgh Five [Fall 2012].

Dr. Cochrane's development of the new drug Surfaxin will not only save the lives of premature infants, but also will reduce the suffering they endure from repeated airway-tube and vascular-catheter placements. Surfaxin is a major advance in patient care.

Richard Trackler (MD '61)
La Jolla, Calif.





ABOVE: Pitt's pathology department in 1961. It included chair Frank Dixon and others who would make up the Pittsburgh Five.
RIGHT: Davenport Hooker.

FAMILY TIES

Thank you for your recent comprehensive piece detailing the study of anatomy at Pitt ["The Great Equalizer," Summer 2012].

Even from early life, I recall the name Davenport Hooker being familiar. It is probably related to the fact that Hooker arrived at Pitt in 1914, and my father, Ralph E. Miller, was a graduate of the School of Dentistry in 1917. It seems likely that Dr. Miller was an early student of Dr. Hooker. (In addition to being the son of Dr. Miller, DDS, I am the father of Ralph J. Miller Jr., MD '84, who leads the Prostate Center at Allegheny General.)

Somewhere in our albums is a framed photo of my father, two or three students, and, I believe, Dr. Hooker, at that early stage in the anatomy lab.

Ralph J. Miller (MD '52)
Indiana, Pa.



RECENT MAGAZINE HONORS

2012 AAMC Robert G. Fenley Writing Award for Excellence, Basic Science, Staff Writing (E. Vitone, "Mars and Venus Revisited")

2011 CASE, District II Gold, Covers ("None of My Memories Are My Own," design by E. Cerri)

2011 CASE, District II Silver, Staff Writing

2011 IABC Golden Triangle Award of Excellence, Feature Writing (E. Vitone, "Mars and Venus Revisited")

2011 IABC Golden Triangle Award of Honor, Magazines

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

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CORRECTIONS

Our sincere apologies and sympathies to the family of David Steele (MD '51). Dr. Steele's name and class year were incorrectly listed in our fall issue In Memoriam.

STEP RIGHT UP

Okay, maybe your life feels like a three-ring circus. But you can spare a minute to let us know what's going on with you, right? Tell us about your career advancements, honors you've received, appointments, volunteer work, publications, and other death-defying acts. And we love to hear old Pitt memories. Quit clowning around and drop us a line at the contact info listed above or friend us on Facebook at www.pittmedfb.pitt.edu/.

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, WINTER 2012/13 (DEC/JAN/FEB)

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FEATURES

Out of Darkness 12

Panayotis Katsoyannis' journey began in war-torn Greece. After arriving in Pittsburgh in the 1950s, he took on the enormous challenge of synthesizing insulin, creating the first man-made protein. Many had initially assumed his accomplishments were beyond the capabilities of chemistry.

COVER STORY BY SHARON TREGASKIS

To Screen or Not To Screen 18

Early detection testing—screening for disease before symptoms manifest—presents a litany of issues. But how much do we want to know? And how appropriate are the technologies we're using? At the recent science festival, Pitt experts spoke to the confusion swirling around mammography, PSA tests, and CIMT.

BY JENELLE PIFER

Visual Thinker 24

Kyongtae Bae pushes the art and application of computer-aided diagnosis.

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A new imaging suite allows researchers and docs to see what cancer and other diseases look like at the molecular level and throughout the body, all at once.

FOLLOW-UP BY ELAINE VITONE

CONTRIBUTORS

Charter Editorial Advisory Board member MARGARET "MAGGIE" McDONALD has carefully reviewed every page of *Pitt Med*, and attended just about every story-brainstorming powwow, since the magazine started 13 years ago. Before she came to Pittsburgh, she was a science journalist reporting on mental health for outlets like *Psychology Today*, *Science News*, and *Psychiatric News*. (McDonald was there, in the smoke-filled room, when American Psychiatric Association officials voted that homosexuality was not a psychiatric disorder. "Voted!" she repeats.) When the late Thomas Detre recruited her to Pitt as his right-hand science scribbler in 1983, McDonald accepted on the condition that she could pursue a PhD in psychiatric epidemiology from the University's Graduate School of Public Health. (She also has an MFA in studio arts). Today, as associate vice chancellor for academic affairs for Pitt's schools of the health sciences, she is still writing (and overseeing the work of others) but also plays a key role as the University embarks on global collaborations and hosts events like the annual science festival, now with some 2,000 serial attendees. "I'm in the same chair, but I'm definitely not in the same job," McDonald says.

Senior editor JOE MIKSCH ["Reconstructed" and other pieces], a member of the *Pitt Med* team since 2005, has acquired a new title: Dad. Jack David Miksch, born Sept. 7 to Joe and his wife, Daisy, joins Edward, Rosemary, Juliet, Amelia, Tonino, Simon, and Lena as the next generation of *Pitt Med* contributors. Miksch's trove of writing honors, including the Carnegie Science Center's Journalism Award, could fill a playpen.

COVER

Panayotis Katsoyannis' ambitious chemistry helped pave the way for treatments used today. He's shown on the left in this photo taken for *LIFE* in 1964. (Cover: Photo by Fritz Goro/Time Life Pictures/Getty Images © 1964.)

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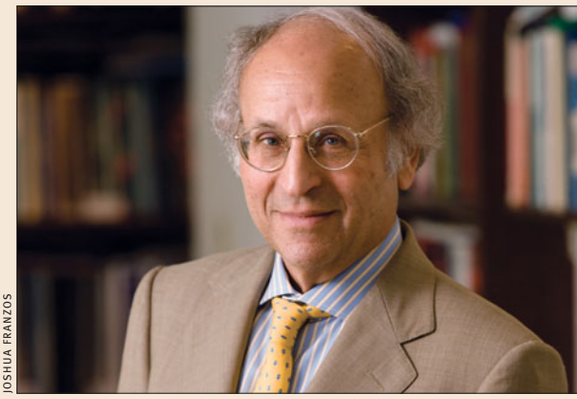
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JOSHUA FRANZOS

Once you get Rachel Reid (Class of 2013) talking about rowing, she will wax poetic. She'll talk about synergy—it doesn't matter whether you are pulling hard if you aren't in sync with the others on your team. She'll talk about the importance of awareness—how the water and winds are shifting, too. She learned a lot about how to be in the world from the many hours she spent on the Harvard women's lightweight crew. Rachel became this top team's assistant captain. She seems to be a natural leader in other ways. The winter of her senior high school year, she started to think back to middle school—a time when many girls become uncomfortable with physical education class and as a result, get turned off by athletics. Those girls are really missing out on something fun and important, she thought. So with a friend, Rachel (then on her school's cross-country team) started Girls Run Amok, a fitness and nutrition program for preteens.

As a teenager, Rachel already displayed the kind of leadership and creativity our profession needs. These are traits we look for in applicants to our medical school. Of course they will have impressive MCATs and GPAs. But what do they do that shows their ability to think critically and imaginatively? Do they direct plays? Write poetry? Build organizations? We need physicians who can help us tackle the complex problems of our age. Since the advent of Medicare, medicine has become the interest—often exclusively—of politicians, administrators, lawyers, and accountants. They all have critical roles to play, but it's time for physicians to be directing where our profession is going; physicians' training and experience endow them with a sensitivity to the subtlety and nuances of patient care that are often inseparable from treatment and its expense.

Rachel got started before she even finished her MD. She took two years off during med school to pursue a master's degree in clinical and translational science as a Doris Duke Fellow. And last year, at the Center for Medicare and Medicaid Innovation, she helped set up a pilot program testing a new payment and delivery model for primary care doctors. At Pitt, she "got to dive in" to research on health policy issues with our own Ateev Mehrotra, asking questions like, "How do retail clinics influence preventive and acute care?"

Once we have bright lights like Rachel here, we want them to learn more than how to diagnose a disease. We want them to learn something about themselves. We will soon launch a program in which each med student, starting on the first day of school, will be paired with a patient coping with a chronic or long-term illness. Throughout their four years at Pitt med, the students will learn from these patients and their families (and see how illness unfolds in the context of an environment). That's something that's often missing in medical education now—students don't have lasting and evolving relationships with patients. They have snapshot moments from a neurology clinic or an ER rotation. A program like this will help future physicians foster symmetry, rather than asymmetry, in patient relationships. In so doing, they'll become self-assured, mature individuals, as well as comfortable members of interdisciplinary clinical teams—as with Rachel, the rower.

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



Devoted to noteworthy happenings

at the medical school

DNA Repair How-to

DNA undergoes a lot of wear—so much that it occasionally breaks. Previous studies suggested cells fixed this with a dab of molecular glue, taking two separate, but seemingly compatible, DNA strands and rejoining them. But such a sloppy process could upset minute segments of DNA and lead to harmful coding errors.

Yuri Nikiforov, MD/PhD professor of pathology, thinks cells are a little more precise. "Our new study dramatically changes our understanding of how these breaks are fixed," Nikiforov says. "This kind of damage is actually repaired by using the complementary parental gene as a blueprint for rebuilding." Instead of gluing strands back together, cells repair the original genes using the matching chromosome as a guide. The researchers believe that contact between the two chromosomes gets the DNA repair pathway started, at the same time offering a template for repair of the broken section.

The study, published in the *Proceedings of the National Academy of Sciences*, used fluorescent probes to monitor the interactions between homologous chromosomes. —*Em Maier*

FOOTNOTE

Medicine is a noble calling. Medicine and economics, for Alvin Roth, are a Nobel calling. Roth, Pitt's Andrew W. Mellon Professor of Economics from 1982 to 1998, is cowinner of the 2012 Nobel for economic sciences for his work on market design. One market Roth influenced was that of med students searching for residencies. As more women entered medicine, more medical couples sought residencies near one another and outside of the system. In 1995, Roth was asked to redesign the match algorithm; his was adopted three years later. Another Roth algorithm is used to match organ donors and recipients.



PHOTO ILLUSTRATION BY JESSE LENZ, BASED ON PHOTO BY ELLEN JAFFE

Lasker Chair Alfred Sommer with Thomas Starzl at the Lasker Awards.

STARZL WINS LASKER

In the 1950s, Thomas Starzl, an MD/PhD, was looking for a "lifetime project"—something with no easy solution or foreseeable timeline, he says. This September, he received the 2012 Lasker–DeBakey Clinical Medical Research Award, which he shares with Sir Roy Calne of the University of Cambridge, for the development of liver transplantation. For decades, the two worked collaboratively at separate institutions, developing a friendship that Starzl says spurred progress more than competition ever could have.

When Starzl's work began in 1958, many doctors scoffed at the notion of organ transplantation. They didn't know whether donor organs could be preserved, let alone how to prevent rejection. "There was no doubt this was going to require a lot of swimming against the current," says Starzl, now Distinguished Service Professor of Surgery at Pitt.

Starzl calls the work a "University-wide project" and is donating his half of the $250,000 prize to the Joy Starzl Scholarship Fund, which is named for his wife and provides need-based aid to students in the School of Social Work. —*Jenelle Pifer*



CAMI MESA

The Latest on Concussions

With Michael Collins and Anthony Kontos

In 2000, UPMC founded its Sports Medicine Concussion Program—which was little more than a handful of docs and one room on the South Side. Today, the program's staff of 24 sees 15,000 patients annually in a 3,500-square-foot facility, which opened in early 2012. Pitt's Michael "Micky" Collins (shown right), a PhD associate professor of orthopaedic surgery and program director, has been there since the early days; Anthony Kontos (shown left), also a PhD associate professor of orthopaedic surgery, was recruited in 2010 to beef up the program's research arm. Lately, the profs have been partnering with the military and delving into how concussion affects the youngest athletes.

Linking mild TBI and PTSD in soldiers.

Kontos: We were able to do a very large study with over 22,000 U.S. Army Special Operations Forces. . . . We found that 13 percent of that population has been diagnosed with at least one mTBI (mild traumatic brain injury). And among that 13 percent, 28 percent were reporting clinical levels of PTSD (post-traumatic stress disorder). So nearly one-third with a history of mTBI are reporting clinical levels of PTSD, which is pretty high. Six percent without a history of diagnosed mTBI had clinical levels of PTSD symptoms.

Surprising findings in youth football leagues.

Kontos: These are 8- to 12-year-olds. What we found is that concussion risk or incidence was much higher in games than it was for practices. That's quite interesting, because some youth leagues, such as Pop Warner, have reduced the number of practices in which you can have contact [in an attempt to limit concussions]. And practice is where kids are learning the [proper tackling] technique. They're still going to be exposed in the games, but with less practice of proper technique.

The future of concussion treatment.

Collins: There's a lot of morbidity with this injury, but it's treatable—and we really don't think concussion is the boogeyman anymore. I saw about 25 to 35 cases today, and there were some people who are . . . having a hard time. But there are not that many people who walk out of here and aren't getting better from this, if you treat it the right way.

What about other repercussions, like the apparent link to PTSD?

Collins: A lot of the time, [experiencing] concussion and PTSD together is like throwing gas on a fire. Each makes the other worse. At the end of the day, concussion is an energy problem, and anxiety is one of the biggest energy-users in the brain. So when we treat the injury, we see improvement in PTSD and vice versa. *—Interview by Joe Miksch*

Next Generation

No longer students, but perhaps not yet independent researchers, postdocs are dipping their toes into the waters of academic medicine. But being something of a neophyte doesn't mean you can't be a roaring success. Witness these award winners.

Lisa Boyette, a PhD working under the guidance of MDs Fadi Lakkis and Diana Metes in the Thomas E. Starzl Transplantation Institute since last October, won the American Society of Nephrology Research Fellowship for examining how different classes of white blood cells function after renal transplant.

Xueqin Gao, an MD/PhD, won the Orthopaedic Research Society's 2012 New Investigator Recognition Award for her project studying the interactions between donor and host cells after stem cell–mediated bone regenerations. Gao, who works in the lab of PhD Johnny Huard (professor of orthopaedic surgery, molecular genetics, biochemistry, bioengineering, and pathology, as well as director of Pitt's Stem Cell Research Center), found stem cells contribute and attract a significant number of inflammatory and vascular cells and inhibit a host's initial immune response at the defect site to promote bone repair. She also demonstrated the importance of an inflammatory enzyme for stem cell–mediated bone healing.

David Boone, in addition to receiving the Susan G. Komen for the Cure Postdoctoral Fellowship Grant to examine how insulinlike growth factor 1 affects breast cancer, landed a fellowship to reach out to the community in Nashville, where he attended graduate school. He taught a science program in a local high school for three years, and last year his students won second place in the Tennessee Junior Academy of Science. Boone, a PhD, is mentored by Adrian Lee, PhD professor of pharmacology and chemical biology.

Matthew Sikora also studies breast cancer, particularly how one gene, HDAC7, influences resistance to endocrine therapy. Sikora, a PhD who works with Steffi Oesterreich, PhD professor of pharmacology and chemical biology, investigates an understudied type of breast cancer called invasive lobular carcinoma. Sikora has received funding from the Department of Defense Breast Cancer Research Program to continue his work. *—EM*

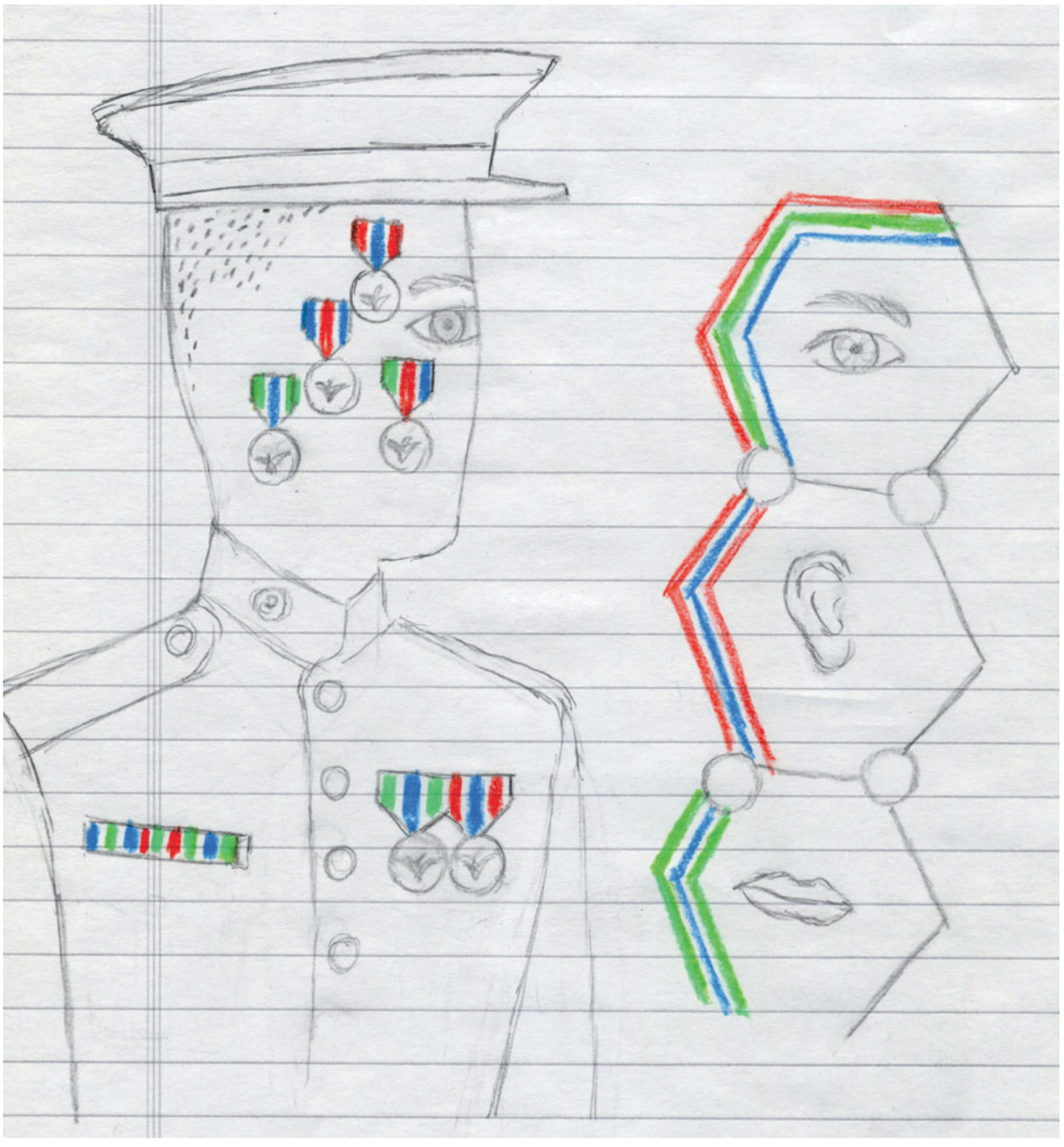
Military Targets

The armed forces and scientific advancement aren't strangers. Since World War II, military-funded and related research has led to Bob Beamon-esque leaps forward in physics, computing, engineering, and electronics. It's medicine's turn.

The new Center for Military Medicine Research here will "serve as a catalytic infrastructure to advance the fields of regenerative medicine, reconstructive surgery, transplant immunology, tissue engineering, neuroscience, and neuroprosthetics," organizers say. With funding from the U.S. Department of Defense, Pitt scientists are already attempting to grow skin, nerves, bone, and cartilage in the lab. And they are experimenting with ways to regrow lost muscle and restore craniofacial tissue.

Founding director Rocky Tuan (a PhD, Arthur J. Rooney Sr. Professor of Sports Medicine, professor and executive vice chair for orthopaedics research, and director of the Center for Cellular and Molecular Engineering) says the military medicine research hub will also promote investigations into numerous therapies and courses for rehabilitation, with plans to accelerate their transition from lab to clinic.

Tuan works closely with Distinguished Professor of Neurobiology and Neurobiology Chair Peter Strick, a PhD who also codirects the Pitt–Carnegie Mellon Center for the Neural Basis of Cognition. "What we're doing now is trying to make the community and federal agencies aware of the science that's going on in Pittsburgh—and at the same time, trying to make the scientists who are making discoveries aware of opportunities to help wounded warriors and veterans," says Strick. "We're making a match between the two, to raise funds for the remarkable work that's already ongoing." *—EM*



CATHERINE LAZURE

A MODEL GRANT

Wet bench work is central to scientific discovery, but it's not the only path available. With a five-year, $9.3 million grant from the National Institutes of Health, the University of Pittsburgh School of Medicine, Carnegie Mellon University, and the Pittsburgh Supercomputing Center will be delving into the realm of the cyber for insight into the central nervous system.

The grant establishes the Biomedical Technology Research Center (BTRC), which will develop computational tools for modeling and simulating biological systems from the big (tissue) to the tiny (the molecule). Pitt's Ivet Bahar, a PhD and John K. Vries Professor and chair of the Department of Computational and Systems Biology, is the principal investigator.

"With these tools, our goal is to better understand and appreciate the impact of defective proteins and interactions at the cellular level, and their effects on the central nervous system behavior," she says. "We hope to bridge the gaps between molecular-, cellular-, and tissue-level information to build integrated models of cell signaling and regulation."

Bahar adds that the BTRC will collaborate with renowned researchers in neuronal- and T-cell-signaling and regulation at Pitt—including Alexander (Sasha) Sorkin, a PhD and Richard Beatty Mellon Professor and chair of the Department of Cell Biology, and Susan G. Amara, the PhD former chair of neurobiology who is now scientific director of the National Institute of Mental Health—as well as with labs at the Allen Institute for Brain Science in Seattle, the California Institute of Technology, and the University of Bristol in England. *—JM*

FOOTNOTE

According to new numbers from the National Science Foundation, in terms of federal funding, the University receives the third-largest sum among public universities and fifth largest among all schools. That's almost $600 million for fiscal year 2010, the time period covered in the report, and an increase of 30 percent from 2009.



WELCOME TO REALITY

Lift your tail, shift yo' body. If you need some help, ask somebody. **It sounds like rap duo 4 Wheel City is enumerating the next dance craze. But Namel "Tapwaterz" Norris and Ricardo "Rickfire" Velasquez, who both ended up in wheelchairs, perform motivational "rap therapy." Their September concert, cosponsored by Pitt's Office of Health Sciences Diversity and the School of Health and Rehabilitation Sciences (SHRS), was held at the August Wilson Center for African American Culture. (Velasquez and Norris are shown here, to the left and right, respectively, of their "hype man," Elsun Gunter.) Jonathan Duvall, an SHRS student who helped organize the event, recalls how Norris grew serious when telling the audience his story. Norris was injured when a gun went off accidentally. That happened three years after Velasquez, a neighbor in the Bronx, was caught in crossfire while walking home. "I remember [Norris] saying, 'How do you tie your shoes in a wheelchair?' The other guy walked him through it." Now the artists are hoping to show how much more people with disabilities can do. They're also sounding a wakeup call to young people. "The lyrics are really powerful," says Duvall.** ***—JP***

COURTESY MICHAEL LAIN/HUMAN ENGINEERING RESEARCH LABORATORIES



Strick

Appointments

Peter Strick, a PhD and Distinguished Professor of Neurobiology, is now chair of the Department of Neurobiology and, he says, thrilled to be in a position where he can facilitate young scientists' careers and enable cutting-edge research.

A member of the National Academy of Sciences (NAS), Strick is codirector of the Pitt/CMU Center for the Neural Basis of Cognition, coleader of the Center for Military Medicine Research (see p. 5), and a senior research career scientist at the VA Pittsburgh Healthcare System. He succeeds Susan Amara as neurobiology chair. Amara is also an NAS member; she recently joined the Maryland-based National Institute of Mental Health as scientific director.



Michalopoulos

This fall, four Pitt med faculty members became Distinguished Professors, a rank acknowledging extraordinary scholarly attainment in a particular field.

George Michalopoulos has been named Distinguished Professor of Pathology. In 1989 his lab was one of three to independently discover hepatocyte growth factor (HGF), a major driver of regeneration in a variety of tissues and cell types. He is the Maud L. Menten Professor and chair of Pitt's Department of Pathology, the biggest academic clinical organization of its kind.



Peitzman

Pitt's Mark M. Ravitch Professor of Surgery, vice chair for clinical services, and chief of general surgery, Andrew Peitzman (MD '76, Res '84), is now Distinguished Professor of Surgery. Peitzman has traveled extensively, particularly in Latin America, to improve trauma care abroad and at home. He opened the trauma center at UPMC Presbyterian in 1984 and maintains clinical interests in complex abdominal surgery, critical care medicine, and hernia repair.



Shroff

Newly named Distinguished Professor in Bioengineering, Sanjeev Shroff is interested in the cardiovascular system. Specifically, he investigates the relationship between contractile and regulatory proteins and heart function, as well as how vascular stiffness affects cardiovascular function. He is also Gerald E. McGinnis Professor of Bioengineering, a professor of medicine, and a member of the Pitt-UPMC McGowan Institute for Regenerative Medicine.



Grandis

Jennifer Grandis (MD '87, Fel '92, Res '93), named Distinguished Professor of Otolaryngology, was also elected to the Institute of Medicine (IOM) this year. She studies the genetic alterations resulting in head and neck cancers and is working towards novel therapies targeting the signaling pathways involved. She is director of the head and neck cancer program at the University of Pittsburgh Cancer Institute, a UPMC Endowed Professor, and assistant vice chancellor for research integration, health sciences.

Joining Grandis in the IOM is Michael Boninger, an MD who serves as chair of the Department of Physical Medicine and Rehabilitation and director of the UPMC Rehabilitation Institute. Boninger's research focuses on technologies to improve the lives of people with spinal cord injury and other disabilities. His team's wheelchair work, primarily conducted at Pitt's Human Engineering Research Laboratories, where he is the medical director, has led to patents for devices used throughout the world. He also helps lead the Pitt neuroprosthetics team. ***—JP***



Jennifer Howison's "Vanity Plate" was one of several pieces created and donated for the Breast Reconstruction Awareness (BRA) Day event in October. Howison says her work often creates an "apparently playful world infused with ... unexpected dialogues."

RECONSTRUCTED

"You hear about breast cancer and about curing it, which is obviously very important," says Carolyn De La Cruz. But what's next? Especially if the cure involves mastectomy.

"There's breast reconstruction," says the University of Pittsburgh assistant professor of plastic surgery, "And that has a different flavor to it, because we're creating something."

With this in mind—and spurred by the American Society of Plastic Surgeons' designation of October 17 as the first Breast Reconstruction Awareness (BRA) Day—De La Cruz enlisted the help of more than a dozen area artists, who employed their creativity to adorn mannequins of female torsos with breast reconstruction–themed art.

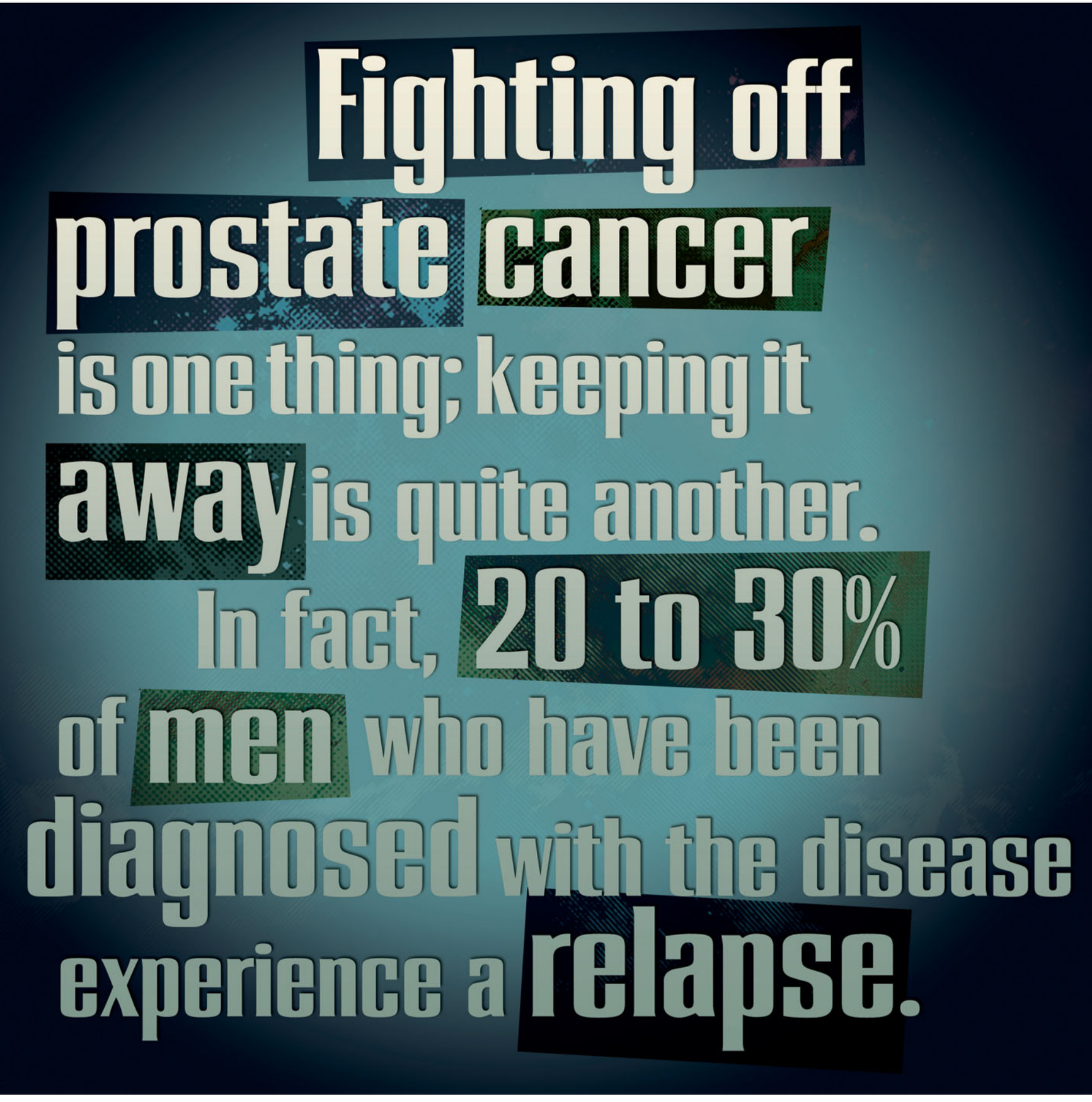
That evening, at the Mattress Factory art museum in Pittsburgh's Mexican War Streets neighborhood, 200 guests assembled to mingle and bid on the mannequins.

Artist Laura Jean McLaughlin (her work can be seen around town at sites ranging from Children's Hospital of Pittsburgh of UPMC to the Pittsburgh Zoo & PPG Aquarium) created a mannequin that depicted, in glass and ceramic mosaic tile, a girl praying to her fairy godmother. The piece commemorated a friend who'd died of breast cancer at age 30.

"She found out too late," McLaughlin says. "I had that in the back of my mind when I was making the piece. And mosaics are a lot of small pieces coming together to create something larger than yourself," like this event did, she says.

—Joe Miksch

—Photo by Martha Rial


Fighting off
prostate cancer
is one thing; keeping it
away is quite another.
In fact, 20 to 30%
of men who have been
diagnosed with the disease
experience a relapse.

REDUNDANCY OF GENETIC REDUNDANCY

BOTCHED DNA DUPLICATION BRINGS PROSTATE CANCER BACK

BY DANA YATES

Fighting off prostate cancer is one thing; keeping it away is quite another. In fact, 20 to 30 percent of men who have been diagnosed with the disease experience a relapse, according to the Prostate Cancer Foundation. At the University of Pittsburgh, though, researcher Jian-Hua Luo is developing a genetic test that could identify tumors that are most likely to return.

Luo, an MD/PhD and professor in the School of Medicine's Department of Pathology, is director of Pitt's High Throughput Genome Center. He is also the senior investigator of a study that showed that genetic changes in the blood and tissue of prostate cancer patients could predict whether their malignancies would reappear and just how aggressive they would be. The findings were published online in the *American Journal of Pathology* in May.

The American Cancer Society reports that one in six men will be diagnosed with prostate cancer during his lifetime. Occurring primarily in men who are older than 65, the disease can be serious, but most men will not die of it (5 percent of those with the cancer will). That's because prostate tumors grow slowly in the majority of cases. Fast-growing cancers, however, are a significant concern.

"To ensure that men get the timeliest and most appropriate treatment, we need a screening tool that can tell us if a tumor is aggressive," Luo says. "This information would improve therapies and put doctors on high alert for the likelihood of metastasis."

Currently, physicians check prostate-specific antigen (PSA) in the blood to monitor tumors. An elevated PSA result is typically considered the first sign of a possible growth. But the tool isn't perfect; a PSA test can provide normal results when a man actually has cancer and abnormal results when he does not. (For an in-depth discussion of this issue, see "To Screen or Not To Screen," p. 18.)

Furthermore, even when a PSA test detects cancer, there is no way to conclude whether the situation truly is dire. To know definitively whether or not a tumor is dangerous, a patient must undergo a needle biopsy or surgery to remove his prostate gland. The former carries a slight risk of infection, bleeding, and pain. The latter can dramatically affect a man's quality of life, leading to problems with sexual function and incontinence.

"To ensure that men get the timeliest and most appropriate treatment, we need a screening tool that can tell us if a tumor is aggressive."

To find a better way of detecting dangerous tumors, Luo used a mathematical algorithm to study gene abnormalities. Specifically, his process looked at copy number variation (CNV)—the deletion or amplification of areas of DNA within chromosomes.

In a study funded by the National Cancer Institute and the University of Pittsburgh Cancer Institute, Luo and his fellow researchers at Pitt analyzed the genomes of samples from men who had prostate gland removal, prostate tumor samples, blood samples from prostate cancer patients, and samples of benign prostate tissue surrounding the tumors. The samples came from three patient groups: those whose cancer had come back and whose PSA level had doubled in less than four months (usually a sign of particularly aggressive prostate cancer), those whose cancer had recurred with a slowly increasing PSA level that doubled in more than 15 months, and those who had not experienced a relapse more than five years after undergoing surgery.

The researchers discovered that elimination or increased redundancy of DNA fragments occurred in the chromosomes of prostate cancer tumors and even in blood samples and noncancerous tissues adjacent to tumors.

What's more, when the CNV results were compared to the different patient groups, the CNV analysis consistently predicted relapses in 70 to 80 percent of the cases.

Now, Luo is conducting a larger study to validate his earlier findings. He hopes that CNV measurement will become a routine screening tool for prostate cancer. ■

TYPOGRAPHY: NICOLE FICHERA

CUT FROM COLLAGEN

AN UNEXPECTED SOLUTION FOR SCLERODERMA

BY ALLA KATSNELSON



COURTESY FEGHALI-BOSTWICK LAB

Thickening in fibrotic skin explants (left) is ameliorated when the tissue is treated with the endostatin peptide E4 (right).

Scleroderma's progress is unpredictable. Some individuals with the autoimmune disease never experience much more than a few spots of thickened skin and a tingling and sensitivity to cold in the fingers and toes. Others, however, are plagued by fibrosis—an overgrowth of connective tissue—not only in their skin, but also in blood vessels, lungs, and other organs. One of the most damaging effects of the disease occurs when collagen, the main component of connective tissue, begins to hijack the lungs, causing scarring that interferes with breathing. So far, not a single treatment can counter fibrosis, says Carol Feghali-Bostwick, a PhD and associate professor of medicine and pathology at the University of Pittsburgh. "There's nothing that's effective."

Feghali-Bostwick may have uncovered a new path to treatment, however. She has been studying the biology underlying fibrosis—particularly in scleroderma and a lung ailment called idiopathic pulmonary fibrosis—for more than 20 years. Her interest is more than academic. Shortly after starting graduate school at New Orleans' Tulane University in 1988, she was diagnosed with scleroderma herself. The physician who confirmed her diagnosis happened to be Dennis Boulware, Tulane's chief of rheumatology. He lured Feghali-Bostwick into making the disease the topic of her dissertation. "I had not yet started my research career, and when given that option, I thought, 'Why not contribute to this?'"

Feghali-Bostwick came to Pitt in 1993 as a postdoc with former chief of rheumatology Timothy Wright. She started her own lab in 2002. A few years later, Feghali-Bostwick's team found two sister proteins—transporters of growth factors within the cell—whose levels were elevated in diseased tissue of people with scleroderma. To see how these proteins contributed to the disease, the researchers trawled for other molecules whose levels were either revved up or dampened by these proteins. One intriguing finding from their fishing expedition had to do with endostatin, a fragment of collagen naturally produced when collagen is cleaved. When other researchers looked back at fibrotic tissue, they found it had significantly more endostatins than their control samples had. Because increased collagen production drives fibrosis and endostatin is cut from collagen, Feghali-Bostwick assumed that endostatin would also promote the condition. But, to her surprise, the opposite occurred—cells bathed in endostatin made less collagen and other connective tissue components, and injecting the molecule into explants of fibrotic human skin decreased its thickness. "It was not the result we were expecting," she says.

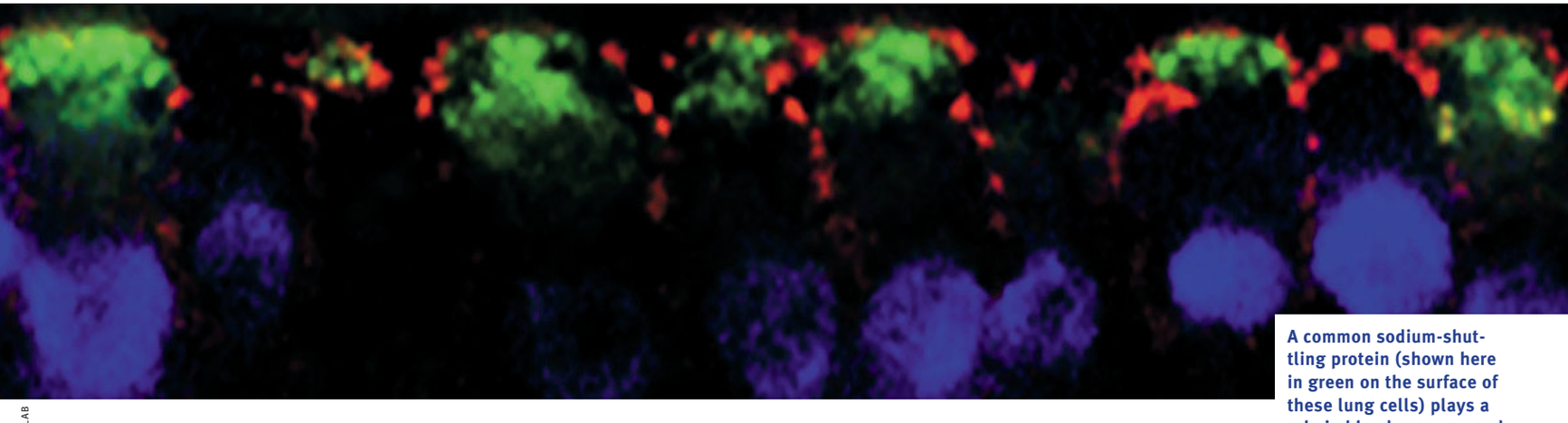
The catch was that endostatin starves blood vessels of oxygen—a property that makes it a promising tumor-fighting agent. (It's being tested against cancer in clinical trials.) It also means endostatin can destroy tissue.

So, Feghali-Bostwick and her team broke down the molecule into three fragments and tested those molecular regions in living mice, as well as in cultured human skin. Both in living mice and in segments of human skin, one of the fragments was found to carry the magic combination of features: it blocked fibrosis—and even reversed it—but did not affect blood vessels. The study was published in *Science Translational Medicine* in May.

Now, the group is trying to figure out exactly how endostatin conveys its antifibrotic properties. One possibility, Feghali-Bostwick thinks, is it dials down levels of an enzyme that stabilizes collagen—thus making its rigid structure more prone to degradation. Additionally, endostatin appears to meddle with a molecule called EGR1, which is a central regulator of fibrosis. That suggests that endostatin could effectively treat fibrosis that presents in other organs because of various causes.

Feghali-Bostwick is looking for industry partners who can help move the molecule into clinical trials. Discoveries like hers emphasize the importance of basic research at a time when cuts loom for science funding, she says. "A lot of people assume that discoveries for potential therapies can come only from drug companies," Feghali-Bostwick says. "This is where it starts. This is where the observations are made." ■

MOLECULAR DOUBLE AGENT



A common sodium-shuttling protein (shown here in green on the surface of these lung cells) plays a role in blood pressure and susceptibility to a dangerous bacterial infection.

COURTESY BUTTERWORTH LAB

ENAC FUELS SOME INFECTIONS, BUT FIGHTS OTHERS

BY MELINDA WENNER MOYER

Most people wouldn't think high blood pressure and a deadly bacterial infection have much in common. Yet recent findings by Michael Butterworth, a PhD assistant professor in the University of Pittsburgh's Department of Cell Biology, imply a link. His work—which spans two vastly different biological systems—suggests that both conditions may arise in part because of the misdeeds of a common sodium-shuttling protein.

Butterworth started studying the epithelial sodium channel (ENaC) more than a decade ago when he was a graduate student at the University of Cape Town in South Africa. ENaC is a protein that embeds itself inside the cell membranes of kidney, lung, and colon cells, allowing sodium ions to pass in and out. It is well known among kidney experts: Mutations in ENaC's gene can result in two serious diseases, Liddle's syndrome and pseudohypoaldosteronism type 1, which cause chronic hypertension and hypotension, respectively. Researchers believe that ENaC plays a role in the development of general hypertension, too, a common condition that increases the risk for heart and kidney disease. When too many ENaC channels become active on a cell's surface, sodium floods the cell along with water—a cascade that leads to a boost in blood volume and thereby blood pressure.

Butterworth's most recent work suggests that regulating ENaC might be easier than previously thought. Researchers have long believed that cell-membrane protein channels (there are many types, and they are responsible for moving molecules in and out of cells) are transported to and from cell membranes from the interior of the cell in tandem and in response to hormonal cues. But Butterworth's study suggests that ENaC actually has its own dedicated transportation vesicle.

"This suggests that you can regulate ENaC separately from other transporters," Butterworth says. So it should be possible to ramp down ENaC's activity with drugs without also affecting other membrane-bound proteins and causing dangerous side effects.

ENaC influences more than just blood pressure, however. People with cystic fibrosis—a disease characterized by a mutation in the membrane channel for chloride, causing thick mucus to build up in the lungs—are at a much higher risk of deadly respiratory infection with the bacterium *Pseudomonas aeruginosa,* and Butterworth's work suggests that ENaC could be a reason why. He and his colleagues recently reported that ENaC affects moisture levels on the surface of the lungs, influencing the lungs' vulnerability to infection. In a series of experiments, Butterworth showed that the bacteria secrete a protein called alkaline protease, which cuts the loops of the ENaC protein on the surface of lung cells, making ENaC more active. This process causes more sodium and water to get pulled inside lung cells.

Ultimately, the sequence of events dries the outer layer of the lung and prevents the lung's cilia, tiny spindles that work like molecular mops, from being able to clear away lurking bacteria and other unwanted debris. "The cilia stop beating in those areas, and the bacteria can take hold," Butterworth explains.

There is good news for these patients, too. To protect their own proteins from being clipped, the bacteria release small amounts of an alkaline protease inhibitor, which could potentially be used in patients to prevent *P. aeruginosa* from transforming the lung environment to the bacterium's favor. Butterworth is testing whether this inhibitor, applied to lung cells, could stave off infection. If so, it might one day be possible to give people with cystic fibrosis an inhalable drug containing the protective molecule.

Then the problematic bacteria would become part of the solution. ■



IN BUILDING THE FIRST MAN-MADE PROTEIN, PANAYOTIS KATSOYANNIS REVEALED VOLUMES ABOUT INSULIN AND PROTEIN CHEMISTRY

BY SHARON TREGASKIS

OUT OF DARKNESS

Panayotis Katsoyannis was in his final year of high school in Athens when Italy invaded Greece in October 1940. Germany joined the fray on April 6, 1941. Three weeks later, a swastika-imprinted flag flew in front of the Acropolis.

Liberation, in the form of British troops, would arrive in October 1944. "For almost four years, it was hide and seek," says Katsoyannis, who still reels off the military dates as easily as that of his own birth, Jan. 7, 1924. "We had our way with the Italians, but not the Germans. They would kill you. That was it. There was not any forgiveness."

Four-hundred thousand Greeks would perish during the occupation. Another 158,000 would lose their lives in the subsequent civil war—the opening salvo of the Cold War. "We were very much restricted, in every aspect of life—work, living, eating," says Katsoyannis. He recalled machine-gunfire blasting through

Panayotis Katsoyannis developed synthetic insulin at Pitt. He went on to create 150 analogs of the protein, manipulating it in ways chemists didn't think were possible at the time. In a photo taken for *LIFE* in 1964, the Pitt prof is shown (left) with his first grad student, Andy Tometsko, and a model of insulin.

PHOTOGRAPHY | FRITZ GORO/TIME LIFE PICTURES/GETTY IMAGES



When Katsoyannis embarked on his audacious project, scientists weren't even sure whether you could build a biologically active protein outside of the body. Students and postdocs, including Tometsko (shown here), were critical to the success of the work.

the windows of his family home and youngsters felled just yards ahead of him on the sidewalk by ricocheting shrapnel. "Those were dark years."

And yet for Katsoyannis (pronounced CAT-so-yawn-nis), at least, grace prevailed. An aspiring civil engineer, he had failed his university entrance exams when the tranquilizers prescribed for a gallbladder attack left him too drowsy to put pen to paper. Not that it mattered: By the time he'd graduated from high school, the Nazis had closed the universities to students.

Katsoyannis' father, a scholar of ancient Greek literature and headmaster of a gymnasium (an upper-level secondary school), bemoaned his 17-year-old's academic hiatus to a friend, peptide chemist Leonidas Zervas, a PhD. An invitation soon followed: Would young Panos assist in the professor's University of Athens laboratory? Students had been barred from the institution, but as much as possible, the faculty continued with its research. "When I started working with him, I forgot about civil engineering," says Katsoyannis, who would spend most of the next decade training with Zervas. "My heart belonged to chemistry."

That passion would propel the young biochemist from Athens to Manhattan, and then on to Pittsburgh, where, as a member of Klaus Hofmann's Department of Biochemistry from 1958 to 1964, he would synthesize insulin, a globe-shaped protein composed of 51 amino acids—a strand of 21 and another of 30—bonded by two sulfur-based bridges. "First Man-Made Protein in History," a *LIFE* magazine article trumpeted in 1964 below a photograph of the Pitt professor—clad in his white lab coat. An array of brightly painted billiard balls illustrated the "200 delicate steps" by which he had constructed the hormone responsible for regulating metabolism.

"Insulin, with its long double chains of amino acids, is one of nature's most complicated compounds," the *LIFE* article explained, "and the job of putting it together in a laboratory was roughly equivalent to working a dozen jigsaw puzzles simultaneously while blindfolded."

The *LIFE* article's rhetoric was far from hyperbolic, says Antonios Trakatellis, an MD/PhD and longtime collaborator with Katsoyannis. Their friendship spans their tenures in Pitt's Department of Biochemistry, Brookhaven National Laboratory, and Mount Sinai School of Medicine, where Katsoyannis would serve as founding chair of the Department of Biochemistry from 1968 to 1998. "Of course today, insulin is made with biotechnical methods," says Trakatellis, who went on to serve as rector of the Aristotle University of Thessaloniki and later as vice president of the European Parliament. "But at that time, it was an enormous accomplishment to synthesize a molecule which is so big."

Not only did Katsoyannis synthesize the molecule, he proved its biological function, heralding a fundamental paradigm shift for organic chemistry. He then went on to create analogs of the molecule, swapping out an amino acid here or a bond there, then investigating the differences in functional activity between the variants.

"There was a question about whether you could actually use peptide synthesis to create a fully biologically active [protein], compared to what was made in the body by biological processes," says endocrinologist Jeffrey Flier, an MD, dean of Harvard Medical School, and a student of Katsoyannis' at Mount Sinai. (His

research investigates the molecular causes of obesity and diabetes.) "There were still questions about whether a protein hormone as complicated as insulin would be fully active when it was synthesized."

Despite those achievements, Katsoyannis' technique was never directly employed to treat diabetes—the production process simply took too long, and yields were too low for commercial viability. Until Genentech cofounder Herbert Boyer (who received his Pitt PhD in chemistry in 1963) developed the technology to engineer *E. coli* to produce a pure form of insulin in the late '70s, it was cheaper to extract the hormone from animal pancreata and tolerate the occasional side effect. Ultimately, Katsoyannis' persistence in crafting and testing the functional activity of his analogs laid the foundation for contemporary pharmaceutical engineering, says Richard DiMarchi, a PhD and retired group vice president at Eli Lilly and Company. DiMarchi is now the Standiford H. Cox Professor of Chemistry and the Linda and Jack Gill Chair in Biomolecular Sciences at Indiana University; his work was key to the development of Humulin, Humatrope, and Humalog (which he designed), biosynthetic insulin analogs widely used to treat both type 1 and type 2 diabetes.

"If you were forced to ID a single lab that contributed most to the structure-function relationship, that would be the Katsoyannis group," he says. "They made the insulin analogs that helped us understand the degrees of freedom in what you could change to create superior medicinal value."

In the 1920s, Katsoyannis' mentor, Zervas, had trained with chemist Max Bergmann in Germany. In 1932, the two had developed the Bergmann-Zervas method of synthesizing peptides (the short chains of amino acids that make up proteins) while preserving their function. Soon after, Bergmann fled Germany to do research at the Rockefeller Institute in Manhattan; he was followed a year later by Zervas.

By the time Katsoyannis came along, equipment was scarce. So, too, were reagents, mostly just leftovers from inventory bought before the occupation. Every six months or so, Zervas sent his young assistant to the barbershop and the fishmonger for raw materials from which he would extract the amino acids their work required. "Today, you just open a catalog and order as much as you want," says Katsoyannis. "In those years, there were not amino acids available; we would hydrolyze proteins such as hair to isolate cysteine. You couldn't just put a kilo of hair in the flask with hydrochloric acid; you were restricted by how much material you could make each time because we didn't have the appropriate glassware."

"It was up to you to find and learn," says Katsoyannis, who mastered English and German to read the papers his mentor had coauthored with Bergmann. "And if you couldn't find a Greek book, you had to learn French, English, German, Italian, and find a book to read—it strengthened your will to do things." By the time the University of Athens reopened and awarded the budding chemist his bachelor's degree—summa cum laude—in 1948, his dissertation research on phosphorylation, the process that activates and deactivates amino acids, was already well under way.

With their nation's economy—and its academic community—in tatters, young Greek scientists of the mid-century aspiring to academic posts on native soil completed their compulsory military service, then established their reputations abroad, relying on the international web of connections woven by their mentors. For Katsoyannis, Zervas' network would prove vital. In 1951, while his protégé devised chemical smoke screens and new lubricants for firearms at the behest of the Hellenic Army, Zervas wrote to colleagues working on the structure and chemistry of peptide synthesis in the United States and Switzerland. Vincent du Vigneaud, a Bergmann protégé in Manhattan, responded first. "Du Vigneaud said, 'If it is a student of Zervas', he will be very close to the work we're doing,'" recalls Katsoyannis. "He wrote right away, and I came to the U.S. without thinking anymore about Switzerland."

In du Vigneaud's laboratory at Cornell University, Katsoyannis would deploy the Bergmann-Zervas technique for stringing together amino acids as part of a five-member team attempting to synthesize two peptide hormones produced in the posterior pituitary. In 1953, they assembled oxytocin—implicated in labor and lactation—and, in 1954, vasopressin—central to the maintenance of blood pressure. Cysteine, the sulfur-based compound Katsoyannis had hydrolyzed using hair swept from Athenian barbershop floors, featured prominently in each of the ring-shaped proteins. In 1955, du Vigneaud would garner the Nobel Prize in chemistry for the "first synthesis of a polypeptide hormone."

"And if you couldn't find a Greek book, you had to learn French, English, German, Italian, and find a book to read—it strengthened your will to do things."

"In this work," du Vigneaud declared in his acceptance speech, "I should like to acknowledge the splendid collaboration of Ressler, Swan, Roberts, and Katsoyannis."

The next year, the Nobel laureate would promote his Greek research associate to assistant professor; the two would forge a fast friendship severed only by du Vigneaud's death in 1978. Yet for Katsoyannis—by then married to Frieda, an American-born Greek, and father to Miranda, their first-born—an independent research career beckoned. "If I had stayed," he says, "I'd have continued working for du Vigneaud because he didn't want independent investigators. I started looking around."

The particulars came into focus during a talk by Frederick Sanger, a PhD who had already published the sequence of amino acids in both chains of bovine insulin. (His subsequent publication of the sequence for human insulin would garner the 1958 Nobel Prize in chemistry for clearly establishing that each protein has a unique chemical composition.) "When he put the structure of insulin on the board," says Katsoyannis, "I said, *My God, it's full of cysteines! I know how to do that. That's the thing I'm going to work on.*"

Katsoyannis was 33. The literature on

insulin—by then a darling of protein chemists worldwide—was only three years older. In 1921, Canadian physicians Frederick Banting and Charles Best had extracted the protein from the pancreas of a dog and proved its therapeutic value in treating diabetes, a feat for which Banting would be awarded a Nobel. In 1922, Indiana-based Eli Lilly began commercial production of the hormone, using pancreata salvaged from slaughterhouses. The next year, Denmark's Nordisk did the same. Diabetes had been transformed from a death sentence into a chronic illness.

Basic science was benefiting, too. Commercial production of pharmaceutical-grade insulin gave researchers access to substantial quantities of a pure molecule with which to work. Insulin was crystallized by an American in 1926; its molecular weight was determined by Swedes in 1931. Even then, however, chemists speculated that proteins were changelings—variable, molecule by molecule, in their particulars. Sanger, an Englishman, devoted a full decade to decoding the order of insulin's components. By stringing together the amino acids, Sanger had detailed and then proved the resulting protein's functionality in a biological system. Katsoyannis would trigger a shift in the basic understanding of protein science. He confirmed that even the fundamental units of biology were chemically and structurally consistent, molecule by molecule.

He would also attempt to outdo the men who had trained him. "Going from oxytocin to insulin is like going from a mountain of 1,000 meters to Everest," says Trakatellis. "Many people can climb a mountain of 1,000 meters, but Everest, that's another story. Panos had an audacious vision."

When he revealed his ambition during interviews, says Katsoyannis, most prospective employers laughed. At Pitt they offered him an associate professorship. Chair of biochemistry Klaus Hofmann—a trainee of both Bergmann and Cornell's du Vigneaud—was just two years away from synthesizing a 23-amino acid version of ACTH, the anterior-pituitary hormone central to the preservation of brain function during stressful times. "You want to go in a place where the groups do a similar type of work that you are doing," says Katsoyannis, who moved to Shadyside in 1958, after a series of interviews at Greek institutions confirmed that his research was more likely to thrive at Pitt. "You have the time to talk about the things that you are interested in; they have similar equipment."

Katsoyannis spent many long days in his 400-square-foot laboratory in Scaife Hall, yet the professor dedicated a special time slot exclusively for his children. On Saturday mornings, from 8 to 9, he watched cartoons—*Bugs Bunny*, *The Magilla Gorilla Show*, and the like—with his young family: daughter Miranda, born in 1956, and son George, born in 1960. "We would all pile onto the bed, watch TV, and be laughing," says Miranda, now a Washington, D.C.–based legislative analyst for the CDC. "It was a ritual." Later in the morning, he would make the 5-minute commute from the family's Fifth Avenue apartment for departmental faculty meetings. ("Klaus told me years later that [Saturday meetings] would keep them from talking too much because they all wanted to go home," says Hofmann's widow, Frances Finn Reichl, PhD '64, who studied protein biochemistry with Katsoyannis and served as a professor of biochemistry at Pitt herself for three decades.)

After the faculty adjourned, Katsoyannis would head to his laboratory, drying, freezing, hydrolyzing, and rinsing to isolate this pentapeptide, that nonapeptide—tacking on one more amino acid here, condensing the desired fragment there. Just four months after Hofmann published his synthesis of ACTH, Katsoyannis submitted the manuscript "Insulin Peptides I. Synthesis of Cysteine-Containing Peptides Related to the A-Chain of Sheep Insulin." The *Journal of the American Chemical Society* published the report in October 1961.

Twenty-one installments would follow, spanning a decade of painstaking research with eight coauthors at Pitt, Brookhaven National Laboratory, and the newly established Mount Sinai School of Medicine. "The way he went about doing it was a *tour de force*," says Clyde Zalut, a one-time research tech at Brookhaven who earned his PhD under Katsoyannis' mentorship at Mount Sinai and coauthored seven of the articles. "Doing the work in a very thorough, careful way proved that the basic science that had been developed up to that point was capable of producing large proteins, not just small proteins."

At Pitt, Katsoyannis' meticulous attention to detail infused his lectures, as well. "He had a great knack for explaining things so you understood them very, very well," says Finn Reichl. "He was systematic, yet it wasn't boring. I think it was because he loved it. The medical students thought he was terrific. They called him Adonis."

"Going from oxytocin to insulin is like going from a mountain of 1,000 meters to Everest."

The feeling was mutual. "I had a teaching rotation I enjoyed very much," says Katsoyannis. "After the lecture was over, the students would applaud."

Yet among the faculty, tensions could flare. Finn Reichl recalls an epic battle over a laboratory exercise for the medical students involving ascorbic acid—vitamin C. Katsoyannis had devised an experiment featuring the volatile compound and charcoal. A colleague, an expert in vitamins, criticized the plan, warning that the ascorbic acid would oxidize. "Dr. Katsoyannis said, *If that becomes oxidized, I will cut my wrists and bleed to death in front of everybody.*" The other professor had a point, says Finn Reichl. "Ascorbic acid will oxidize if you look at it. But Panos won that one."

On another occasion, says the Pitt professor emerita, Katsoyannis got into a spat with Seymour B. Koritz, a PhD expert in steroid hormones. "He nicknamed him Seymour Oscar Benjamin Koritz," says Finn Reichl. "S.O.B. Koritz." The hard feelings didn't last. When Katsoyannis assumed the chairmanship at Mount Sinai in 1968, Koritz was one of his first recruits.

"He was very forceful in his thinking,

although he would not oppress other people," says Zalut, now retired from Harvard Medical School. Katsoyannis always let him speak his mind, debating laboratory tactics and suggesting alternative approaches. "He was outspoken about how he wanted to do the research, and he was usually correct," says Zalut.

In 1964, the *Journal of the American Chemical Society* published "Insulin Peptides. X. The Synthesis of the B-Chain of Insulin and Its Combination with Natural or Synthetic A-Chain to Generate Insulin Activity." In 1963, the ninth installment in the series had detailed the reverse: synthesis of the A-chain and its combination with a natural B-chain to generate activity. Teams in Germany and China published similar achievements, minus the thorough evidence of functional performance. *LIFE* sent reporters. The same year, Hofmann resigned as chair of the department to launch the Protein Research Laboratory at Pitt, and Katsoyannis accepted an appointment at Brookhaven. He took Trakatellis and two postdoctoral associates along with him. "Because Panos was in the same field with Klaus, they were good friends," says Finn Reichl. And it came as no surprise when Hofmann's first round of recruits departed, his friend Katsoyannis included. "If you hire good ones, it's what you expect to have happen," Finn Reichl notes.

When Mount Sinai came calling a few years later, Katsoyannis leapt at the opportunity to assemble a biochemistry faculty for the nascent medical school. Besides recruiting Trakatellis and Koritz, he hired Pitt's Gerald Schwartz (PhD '64) and Diana Beattie (PhD '61), who is now dean of premedical and pharmacy programs at Oman Medical College. She had been a trainee of Segal and Hofmann.

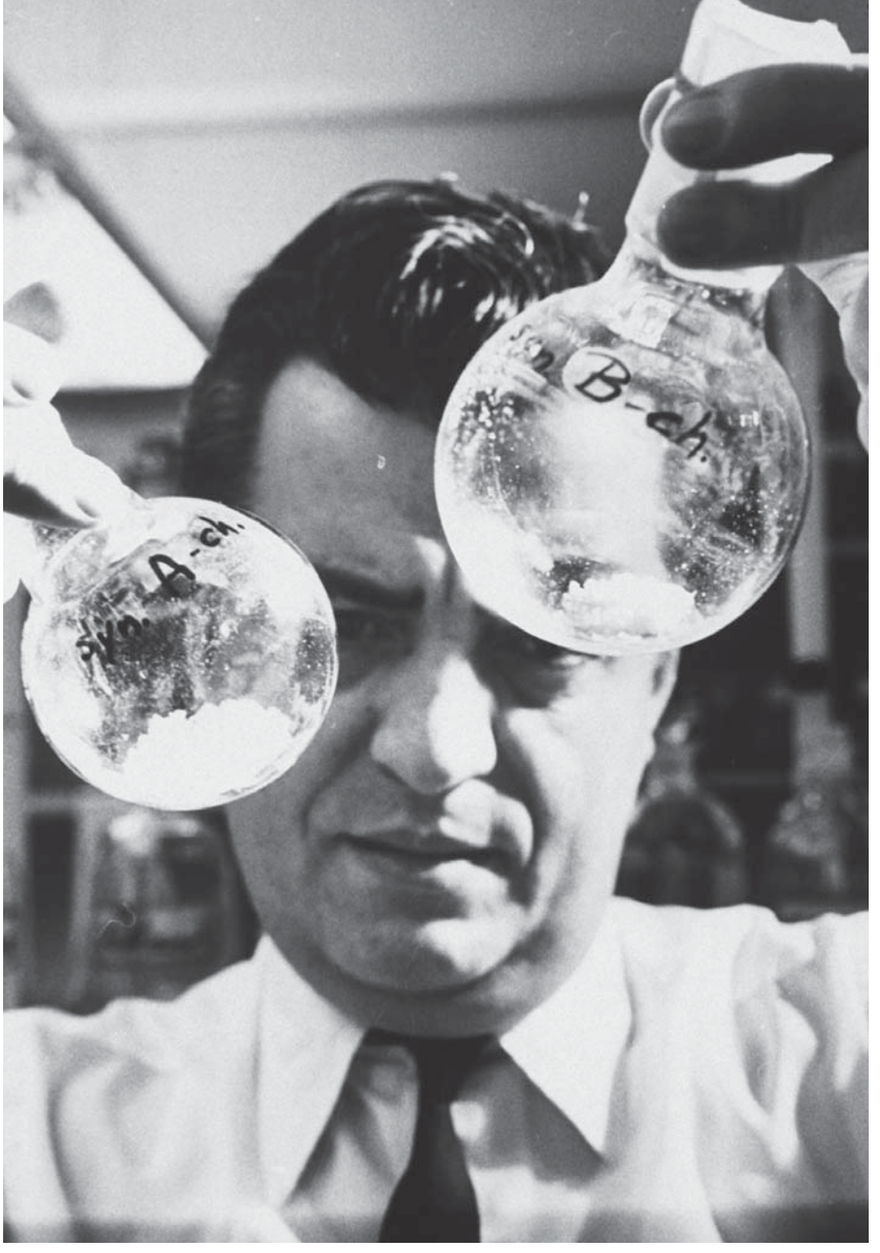
"Women had a hard time getting jobs in 1968," says Beattie, an expert in mitochondrial biogenesis and metabolism. "He paid me the same amount as the men he hired, promoted me to associate and then full professor, and certainly treated me well."

What else could he have done, muses Katsoyannis, now retired and living near Washington, D.C., just minutes from his daughter and her family and responsible for the care of his wife since a 2007 stroke. "I have a daughter, a daughter-in-law, and a wife," he says. "They would kill me if I didn't hire women." When West Virginia University—where Beattie would spend 21 years as chair of its biochemistry department—called for a reference, Katsoyannis did as Hofmann had decades earlier for his good friend. "She was a very good scientist and teacher, established in student affairs," he recalls. "It was with a heavy heart that I recommended her, because I could not hinder her career."

After his final installment on the synthesis of insulin in the *Journal of the American Chemical Society* in 1971, Katsoyannis would go on to craft some 150 analogs of the molecule, analyzing their interactions with insulin receptors for new insights into the relationship between structure and function.

"We started to play quite a lot with that," says Trakatellis, who visits his friend every time he returns to the United States. After Trakatellis moved back to Greece in 1972, Katsoyannis continued the effort, swapping out this amino acid, replacing that one, hinging and unhinging the chains in new locations, and in the process heightening and shifting the molecule's biological activity. The work began, says Trakatellis, when the pair started combining chains of the molecule from multiple species, making versions half animal and half human, joking to themselves about the mythological Greek heroes whose superpowers derived from their mixed parentage.

"Before we did our work, nobody would dare even think of manipulating a protein, changing its profile," says Katsoyannis. "People would think it was beyond the capabilities of chemistry." ■



In 1964, Katsoyannis holds beakers of synthetic A and B chains of insulin. The Pitt prof thought he wanted to be a civil engineer but later found his "heart belonged to chemistry."


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1.5 MILES

THE COURSE IS NOT ENTIRELY CLEAR

BY JENELLE PIFER

TO SCREEN OR NOT TO SCREEN

In this country and elsewhere, popular screening technologies for prostate cancer, breast cancer, and cardiovascular disease are being reevaluated. Do less-than-ideal findings prompt unnecessary worry for otherwise healthy patients? How do we know when a screening method helps more than it hurts? What if the up front costs outweigh the long-term savings? What can our society afford to do?

None of this is straightforward. Much is contentious. Most of us know someone who has been affected by one of these serious, and sometimes deadly, diseases. There is an awful lot at stake.

We recently heard from experts at the University of Pittsburgh who are helping patients and doctors navigate this treacherous territory. This panel of leading authorities—including Wendie Berg, an MD/PhD; Emma Barinas-Mitchell, a PhD; Steven Shapiro, an MD; and Joel Nelson, an MD—recently delved into these issues at "To Screen or Not To Screen," a presentation at this year's Pitt science festival, Science2012—Translation.

Proceed with caution.

In these excerpts from a discussion at the University's recent science festival, Pitt experts help us traverse the befuddling issues surrounding mammography, PSA testing, and cardiovascular disease screening (specifically, an imaging technology known as CIMT). Are the benefits of popular early detection methods outweighing the harm they do?

ILLUSTRATIONS | JESSE LENZ

The discussion also gave us a glimpse into how Pittsburghers are building a road to personalized medicine. This approach, many believe, could drastically change outcomes and help avoid pointlessly harmful (and did we mention costly?) testing, as well as treatment, down the line.

PROSTATE CANCER

"If you go looking for prostate cancer, you're going to find it," says Joel Nelson, an MD and the Frederic N. Schwentker Professor and chair of urology at Pitt, who coleads the University of Pittsburgh Cancer Institute's Comprehensive Prostate and Urologic Cancer Center, as well as its Prostate Cancer Program.

As far as cancers go, prostate cancer is pretty common: It accounts for nearly a third of all cancer diagnoses among American men. Nearly one in every four men harbors the disease, most after age 50; and one in six will be diagnosed. Though for most, having prostate cancer isn't necessarily a health problem. (More on that soon.)

The number of diagnoses has been increasing since the 1970s, says Nelson, but skyrocketed around 1994, when the prostate-specific antigen (PSA) test was approved by the FDA for asymptomatic men.

PSA is a protein produced specifically by the prostate that liquefies semen and helps sperm swim freely. It's found naturally in small quantities in the blood, but elevated levels are associated with prostate cancer, among other conditions.

The PSA test became the premier method for detecting prostate cancer in men without symptoms, but it's now beset with controversy: In general, the higher a man's PSA, the more likely it is he has prostate cancer. However, there is no specific "normal" amount of PSA in the blood, and fluctuations are often caused by benign factors, like having an enlarged prostate, recent ejaculation, and urinary tract infection. So, if a man receives a positive result, that really only leads to new questions and more screening—in the form of another PSA test to verify the numbers, or a biopsy.

In the end, at least two-thirds of men with elevated PSA levels do not have prostate cancer. It's easy to adopt a better-safe-than-sorry attitude, but the consequences of a false positive are not to be underestimated—including anxiety, stress, and the pain and side effects of biopsy, which involves inserting hollow needles into the prostate to remove tissue.

If two-thirds of men receive false positive test results, then it follows that the remaining one-third tested actually have the disease. Right? But even this could be considered "overdiagnosis," says Nelson. "Prostate cancer doesn't always behave in a malignant fashion," he says. Most of the time, it's indolent, meaning it's localized and might never progress to a clinically significant level over a lifetime. In fact, only about 16 percent of men diagnosed will develop metastases, Nelson says.

Unfortunately, the PSA test can't distinguish between the two forms of the disease, so doctors are presented with the challenge of figuring out which cancers are problematic.

With the PSA test, more men with the disease are finding out about it, and earlier. "There's been a real change in how men present with prostate cancer," says Nelson, noting that before the PSA test was standard, about half of men diagnosed had disease that was clinically localized. "A quarter . . . had metastatic prostate cancer, which is a lethal form of prostate cancer. Once the cancer leaves the prostate, there is no curative therapy for it.

"It's very different now: About 85 percent of the men we diagnose when they present have this clinically localized disease. Only 2 percent present with metastatic disease."

The metastatic group begins treatment, and the localized patient is left perplexed as to whether he should, too. Depending on how aggressive his cancer is, a man with localized disease can either: wait and watch for clinical symptoms, wait and continue testing ("active surveillance"), receive hormone treatment, undergo radiation (from an external beam or implanted seeds), or have his prostate removed. Side effects include erectile dysfunction, incontinence, and impotence.

"There's no question the treatments we apply are harmful. And this is a very expensive proposition if you assume that one man in six in the United States will be told that he has prostate cancer, and we have to do something about it in every case. It's going to bankrupt the country," says Nelson.

In February 2010, the American Cancer Society (ACS) advised that men with no symptoms who are expected to live at least another 10 years have a chance to make an informed decision about whether to get screened. PSA screenings would no longer be routine. There was great outrage, Nelson says. "Here's the cornerstone of cancer care in the United States telling us not to do what we think is a very important cancer test." Many physicians feel this early warning system, despite its flaws, is essential. "We're not talking about a disease here that's rare; we're talking about a disease that every 15 minutes somebody dies of," says Nelson.

Nevertheless, in May 2012, the U.S. Preventive Services Task Force, an independent group of national experts, echoed the ACS's conclusion when it recommended against using the PSA test for healthy men. It gave the procedure a "D" rating, meaning the task force had "moderate or high certainty" that the procedure is ineffective or that harms outweigh benefits.

Physicians nationwide are in a dilemma, says Nelson. "And if you remember your logic, a dilemma is being on the horns of something where you could go either way." On one hand, you use a less-than-ideal test to diagnose more men than you intend with a disease that may or may not be life threatening. On the other, what about the men really at risk of developing the lethal form of the disease? Isn't the test helping to reduce mortality?

A project known as the European Randomized Study of Screening for Prostate Cancer investigated this idea. It was conducted in eight countries throughout Europe from 1991 to 2003 and sought to answer the question, "If we screen for prostate cancer, can we reduce death from prostate cancer?" The study was vast: It included more than 180,000 men considered at risk for developing prostate cancer—that is, men ages 50 to 74. About half were screened regularly with the PSA test and half were not.

"If you go looking for prostate cancer, you're going to find it."

The results, published in *The New England Journal of Medicine*, indicated that about 16 percent of tests were positive. Of those patients, 80 percent received biopsies, of which a quarter had prostate cancer. "As you can see, if you go looking for prostate cancer, you're going to find it," Nelson repeats. That's about 6,000 cases of

prostate cancer and nearly double the diagnoses of the control arm.

The difference in mortality between the two groups, though, was minimal. The screened arm benefited by .71 lives saved per thousand. In other words, the study concluded that more than 1,400 men would need to be screened and 48 additional cases treated to prevent one death from prostate cancer. The conclusion was a little grim: Screening didn't do all that much to prevent prostate cancer deaths.

What's interesting, Nelson says, is what happened when the study updated its results in 2012 after an 11-year follow-up. The new number was 1.07 men saved per thousand. Nearly 500 fewer men needed to be screened to save one life. According to proscreening physicians, this speaks to the incremental benefit of the test.

"The longer you wait in a population that you've treated and intervened in, the better the results are going to be," says Nelson. Initially, the European study found 48 additional cases needed to be treated to save one life. In the follow-up it was down to 37. "If we waited another decade it would probably drop to 25. … The benefit is not in the first five years, it's [likely going to be] in the years 25 and 30 later." The idea, urologists feel, is that these curves will continue to widen. That is, the screening group will do better with time, and the control group is going to do worse.

The argument could also be made today, Nelson says, that reducing deaths from prostate cancer shouldn't be the only endpoint. Prostate cancer progresses slowly, rarely metastasizing to the vital organs, and many men with the lethal form die of unrelated causes. "It sits in your bones for about a year, a year and a half, painfully, before you actually die of the disease," says Nelson. "Really, we should think more about, 'What is the morbidity of the disease?' Because a lot of men who have metastatic prostate cancer may die of another cause, but they suffer from their prostate cancer."

Ultimately the recommendation of the ACS and the task force, Nelson says, has turned many patients away from screening. However, "it is still unfortunately true that the only effective therapy—and when I say effective, I mean curative therapy—is when you have localized disease. Once you have metastatic prostate cancer, the best we can do is delay progression. And although PSA is not at all specific for prostate cancer [it can be elevated for other reasons], it is actually quite sensitive. … It will clearly detect it when the cancer is localized and much more curable."

In upcoming years, Nelson fears, the move away from screening will likely mean a reversal of recent trends; growing numbers of men will present with disease that is metastatic and incurable.

What's more: Prostate cancer is a disease of the elderly. Screening typically doesn't even begin until a man is 50 years old; the median age of death from prostate cancer is 80. A huge segment of our population—the baby-boom generation—is approaching its most at-risk age. "There are going to be lots more much-older people around than there ever were in the history of mankind," says Nelson. "So we're caught: We see our population aging, and we have a test that doesn't work very well. How do we make [a solution] happen? Well, that's the challenge we face in our field."

For Nelson and many physicians, it's not whether to screen, but how to.

BREAST CANCER

Wendie Berg, an MD/PhD Pitt professor of radiology and an international leader in breast-imaging research, begins her Science2012 presentation with a claim that is simple and, some might say, pretty bold: "To some extent, mammography has been oversold."

To contextualize: Mammography is the best way overall to detect breast cancers when they're small and most treatable, and it's the only screening test proven to reduce death from the disease. It's still widely recommended for women age 40 and older, though there is some dispute over whether the test should be annual or biennial.

The newest controversy, however, lies in the increasing evidence that the test fails to detect many cancers in women with dense breast tissue. Of this population, more than 50 percent of women receive a false negative result.

"This is becoming a very hot topic right now," says Berg. In fact, a number of states, including Pennsylvania, are considering new legislation that would require doctors to inform patients when they have dense tissue, the dominant risk factor for a false negative after a mammogram.

Breast density is the proportion of glandular and fibrous connective versus fatty tissue present in the breasts. About half of all women in their 40s, and one-third of women older than 50, fall on the dense end of the spectrum and can be up to six times more likely to develop cancer. Unfortunately, dense tissue can also make it harder for doctors to spot problems on mammograms.

Consider this visual: On a black-and-white mammogram, tumors and their byproducts often appear as light masses on top of a darker backdrop. However, dense breast tissue, with cells bunched more closely together, brightens the entire scan, making it more difficult for doctors to distinguish between light and slightly lighter.

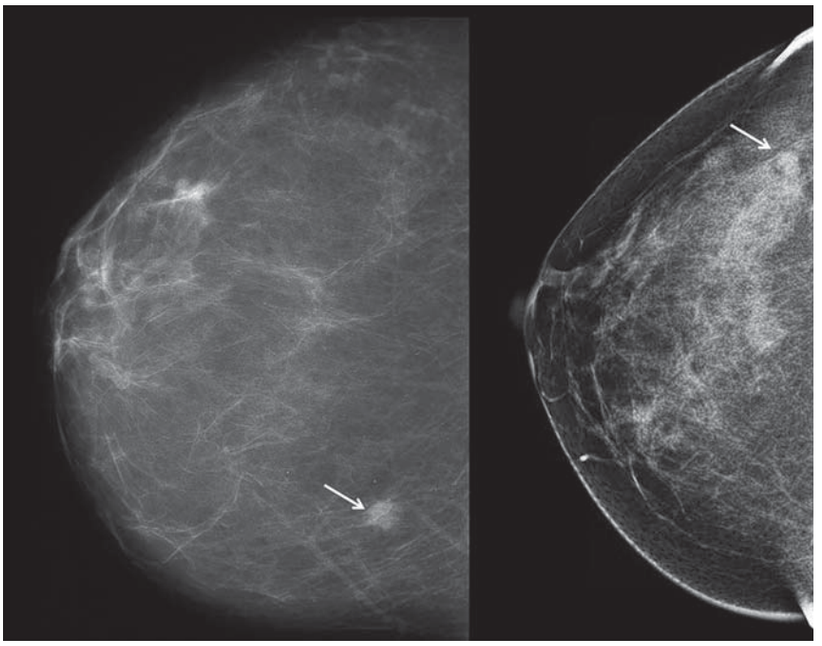
Traditionally, a radiologist would disclose tissue density on a mammogram report to the care provider by identifying the patient in one of four categories: almost entirely fatty, minimally scattered fibroglandular density, heterogeneously dense, or extremely dense. However, the new legislation would require a degree of increased transparency: Every mammography result letter given to a patient with dense breast tissue would have to inform the woman in plain language of her condition and note that she might consider asking her physician about the benefit of further testing. This legislation has already been passed in Texas, California, Virginia, New York, and Connecticut.

"Well, is additional testing a good idea?" says Berg. "This is a matter of some debate."

Often, additional testing comes in the form of an ultrasound or MRI (see "Lessons in Survival," Summer 2011), both of which are associated with a high rate of false positives. For example, of all the women biopsied after an ultrasound, only 10 percent have cancer. "That's a lot of unnecessary biopsies," says Berg. Essentially, we may run the risk of overcorrecting false negatives with false positives and subjecting healthy women to potentially harmful tests.

Nevertheless, in a study conducted at Pitt and Magee-Womens Hospital of UPMC and published in *Radiology* in March 2006, Marie Ganott, an MD assistant professor of radiology, determined that, of 1,500 patients in the breast-imaging suite, 86 percent were willing to go through the stress of recall and extra testing if it increased their chances of earlier detection.

"It is a very complex situation that we have in breast imaging, with a lot of opportunities," says Berg, who was recently recognized as a Medical Advancement Champion for Ground-Breaking Research Advances by the Avon Foundation and just won her second and third "Minnies"—Most Influential Radiology Researcher (2010 and 2012) and



COURTESY WENDIE BERG

In mammograms of two women with breast cancer, a tumor is easily visible in the patient with mostly fatty breasts (left). The patient with denser breast tissue (right) has cancer that is more difficult to detect. Comparing this image to prior mammograms helped her doctors detect the cancer.

Scientific Paper of the Year (2012)—from auntminnie.com.

"The only way I can wrap my hands around this is to at least propose that we are very strict about looking at the outcomes of women who are diagnosed with cancer and collecting information," about a patient's screening history, how the cancer was diagnosed, and her outcome, says Berg. "I think without this information, we're never going to be smarter."

The role of personalized medicine should also come into play when helping elderly women decide when to stop screening, Berg says. And that's a conversation that is often never held in this country. "It's very hard to tell someone not to get a mammogram. *What? They're not worth it anymore?*"

But the truth is, it typically takes nine years for the benefits of screening to be realized. "So, it really doesn't make a lot of sense, if a woman doesn't have at least a seven- to nine-year life expectancy, to push her to get screened," says Berg, because she's only going to experience the harms, not the benefits, of screening.

CARDIOVASCULAR DISEASE

When it comes to cardiovascular disease, the news is mixed. The bad part: It's the leading cause of death for both men and women and accounts for nearly one in three deaths in the United States. The good news: Deaths from the disease have been decreasing since the 1960s, largely because of improvements in how doctors focus on risk factors and better treatments.

Some of the most lethal iterations—coronary heart disease (number 1) and stroke (number 4)—have strong roots in atherosclerosis, a chronic process that begins early in life and truly lends itself to screening, says Emma Barinas-Mitchell, a PhD, assistant professor of epidemiology in Pitt's Graduate School of Public Health, and associate director of Pitt's Ultrasound Research Lab. "We can potentially detect individuals [who] are asymptomatic … and hopefully prevent events and death." But unfortunately, she says, "We don't have a perfect assessment."

Atherosclerosis is a chronic process wherein cholesterol and fatty substances accumulate in the arteries, harden into plaque, and disrupt blood flow. Screening is important, says Barinas-Mitchell, because, she explains, 40 to 60 percent of major atherosclerotic cardiovascular disease events show up seemingly out of the blue, as the first definitive sign of the disease. Atherosclerosis can remain asymptomatic for decades.

Typically, screening is performed by individually assessing established risk factors, like age, sex, cholesterol level, smoking status, and blood pressure, as part of a risk score, says Barinas-Mitchell. She cites the Framingham Risk Score, which predicts risk of cardiovascular disease over a 10-year period, as a widely used and valuable tool. However it has some drawbacks, she says. Namely, it hasn't proven to be accurate across all ages and ethnic populations.

So, wouldn't it be better if there were a way to physically see atherosclerosis and measure risk? That's the idea behind the carotid intima-media thickness test (CIMT), which uses ultrasound to measure the thickness of the inner layer (intima) and the second layer (media) of the carotid artery in the neck. This thickness represents a measure of atherosclerotic potential.

"The more risk factors you have, the thicker IMT you tend to have," says Barinas-Mitchell. "So, we know that [CIMT] predicts disease," Barinas-Mitchell says, but is it a better predictor than other methods, like the Framingham Risk Score? The answer, in short, is no.

Recent studies have cast doubt over the effectiveness of the test: CIMT was not associated with a reduction in cardiovascular events, and some studies proved it was a poor predictor compared to coronary artery calcification scores, which directly measure the calcification in the coronary arteries.

CIMT may have some incremental value. There is evidence the test is useful for patients considered at intermediate risk for developing heart disease, says Barinas-Mitchell. But that doesn't mean it is effective for widespread clinical use. "In terms of making global recommendations, I don't think we're there yet," she says. "Although, I think we can continue to use CIMT as a valuable research tool for understanding how and why atherosclerosis develops."

WHAT EXIT?

Is there a better way to approach early detection? What's ahead?

Perhaps the most fundamental way to think about the future of medicine is to remember we're all just a combination of genes and environment, says Steven Shapiro, professor of medicine at the University of Pittsburgh, as well as executive vice president and chief medical and scientific officer for UPMC and president of its Physician Services Division.

Genes and environment: These are two big columns with a million tiny variables that, when acting together, could spark a chain reaction toward a pathology. A predisposition for



Increasing evidence tells us that for women with dense breast tissue, mammograms fail to detect some noncalcified masses resulting from cancer and lead to an unacceptable number of false negatives. In these cases, supplemental screening with ultrasound can detect more cancers, but at the risk of more false positives.

developing lung cancer, for instance, adds up with the number of packs smoked on the front stoop. Poor diet and lack of exercise collude with family history of cardiovascular disease.

These are well-known examples of risk factors, but how we end up ill or healthy is not at all straightforward. So, amid a cacophony of cofactors, how can doctors efficiently assess what's wrong and how to fix it?

Historically and still today, doctors measure our health based on "a constellation of symptoms," like results of physical exams and laboratory tests, says Shapiro. "And to simplify things, we put them in categories." Doctors lump similar clinical presentations together and diagnose the problem, for instance, as diabetes or another chronic complex disease. "But these really are syndromes with multiple discrete molecular pathways, and because of that, patients have different manifestations of their disease."

With personalized medicine, rather, the emphasis is on using new methods of molecular analysis to understand the nuances of a person's genetic profile and optimize care with more precise diagnoses and targeted treatments.

The idea is that by studying molecular-level goings-on and environment, rather than symptoms, doctors can more precisely place patients into subpopulations and understand who is more likely to contract disease and how to prevent it. The foundation of personalized medicine, it is said, rests at the intersection of big data and big science. Or, put another way: First you have to know what you know, and then you can figure out how to use it.

In October, UPMC announced its commitment to fostering personalized medicine through big data. It launched a five-year, $100 million initiative to create a data warehouse that brings together clinical, financial, genomic, and other information that today is difficult to integrate and analyze.

Will there be growing pains associated with a personalized approach to care, as there are with today's early detection technologies? Perhaps. Yet, notes Shapiro, "The challenge that we have is greater than just taking care of patients, it's taking care of patients in a better way and saving the health of our economy." ■



TY BAE PUSHES THE ART AND APPLICATION OF COMPUTER-AIDED DIAGNOSIS

BY ELAINE VITONE

VISUAL THINKER

In the 1960s, Korea's postwar capital city swelled with a baby boom and an influx of displaced farmers from the countryside. At one point, a grade school in Seoul was said to have 12,000 students, more than any other on the planet. The children of this rapidly industrializing city often left the classroom for the factories at age 12—that's as far as public education went. There was no roll call. Teachers used a map of the desks to track attendance, each child represented by an assigned number.

PHOTOGRAPH | JIM JUDKIS

Kyongtae (Ty) Bae is an engineer-cum-radiologist-cum-artist. (He's shown here with some of his own paintings.) The visual thinker is now helping other docs decipher the intricate detail revealed by current medical imaging technology (which he helped improve).

Number 98 was Kyongtae Bae.

Against the odds, young "Ty" would excel at his studies. His family could not afford to send him to middle school—Ty Bae is the sixth of eight children, and his father had died when he was a teenager. But merit scholarships enabled him to ultimately become the first in his family to earn a bachelor's degree (from Korea's prestigious Seoul National University).

After he graduated, the Baes immigrated to Los Angeles. For a year, Bae worked three jobs—through the days, evenings, and weekends—pumping gas and mopping floors, earning minimum wage.

"Like any other immigrants, we had to adjust to the system. We had no money. We had borrowed to pay our airfare," he says on a recent fall afternoon, standing at his desk (sitting isn't really his style) in UPMC Presbyterian South Tower, where he now heads the University of Pittsburgh Department of Radiology, among the largest academic radiology departments in the world.

In L.A., Bae longed to return to academia. He had a chemical engineering degree and wanted to use it. He contacted a professor he knew at the University of Iowa and asked for a reference letter for graduate school. The professor told him to forget the letter and offered him a graduate position.

Bae had always wanted to invent something. Early on, he seemed to understand that if you want to bring something new to a field, it helps to be able to approach it from multiple disciplines. He calls this "learning new languages." He earned a master's degree in chemical engineering while holding down a research job in the biomedical engineering department—to prepare himself for a PhD in that field, and then, ultimately, med school.

"As an engineer I'm trained to solve problems," says Bae. "But I know it's equally important, if not more important, to define the good problem. Without that, you end up getting a solution you don't really need.

"I figured medicine is the engineering of biology."

As a med student, Bae worked in the University of Chicago's Rassman Lab, a player in the then-nascent field of computer-aided diagnosis. These early programs aimed to help physicians flag problem areas in 2-D imaging scans like X-rays and mammograms. But Bae's PhD from the University of Pennsylvania had given him the training needed to take things a step further, into 3-D, using CT scans. "So that's what I did," he says. "It was sort of my pet project. I was working weekends and evenings making a computer program." This "pet project," which kept him crafting code through many nights, would result in his first patent; it was filed in his second year of medical school. In 1994, he published the first paper on computer-aided diagnosis of pulmonary nodules from CT images.

It was becoming clear to Bae that radiology was the ticket for him. It married two of his skill sets, technology and medicine. Plus, he was a born visual person. (Laughing, he admits to not having much of an ear for the stethoscope.) He has an art studio at home, and his oil paintings and color photographs adorn the walls of his department. ("I think maybe they are tolerating them because I am chair," he says with a smile.) He might have pursued an MFA if it had been less of a financial gamble.

"I figured medicine is the engineering of biology."

In 1992, as Bae began his residency at Washington University in St. Louis, computed tomography had just taken a giant step forward with the invention of the helical CT scanner. Previously, to create individual cross-section images of the body, the X-ray beam and its sensors were mounted to hardware that made a 180-degree arc across the patient, then paused to allow the patient gurney to move ever so slightly in preparation for the next pass. With the helical model, the scanner and patient could both move simultaneously and continuously, the beam moving through the patient like a spiral slicer through a ham.

"It used to take several minutes to scan a body. You would inject the contrast, wait and have a coffee break, then come back and do the scan. Now it would take seconds. Because the scanner is faster, you get much better quality if you hit it right. But if you miss it, you won't get good quality."

Curious about how he might improve upon scanning technology and dynamic contrast agents, he decided to study the literature on the subject. He found little in this new field. Here was a good problem.

Bae's engineering brain kicked in: You have the blood vessels and organs, and the input moving through them—the contrast agent. Depending on how you move your input through, you get a different product—the images.

"To me it was like a factory," he says.

Bae enrolled in a class to brush up on physiology, then conducted a series of experiments on pigs, working out the effect of different rates of IV-contrast input on different rates of cardiac output. Once again burning the midnight oil in his free time, he created a mathematical model that takes all of the variables into account—the patient's height, sex, weight, age, etc.—and projects how best to image each organ of the body. (After 15 years of work in the field, in 2010 he published a landmark article in *Radiology* describing the state of CT intravenous contrast medium and timing technology.)

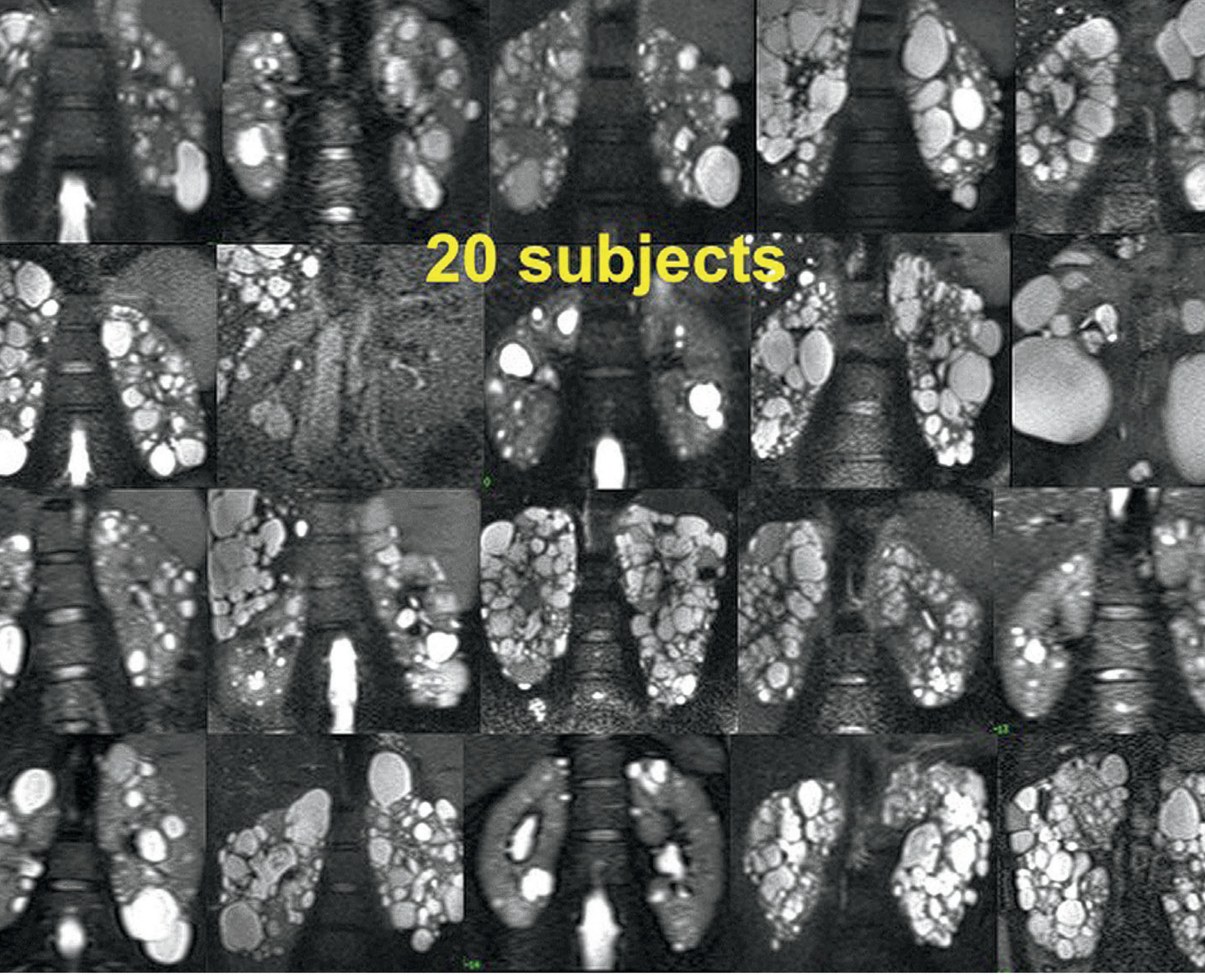
While Bae's methods weren't universally adapted, they did get people thinking about how best to use the tools that were available to get the most detailed information, says Vamsi Narra, professor of radiology at Washington University, who trained alongside him there. "Just like Google was the one that started people thinking about indexing. … I see things coming out now as an offshoot of [Bae's] work."

Bae was invited to join the faculty at Wash. U. and stayed for eight years. Then, in 2006, he joined the University of Pittsburgh as visiting professor of radiology and bioengineering, bringing several of his research endeavors with him. Three years later, he became chair.

It's an exciting time to be in radiology, Bae says. He reaches over to his computer and opens presentation slides (he's on the international radiology circuit), comparing the first CT scan from 1972—a single, grainy, gray slice of the brain that took 20 minutes to scan—to the staggeringly intricate 3-D renderings that take seconds to conjure up today. Now we can scan the entire body, head to toe, in less than a minute and scrutinize any organ from any angle. We can spot disease where it lives, as well as aberrations not yet causing any symptoms whatsoever.

Therein lies the rub, and Bae's next big problem to solve: Yes, we can see the body in stunning detail, but … now what? At Pitt's Imaging Biomarker Lab, which Bae directs, he and his colleagues are decipher-

COURTESY BAE LAB



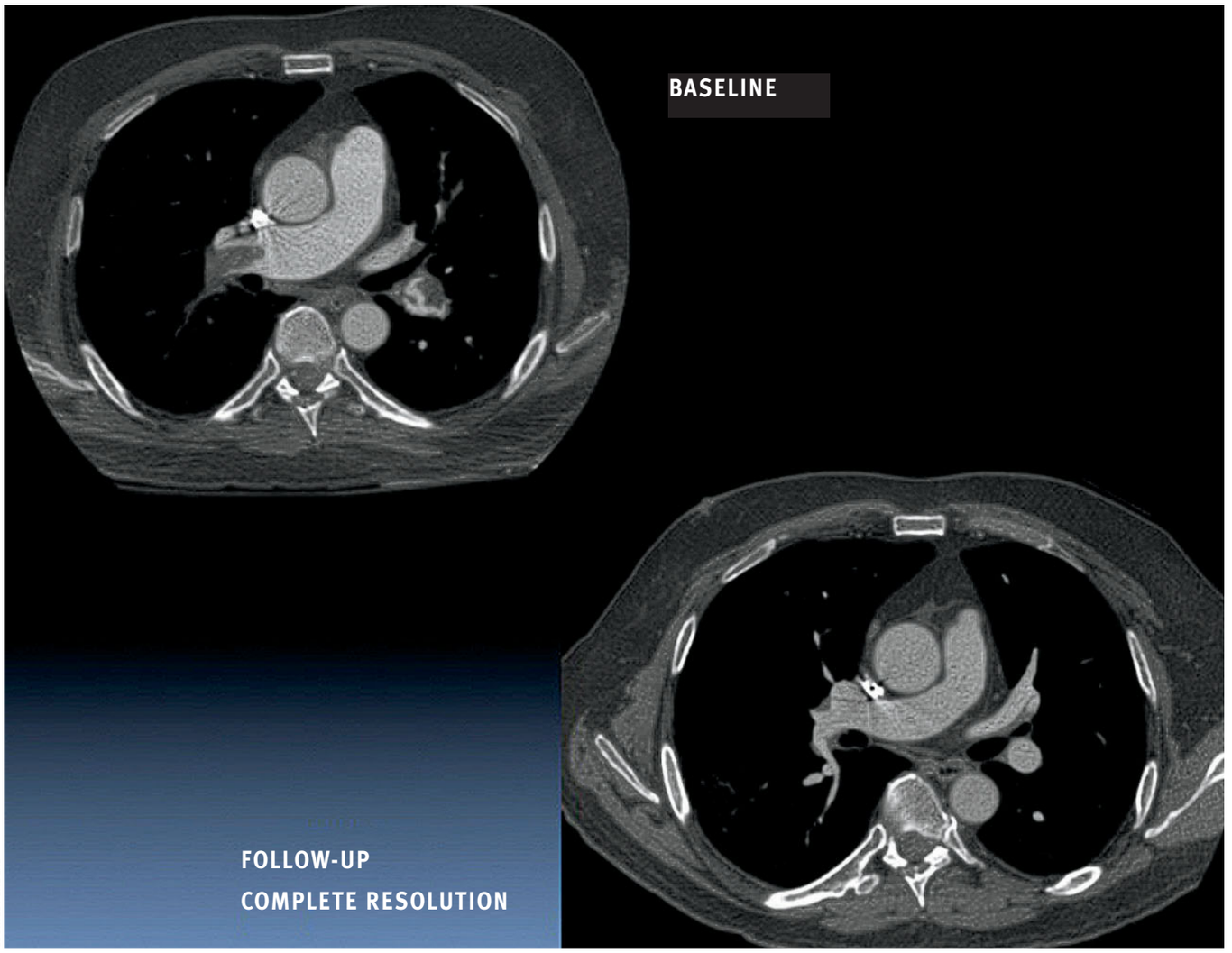
Half of patients with polycystic kidney disease progresses quickly to renal failure, while the other half "is doing fine," says Bae. Using algorithms on measurements of cyst volume, distribution, density, and other characteristics, he has developed a tool to help doctors determine which path a patient is likely to take.

ing what to do with the massive amount of information that comes with each new imaging technology. They're looking for new imaging biomarkers—visual indicators of diseases—and also evaluating how best to use the biomarkers that are already known.

For the past 12 years, one focus of Bae's research has been polycystic kidney disease (PKD). Characterized by a plague of fluid-filled cysts in the organ, PKD can cause back pain, high blood pressure, and urinary tract infections. And, for about half of these patients, the cysts eventually overtake the organ and cause renal failure. "But the other half [of the patient population] is doing fine," says Bae. Right now we have no way to tell at the onset who's going to be a rapid progresser, and who's going to be okay.

In 1999, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) formed the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP), a 10-year prospective study. As chief radiologist and PI of the data center for the study, Bae has been analyzing MR images from sites across the country and developing algorithms that use these images to calculate the volume, distribution, density, and other characteristics of cysts. He's finding patterns, linking various characteristics of disease progression with their outcomes, and developing a prognostic tool. And in recent years, a spinoff study funded by the NIH has been putting this new tool to the test. Dubbed "Halt PKD," the ongoing trial applies what has been learned to improving treatments.

Bae is working on similar projects for pulmonary embolism, emphysema, osteoarthritis, lung cancer, prostate cancer, breast cancer, Parkinson's disease, brain tumor perfusion,



COURTESY BAE LAB

Mark Roberts and Bae are finding that not all pulmonary embolism clots are created equal. The two are developing CT biomarkers to distinguish which patients need less anticoagulant, a potentially dangerous medication. Here, a pulmonary embolism (left) is completely resolved in the follow-up scan two months later.

and multiple sclerosis, as well.

Mark Roberts, MD professor and chair of the Department of Health Policy and Management in the University of Pittsburgh Graduate School of Public Health, calls Bae forward thinking. "I have been involved in some other projects back in Boston, where I came from, where there was this incredible urgency to find the most accurate test, the most robust test—not the impact of the test on decisions doctors were making in real patient care. I personally find that what's atypical about Dr. Bae is he's not just a radiologist; he's a doctor first. What he cares about is how the diagnostic tests he's using affect patient outcomes."

Roberts is collaborating with Bae on a CT biomarker project involving pulmonary embolism—blood clots gone rogue.

He explains: When you have an injury, several processes kick in at roughly the same time. The clotting process, which stops the bleeding; the repair system, which heals the vessel; and the clot-dissolution system, which eats the clot away from the inside out as the vessel heals so that the normal diameter of the vessel remains intact.

Here's the problem: The body's strongest signal to produce clot is . . . the presence of a clot. And in the case of a pulmonary embolism, unfortunately, the clot didn't get there in the first place because it was needed (because the lung is bleeding); the clot got there because it formed elsewhere, somehow became dislodged, and then traveled to this most precarious spot. Yet there it is, stuck and sounding alarms—which, in spite of their best intentions, could cause further clotting that could choke your lung and kill you.

Docs do not take pulmonary embolism lightly. Right now, an extended course of anticoagulants is recommended for all cases—though exactly how extended, no one can agree. Some say six months, others nine, and still others a full year.

Mind you, anticoagulants don't dissolve the clot in your lung. They just allow your clot-dissolution process to catch up and prevent further clotting activity. Disabling your body's clot production for months on end comes with its own risks. (You do not want to cut yourself while you're on these meds.)

Bae is applying his algorithms to pulmonary-embolism CTs scanned at sites across the country. The tool has increased the team's ability to predict outcomes by a "nontrivial," says Roberts, 10 to 15 percent.

With Pitt's Donald Yealy, professor and chair of emergency medicine, and others, Bae had submitted a new clinical trial proposal to the National Heart, Lung, and Blood Institute; that study will attempt to answer the nagging question of how long these patients should be given anticoagulants. The answer, they suspect, is: It depends. They're building data stores to prove that not all clots are created equal;

and, therefore, they do not all require the same treatment. In fact, the researchers believe some clots are probably so small they don't need treatment at all.

This is one of the reasons Bae's work is so exciting, Roberts says. "Most of the recommendations we have about diagnostic testing and treatment are pretty blunt. We have to understand ways of making them more tailorable, more personalizable. I think his work can help us do that."

In doing so, Bae's research also stands to help bring down health care costs, improve reliability and consistency in what happens with diagnostic imaging, and ultimately help patients recover faster.

But research is just one of the plates Bae is spinning at any given moment.

This is a guy who has 10 patents to his name, has secured more than $16 million in NIH grants in the past 13 years, and still sees patients and runs a very large department. (In addition to 220 clinical and research faculty members, it's academic home to 57 residents and 28 fellows at last count.) Bae is an engaged leader, frequently meeting one-on-one with mentees and reviewing grant applications and manuscripts for junior faculty members. In his relatively short time here, he has overseen the hiring of more than 30 new faculty members.

And in his spare time, just for kicks, he's learning Chinese.

None of this surprises Narra, who likens his friend to "some kind of movie hero." (Apropos of nothing, he mentions that he has seen Bae, who is a lifelong student of martial arts, do thumb push-ups. And one-legged squats.)

"Ty is one of the most brilliant guys I've come across. And he's not only bright, but he also has this unending energy and enthusiasm. It's amazing. You never hear him say he's overwhelmed, or he's busy. Never! You say, 'Ty, I hear you got this [grant application] out,' and he says, 'Yeah, we took care of it. There was a problem, and we got it out, and we got a paper, and yeah, I got a $5 million grant from the NIH.' And it's all in the past tense!"

Bae, who, after a two-hour interview still has yet to make use of a chair, shrugs it off.

"For me, working hard is no big deal." He wonders aloud whether his drive stems from being one of eight kids and always wanting to distinguish himself by creating something all his own. Having the chance to do so here in the States fills him with gratitude. He hopes to return the favor by realizing his ambitions and helping others to do the same.

"I appreciate the opportunity," he says. "There are a lot of people who work in factories doing the same stuff over and over, without any additional creative opportunity. So this is wonderful." ■

Bae's next big problem to solve: Yes, we can see the body in stunning detail, but … now what? He and his colleagues are deciphering what to do with the massive amount of information that comes with each new imaging technology.

NIGHT SHIFT

They have the graveyard hours. Although, considering their line of work, they prefer to call it the nighthawk shift. Whatever the name, 10 UPP (University of Pittsburgh Physicians) radiologists are now staffing a UPMC Emergency and Teleradiology Division during those hours (5 p.m. to 7 a.m.), when most people have already called it a day.

The unit started somewhat modestly back in 2008, but has continued to expand as technology continues to advance. "Obviously, imaging has evolved and become more complex, pushing the need for in-house coverage," says Omar Almusa, an MD, division chief, and Pitt assistant professor of radiology.

The need is about having a trained subspecialist (for example, a neuroradiologist interpreting brain and spinal cord film) taking an active role in a patient's trajectory of care.

In the not-so-distant past, imaging was considered an adjunct to patient management at UPMC. But now with the teleradiology division in place and located on the Presbyterian campus, final reports are available within an hour (as opposed to 15), and radiologists are available for consultations in real time.

Almusa sees the radiologist as the doctor's doctor. A radiologist might also be thought of as the air traffic controller who assists the ER physician or surgeon in charting the right course.

The concept of a 24/7 academic medical center radiology division is not a new one. But, says Almusa, UPP was an early adopter. These days, its coverage area extends to UPMC Presbyterian, Shadyside, Magee-Womens, and Mercy, other UPMC facilities (including its urgent care centers, Bedford Memorial, Northwest, and Hamot hospitals), and Trinity Health System in Steubenville, Ohio, as well as Monongahela Valley Hospital.

Typically, the four overnight radiologists on site will handle anywhere from 160 to 480 cases; most are related to car accidents, strokes, and abdominal or chest pains.

"One moment you may have nothing to do," Almusa says, "and the next it's all you can do to keep up." But he has taken note of predictable patterns of behavior, bracing himself for an onslaught of work from 8 p.m. to 2 a.m.; he knows the summer months will keep him busier than any other time of year. (Exceptions are winter days of bibulous revelry: New Year's Eve, St. Patrick's Day, and the Super Bowl, especially if the Steelers are on the field.)

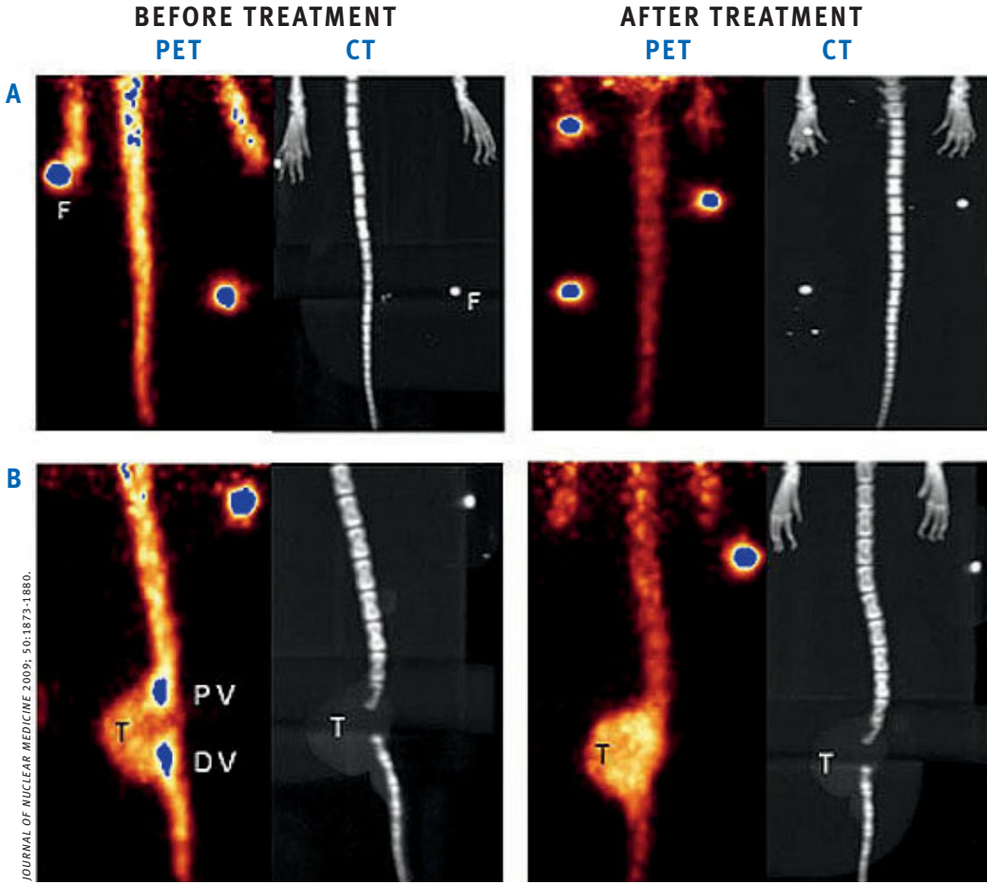
Almusa is looking forward to expanding the division's reach to rural areas and its expertise to include more subspecialties like pediatrics and obstetrics. "It's very rewarding," he says, "to have such an impact on patient care."

—Barbara Klein

BIG SHOT

ALL THE IMAGING A BASIC CANCER RESEARCHER COULD EVER WANT

BY ELAINE VITONE



At the new Pre-Clinical PET/CT Imaging Suite, scientists can not only study a disease down to the molecule, but also follow its movements within the entire, living host. Here, we can see osteoclasts in the PET scans of mouse models A and B absorbing an imaging agent developed by Carolyn Anderson and her team. In model A, osteoclasts migrated before tumors developed; their presence may predict future bone metastases. And in the "after treatment" images, we can see less of the agent absorbed: The treatment appears to be working in both mice.

At Pitt, radiology is no small potatoes. Now ranked 11th in National Institutes of Health funding, the department has seen a number of big moments in radiologic research since its founding in 1956. Among them: Pittsburgh Compound B, a PET-scan dye that made amyloid plaque (a hallmark of Alzheimer's) visible in living people for the first time; the PET/CT, which combines detailed functional and anatomical information together in one scan (since it was first tested at UPMC some 15 years ago, it has become standard, with more than 2,000 PET/CT scanners in hospitals across the country); and Stentor, an intranet-based radiological-image storage, management, and distribution system. Stentor helped make the move to filmless radiology efficient and user-friendly.

So what's next for what may be the country's largest academic radiology department? To think small. Very, very small.

In October, the Department of Radiology and the University of Pittsburgh Cancer Institute cut the ribbon on the Pre-Clinical PET/CT Imaging Suite at Hillman Cancer Center, which was the brainchild of Kyongtae Bae, Pitt professor and chair of radiology. What's unique about it, says Carolyn Anderson, whom Bae recruited last year to lead the initiative, is that it brings together all the imaging technologies a basic cancer researcher could want—including bioluminescence for tagging molecules, as well as special PET/CT, MR, and ultrasound equipment scaled down for rodent models—all under one roof. It's a first for Pitt, and a rarity in institutions across the country, she says.

With this facility, Pitt's scientists can track how cancer interacts with its host at the cellular and molecular levels and see its interplay with the whole dynamic, living organism.

"Sometimes you see changes not so much in the cancer cells, but in the mechanisms of how the cancer is spreading," says Anderson.

For example: Other groups have shown that a particular cell type within bone marrow, known as a hematopoietic progenitor cell (HPC), arrives at the site of metastasis in advance of the colonizing cancer, signals it in, and primes the new location (the premetastatic niche, as it's called). In May, Anderson and colleagues at Washington University in St. Louis showed for the first time that it's feasible to image this cellular welcoming committee in action. Her group developed a PET agent that makes this possible.

Soon, Anderson's team will begin the process of validating these preliminary findings in a more-true-to-life model of metastasis: a rodent model of breast cancer spreading to the lungs. HPCs encourage these secondary tumors in mice just as they do in humans.

The new center makes it easier to do "nice, quantitative imaging" of a variety of possible cancer therapies, says Anderson.

Cancer research is the focus of the imaging initiative, but Radiology Department faculty members are using it to delve into other diseases, as well: For instance, Mike Modo, a PhD associate professor, uses novel MRI contrast agents to explore neuronal-stem-cell transplantation as a possible therapy for brain damage and neurodegenerative disease. Mingfeng Bai, a PhD assistant professor, is working with Chet Mathis (a PhD professor of radiology and coinventor of Pittsburgh Compound B) to develop a low-cost method of imaging neurofibrillary tangles—a marker of neuronal loss in early Alzheimer's disease.

Pitt's Nancy Davidson, director of UPCI and UPMC CancerCenter, says her team's focus is "ever more on precision cancer medicine." She's delighted to have the new resource, "which will accelerate translation of findings between the lab and the clinic to facilitate optimal individualized patient care." ■

People and programs that keep the school healthy and vibrant



PEACE, LOVE, AND TREVOR

A FAMILY HELPS OTHER FAMILIES

BY BARBARA KLEIN

There are not a lot of happily-ever-after stories at the Program for the Study of Neurodevelopment in Rare Disorders (NDRD). In fact, just about every child seen at this clinic will die—not one day in the distant future, but one day soon.

That's because of the 20 different diseases and syndromes (like Krabbe, Sanfilippo, and Hurler-Scheie) the NDRD at Children's Hospital of Pittsburgh of UPMC treats, all 20 are fatal unless discovered early. And the chances of that happening are as rare as the disorders themselves.

We're talking really rare, like one in 100,000 or one in a million. Many pediatricians may never encounter a single case. And if they did, they would think horses instead of zebras, further delaying the diagnosis.

"These are complex diseases that manifest in so many different ways," says Maria Escolar, an MD and NDRD's director. "Parents are usually running after the progression of the disease."

That was certainly the case for Nicole and Steve Aldrian. Four years ago, the couple had fraternal twin boys, Trevor and Tyler. Although they were born five weeks early, both appeared to be healthy, strong, and vibrant, hitting all the early benchmarks.

But things started to change around three months. That's when Trevor began projectile vomiting. But because he was maintaining a normal weight, his pediatrician wasn't too concerned.

The Aldrians remained uneasy. They took Trevor to a GI specialist near their hometown of Murrieta, Calif., for what seemed like a reflux problem. By six months, the differences between the two boys were impossible to ignore. Tyler was thriving and growing. Trevor was gagging and choking; he was experiencing stiffness and extreme irritability. Then one day he was no longer able to hold his head up.

That prompted a trip to the ER, an extended hospital stay, and ultimately a diagnosis of Krabbe disease. Also called globoid cell leukodystrophy, Krabbe is a degenerative disorder affecting the nervous system. It is caused by a shortage of the enzyme that surrounds and protects nerve fibers. For the few children who are diagnosed early enough, Krabbe can be thwarted by a stem cell transplant. Trevor's disease had progressed to the point where that was no longer a viable option.

"We were told Trevor would die before he was 2 and that we should consider sedation and hospice care," Nicole Aldrian says.

Instead, they called Escolar, who at the time was working at the University of North Carolina at Chapel Hill. She thought she might be able to control Trevor's symptoms with various medications while also gaining unique insight into Krabbe disease from the twin brothers.

"That first appointment was four hours long. Four hours long!" Nicole Aldrian says. "She helped us understand what was going on, and she's been helping us manage the disease ever since."

When Escolar moved to Children's Hospital in 2011, the Aldrians made the transition, as well. "We come to Pittsburgh once a year," Nicole Aldrian says, "and I know when I call, text, or e-mail, someone is available 24 hours a day, every day."

COURTESY ALDRIAN FAMILY



The Aldrian family: Nicole, Tyler, Steve, and Trevor

The NDRD staff includes a geneticist, child development specialist, speech therapist, physical therapist, audiologist, research manager, epidemiologist and statistician, two pediatric nurse practitioners, an administrator, and a clinic coordinator. In the past year, the team saw nearly 120 patients from around the world. Eight of these children with rare diseases and disorders were referred for stem cell transplants. But even though a transplant can stop the progression of a disease, it may not be able to reverse the damage that has already occurred.

During their most recent visit, the Aldrians learned that Trevor is in the final stages of his illness. However, the Peace, Love and Trevor Foundation (PLT), which they established in 2010, will continue.

"We absolutely love Dr. Escolar and her staff," Nicole Aldrian says. "Our primary mission, our driving force, is to help other families get to the right doctors." To that end, PLT will provide financial assistance and support as parents find their way through the insurance claims, medications, feeding tubes—the realities of a story with no happy ending, at least not yet.

"Most of the advancements we are making are because of the families," Escolar says. "We've gone from saying there's nothing we can do to offering two or three different medical treatments to improve children's quality of life." ■

To learn more about Krabbe disease:
www.peaceloveandtrevor.com
To support the NDRD directly:
www.givetochildrens.org



This photo was taken after a 2009 guerrilla bombing in the city of Neiva, Colombia. In Neiva, and throughout the country, a dizzying number of trauma patients keep doctors busy. A Pitt partnership has helped Colombian doctors, and some Pitt students, find ways to do clinical research that could help many others in low-resource settings.

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FITTING INTO THE SYSTEM

WHILE THINKING BIG ABOUT TRAUMA CARE IN COLOMBIA | BY ALLA KATSNELSON

The two young men are fixed firmly in Matthew Kesinger's mind. Each was a 25-year-old soldier who had been tracking guerrilla fighters in the jungle of southern Colombia. Each found himself in the emergency room of the University Hospital in Neiva after stepping on a land mine.

The first man was brought in around 7 p.m., his left shin, foot, and ankle hanging by the tendons, and the bones of his lower leg completely severed. Kesinger helped Andrés Rubiano (Fel '09), director of the hospital's trauma department, stabilize the patient in the cramped trauma bay. Working with nurses and a resident, they warmed plastic sacks of platelets in their armpits before setting the bags up to transfuse into the man's body. When Kesinger and Rubiano stopped by the next day to check on him after his surgery, he was sitting up in bed, lucid, eating, and ready for transfer out of the intensive care unit.

The young amputee's doppelganger arrived a few weeks later, also with his left lower leg destroyed. But this second man was less lucky. Before arriving at the ER in Neiva, he had been pumped full of fluids in an effort to control his blood pressure, so he developed a dangerous build-up of fluid in the lungs, pulmonary edema. That, in turn, meant he had to be put on a ventilator. He spent 10 days in the ICU, the doctors unsure whether or not he would live. "This is a simple amputation. There's no reason this guy should die—but he barely made it," says Kesinger, a second-year medical student at the University of Pittsburgh who spent last summer in Neiva working with Rubiano.

The fate of these two patients was linked to the care they received before they arrived at the hospital in Neiva. Although it might be clear in hindsight that a particular intervention—such as administering lots of fluids—created problems, little or no guidance exists in Colombia for the care provided by rescue crews in the field. And the only way to determine what works best for specific types of injuries (or patients) is to take a systematic look by conducting a clinical research study. But despite the fact that about 80 percent of trauma care worldwide is administered in low-income environments, says Rubiano, the vast majority of clinical research on trauma—particularly in specializations such as neurosurgery—takes place in high-income countries. Those findings, he explains, are often not applicable to a setting like Neiva's critical care facility, where miniscule budgets, scant equipment, and a dizzying number of patients make conditions less than ideal. "People are not too motivated or prepared to do clinical research in this kind of environment," he says.

But Rubiano is part of a growing core of Colombian clinicians working to change that, with help from a program launched seven years ago at the University of Pittsburgh. It started with a five-year training grant funded in 2006 by the Fogarty International Center of the National Institutes of Health. The project, dubbed Trauma and Injury Excellence in Education on Research (TraInEER), was designed by Juan Carlos Puyana, an MD associate professor of surgery and critical care medicine at the University of Pittsburgh. The idea was to bring Colombian physicians to Pitt's Clinical Research Training Program and send them home with insight on how to apply for grants and conduct clinical research—and to teach others to do the same. That's how Rubiano found himself at Pitt in the summer of 2007 as one of two fellows chosen to kick off the program.

Rubiano has a round face and a warm, calm demeanor. Medical students at Neiva's South Colombian University consider him one of the school's toughest professors, yet they flock to him because of his reputation as a mentor. Many of them willingly wake up at 4 a.m. on weekends to accompany him on neurosurgery rounds. Neiva is Rubiano's hometown, but he studied medicine at the University of Valle in Cali in the mid-1990s. There the emergency room overflowed with trauma patients—casualties of the decades-old war between drug cartels or of liquor-induced violence and car crashes. He started running with the ambulances in his off hours, witnessing firsthand how strongly patients' outcomes were linked to prehospital care. After medical school, he returned to Neiva to start a program for trauma care in ambulances and then pursued his interest in neurosurgery with a residency in a private hospital in Bogota. The disparity between it and the overcrowded, underresourced public hospitals in Cali and Neiva shocked him and set him on this path.

At Pitt, he and the other fellows were tasked with writing a grant proposal, and Rubiano chose to focus his on a problem that had long bothered him. In high-income environments, patients who arrive with severe TBI are normally monitored in intensive care and sent to surgery only if brain inflammation and swelling swing out of control. But in Neiva,



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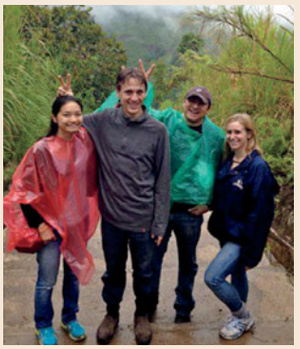
he says, "We do not have enough resources for ICU care." Hospitals like Neiva's generally lack intracranial pressure monitors—standard equipment in high-income settings. So knowing when to intervene becomes guesswork. As a result, death rates from TBI are two to six times higher. Rubiano thought a procedure called decompressive craniectomy, in which a piece of the skull is removed to alleviate pressure, could help in some cases. But the few clinical trials evaluating the procedure also relied on intracranial pressure monitoring. Rubiano wanted to design a trial that would identify other methods and parameters (such as eye, motor, and verbal responses; the presence of other injuries; and clues from CT scans) for deciding whether a TBI patient needs the procedure.

Garnering the experience to conduct such a trial would take some time. "The idea when I returned [to Neiva] was to apply all this knowledge," says Rubiano. "At the beginning, it was really difficult to try to fit that into the system." While at Pitt, Rubiano had dug into the literature on trauma management in military hospitals in Iraq and Afghanistan, which shared some key similarities to the level of resources and the types of patients that existed in his ER. Once home, he conducted a preliminary study with the World Health Organization that examined variations of care administered in the ER. Based on those data, he devised a standard protocol for treating trauma patients in low- and middle-resource countries and started using it at the hospital. In the United States and other high-income countries, surgeons routinely operate with the help of well-established protocols, but Rubiano believes his trauma protocol is a first for Latin America. He has faced some resistance from surgeons at the hospital who don't believe the protocol is necessary. But without data about the bigger picture, says Rubiano, surgeons are working in the dark. "When you don't have this view, you only discuss one case. And you feel like that is the entire reality of the system."

That's where Kesinger entered the picture. The two years he had spent as an emergency medical technician in the poorer neighborhoods of Boston before coming to medical school had fueled his interest in working again in a low-income setting. During his first year in school, he surveyed the options for a research project abroad and found Puyana; he became the first medical student from Pitt to sign on to this side of the exchange with Colombia. Puyana connected him with Rubiano, and the trio worked out a plan: comparing mortality and morbidity in TBI patients before and after August 2011—when the standardized protocol had been instituted. Kesinger recruited two other Pitt students—Lauren Salesi, a second-year Pitt med student, and Sandra Truong, a second-year student in Pitt's Graduate School of Public Health—to conduct summer research projects in Neiva, as well.

The Pitt med students worked with medical students from Neiva, training them to comb through patient medical records to identify the data necessary for their respective studies. It was a tough slog. Kesinger and five Colombian peers pulled data from some 5,000 medical records, mostly handwritten and some 600 to 1,000 pages long. The idea was to retrieve data on 100 parameters: Where was the patient transferred from? Was alcohol implicated? Did the patient develop sepsis? Pneumonia? Meningitis? When he wasn't on service with Rubiano, Kesinger would hike out to a tin-roofed warehouse that held shelves and shelves of brown manila folders; this was the hospital's records room. Kesinger would give the staff long lists of patient names, and they would either pull the physical files or copy an electronic version of them onto a flash drive. Sometimes he would walk over with the jovial director of the records department, and the two would brainstorm about how to raise $5,000 to hire one person for a year to build a comput-







COURTESY S. TRUONG AND L. SALESI



OPPOSITE PAGE: The countryside in southern Colombia, near a coffee plantation. CLOCKWISE, FROM TOP LEFT: Neiva students (shown here) Juan Camilo Barrios Torres and Astrid Ordóñez Muñoz worked with Pitt public health student Sandra Truong. Truong is doing a study on alcoholism, a major source of violence and car wrecks in Neiva. TOP RIGHT: Truong with Matt Kesinger, Andrés Rubiano, and Lauren Salesi in the mountains near San Agustín. Second-year Pitt med student Salesi investigated the epidemiology of pediatric brain trauma for a summer research project in Neiva. ABOVE: Students working in a courtyard behind their Neiva residence. BOTTOM LEFT: The Pitt students with Rubiano and Juan Carlos Puyana.

erized trauma registry with these 100 data points on every trauma patient admitted. "That could revolutionize health care in Colombia: $5,000," he says.

The group is still analyzing data from the study's 5,000 patients, dividing them into subgroups based on diagnoses. After returning from Neiva, Kesinger also trained three Pitt undergraduates to help collect data from the patient charts. The preliminary findings look promising: In patients diagnosed with intracranial trauma, mortality fell from 30 percent to 8 percent. And for all trauma patients, it dropped 26.5 percent (from 3.8 patients per 100 patients to 2.8) in the 10 months after the protocol was initiated. The plan is to publish the findings as soon as possible and also to publish the protocol in English in an open-source format. "We hope that in the coming years the protocol will be used and adapted to low-resource hospitals all around the world," Kesinger says.

Puyana longs to do more. In an urgently worded e-mail, he notes that the level of violence in Colombia has ebbed in the past six years, but in the rest of Central America and Mexico, damaging drug-control policies have ignited violent crime. "These countries are just beginning to live what Colombia has faced over the last 30 years," he writes. "We need to engage in a social revolution that can deal with the real roots of ever-growing violence in Latin America."

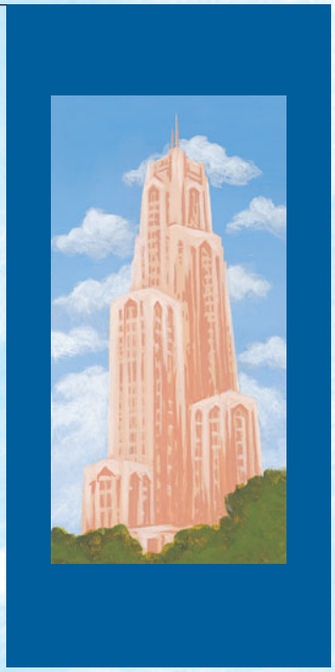
Yet the physician can take pride in instigating a smaller revolution of sorts—a clinical research movement that aims to help victims of trauma in Colombia and elsewhere.

Although the original 2007 grant to Pitt that trained Rubiano ran its course, the Fogarty Center recently approved funding for his clinical study on the efficacy of decompressive craniectomy. A larger Fogarty grant, from 2009, aims first to train 10 Colombian researchers in medical informatics at Pitt, then to establish workshops and seminars in clinical training back in Colombia. Ultimately, the hope is to set up a formal medical informatics course in Bogota's Javeriana University, Puyana's alma mater. "The beauty of these programs is that people are learning how to do their own thing," he says. "It began with a small seed, but now it's growing."

Rubiano's cofellow at Pitt that first year, Alvaro Sanchez-Ortiz (MS '10, Fel '13), stayed on to get a master's degree in clinical research and is now a research associate in Pitt's Division of General and Trauma Surgery and finishing his doctorate. He is examining the link between soccer matches, alcohol, and homicides. Another fellow alum, Carlos Ordoñez, now at the University of Valle, in Cali, is publishing often on trauma care. Ordoñez has also created a trauma fellowship program in Cali for surgeons—the first of its kind in Latin America. Rubiano would like to create a second fellowship specifically for neurosurgeons—one that would include extensive clinical research training. "We need to train people here the same way we have been trained," he says.

Kesinger is planning a longer research trip to Neiva. The two land-mine victims gave him an idea. Land mines, tools of destruction in the continuing drug war, wreak more havoc in Colombia than in any other country in the Western world. During his three months in Neiva, he saw about one land-mine injury per week. Inspired by Rubiano's efforts to develop national guidelines for treating TBI, Kesinger decided to try to do the same for land-mine injuries. He has applied for a Fulbright scholarship to fund such work in Neiva for a year. Kesinger has also been spreading the word among medical students interested in doing research on global health, hoping to spark others' interest in traveling to Colombia next summer to conduct projects of their own.

"Matthew has opened the way for other medical students to go down there and do similar work," says Puyana. The recruiting effort seems to be going well, Puyana notes. "I get an e-mail from him every other week that says, 'I told so-and-so about Colombia, and she wants to go.'"



CLASS NOTES

'60s

William Capello (MD '68) and **James D'Antonio** (MD '68) have been very close friends for more than 51 years. Fraternity brothers and football teammates at Rutgers, the two applied to and got admitted to Pitt med together.

Both Capello and D'Antonio specialized in orthopaedics—the former in academic medicine from the start, owing to inspiration from mentors Albert "Ferg" Ferguson and Jack Meyers. In 1984, as Capello was chairing the American Academy of Orthopaedic Surgeons' hip committee, he convinced his friend to join in on the fun.

D'Antonio, who has a bachelor's degree in materials engineering, now coleads an ongoing study on hydroxyapatite-coated hip implants with Capello, professor emeritus of orthopaedic surgery at Indiana University. The two have investigated and designed new hip implants, as well as knee-instrumentation systems, since 1988.

'80s

Recently, while catching up with *Pitt Med* via phone, **Waldo Concepcion** (Transplant Surgery Fellow '89) opened a card someone handed to him. It was from a college freshman who, as a child, had been on constant dialysis. Then, three years ago, he had a live-donor kidney transplant. Now, his life is no longer tied to a machine. In his card, he wrote of his bike trip at college.

Moments like this are not uncommon for Concepcion, professor of surgery, chief of clinical transplantation, and chief of pediatric kidney transplantation at Lucille Packard Children's Hospital at Stanford. He has founded liver transplant programs at California Pacific Medical Center and Loma Linda University Medical Center, which are lauded for their high survival rates. Concepcion's hope is that advancements in immunosuppression and diagnostic tests will mean even better outcomes. "We need to hone down and go deeper into every patient's response, to modify suppression for each person," he says.

'90s

Edwina Kinchington (Pharmacology PhD '97) launched her career in cancer research at Pitt. And as she trained, she realized her passion for teaching. "I really wanted to get to the students before they knew what they wanted to do because there are so many opportunities out there in the biomedical fields," she says. Then, in the spring of 2009, fate smiled: The Pittsburgh Science & Technology Academy (a.k.a. SciTech)—a new public science-oriented high school—was looking for teachers who had worked in the field. It was perfect. Kinchington could even build her own lab and create her own program. Now, as lead teacher for SciTech's Body and Behavior track, Kinchington opens 10th- and 11th-graders' eyes to biomedical technology and the life sciences, emphasizing hands-on learning and problem-solving. And as orga-



Kinchington with Candy (in the life vest) and Toby.



Jou (far right) with sister Annie and Adedotun Adebamiro (PhD '06, MD '08, middle) at a block party in New York City in June 2012.

GREGORY DUMANIAN

THE BIONICS MAN

Gregory Dumanian (Plastic Surgery Fellow '93, Plastic Surgery Resident '95) is one physician-scientist who could be excused for resting on his laurels. Dumanian, chief and program director of the Division of Plastic Surgery at Northwestern University, pioneered targeted muscle reinnervation (TMR) with Todd Kuiken, a physiatrist and engineer, in the early 2000s—a procedure noted for bettering the lives of upper-limb amputees. But Dumanian isn't one to sit still.

Conventional upper-limb prostheses, which are controlled by systems of cables or electronics, are very limited; they can only handle one motion at a time (the elbow bend or the hand grip, for example). So in the late-1990s, Kuiken and Dumanian began to experiment with the residual nerves in upper-limb amputees—rerouting nerves to remaining muscles, which motorized prostheses could be built to respond to.

Since the first human TMR surgery, performed by Dumanian in 2002, this so-called "bionic arm" procedure has gone from experimental to fairly commonplace, with remarkable results: Dumanian says that his operations, as well as those performed by military and overseas colleagues, have a 95 percent success rate.

Dumanian, who is a renowned expert on reconstructive surgery (of the abdominal wall, in particular), has contributed to studies on the feasibility of lower-limb TMR, as well. Leg prosthetics don't need the precision of TMR, he explains; for them, strength and durability are more important. But TMR shows promise for

nizer of the SciTech Science Forum seminar series, she frequently calls in colleagues from the school's partner, Pitt, for demonstrations and guest lectures.

'00s

Roger Jou (MD '03) is fascinated by how physical brain structures generate and influence behaviors. His curious nature and talent for working with computers led him to neuroimaging research, with a focus on structural MRI and diffusion tensor imaging. As an instructor in Yale's Child Study Center, he's investigating whether a specific phenotype in autism can be defined by patterns of disconnection in the brain. "There may be one pattern that emerges, but I think there's so much heterogeneity," he says. "I like to think of it as traffic on the road. If you want to get from A to B, there are a number of routes that get there, but also a lot of delays and blockages you might find, too." In January 2011, the National Alliance for Research on Schizophrenia and Depression honored Jou with a Young Investigator award.

When **Elizabeth Tyler-Kabara** (Neurological Surgery Resident '04) was a resident at Pitt, she heard about an investigator out in La Jolla, Calif., named Andy Schwartz, a PhD who had working animal models of exactly what she had long dreamed of doing for her patients with brain or spinal cord injuries, strokes, and neurodegenerative disease: helping them regain function by rerouting around the injured portions. Schwartz's monkeys moved robotic prosthetics with their minds—the beginnings of brain-computer interfaces.

"I literally scraped together my pennies to rent a car and called him and said, 'Can I come visit your lab for a day?'" says Tyler-Kabara.

In California, they had the first of many conversations where they lamented the distance that kept them from working together. And a few years later, they finally bridged it. Schwartz had been recruited to Pitt (the PhD is now professor of neurobiology). And Tyler-Kabara, who'd just completed a fellowship in Alabama, realized it was time to come back to Pittsburgh. In addition to the opportunity to finally work with Schwartz, she also saw that the place that had formed her as a surgeon would be an ideal launchpad for her as a physician-scientist.

Migrating back to Pitt worked out even better than she'd hoped. In 2008, Tyler-Kabara, a member of the Pitt/UPMC McGowan Institute for Regenerative Medicine and an assistant professor in the Department of Neurological Surgery, won a Clinical and Translational Science Institute (CTSI) pilot award, giving years' worth of insights gained in Schwartz's animal studies the chance to prove their mettle in humans. In October 2011, the team enabled a Pennsylvania man, paralyzed years ago, to control a robotic arm with his thoughts and reach out and touch his girlfriend's hand.

At Rochester, Minn.'s Mayo Clinic, **Timucin Taner** (Immunology PhD '05) investigates a phenomenon seen in multiple-organ transplants: When they involve a liver, the other foreign organs are protected from organ rejection and other immunological problems. This protective quality is only seen when all the new organs have the same origin.

"If we can understand the immunology behind it, it will first help our overall understanding of the transplant immunobiology," he says. "It has a potential to change our practice, too."

Of course, not every liver-transplant recipient needs a second organ. One modification that could arise from this research, Taner suggests, would be partial liver transplantations to add this immunological benefit.

Wendy Anderson (Palliative Care Fellow '07), an assistant professor in the Division of Hospital Medicine and Palliative Care at the University of California, San Francisco, completed CTSI's Master in Clinical Research program. While at Pitt, she designed a study on provider-patient and provider-family communication in end-of-life care, a topic she published on twice before graduation. This work led to a faculty job and funding from the National Palliative Care Research Center, as well as a coveted career-development award from UCSF. "CTSI is a lot of the reason I chose a fellowship at Pittsburgh," she says. What made the difference: great mentorship in both translational medicine and her specialty. "Bob [Bob Arnold, the Leo H. Criep Professor of Patient Care and professor of medicine at Pitt] is a wonderful mentor and continues to be a mentor to me today—probably the best I've ever met. ... I always have a voice in the back of my head asking, *What would Bob say about this?*"

—Em Maier and Elaine Vitone



Dumanian (right) with Northwestern Memorial Hospital colleague Todd Kuiken (left) and Oskar Aszmann (middle), a plastic surgeon from Vienna, at the first conference on targeted reinnervation in October 2011.

controlling these patients' neuromas—the painful severed nerve endings associated with amputation. "If you give that nerve somewhere to go and something to do, it quiets the nerve down," he says.

Now, along with Kuiken, Dumanian is working on true osseointegration—the integration of metal into living bone—in attaching prosthetic limbs. Though long successful in dental medicine and joint replacement, the process has had a high infection rate when attempted with prostheses. But Dumanian sees hope.

"People have always looked at it as an orthopaedic problem," says Dumanian. "But it's not—it's a soft-tissue problem; it's a plastic surgery problem. How you put a metal pin through the skin into the bone without getting infected depends on the seal of the soft tissue.

"Osseointegration would help a thousand times more people than TMR could." *—Justin Hopper*

CHECKUP

So, Doc, how are *you* doing? Don't keep it a secret. Share your personal news with old friends on the School's Facebook page. And here at the mag, we'd love to hear about novel and nationally newsworthy goings-on: honors you've received, appointments, volunteer work, publications, and the like.

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CAROLYN CARTER

NOV. 25, 1932–SEPT. 15, 2012

As the second dean of the Office of Minority Affairs in the School of Medicine's history, Carolyn Carter coordinated recruitment efforts, academic support, and other services for students from underrepresented groups. And to entice high school students into medicine, she founded a medical-professional shadowing program now known as the Summer Premedical Academic Enrichment Program, which is still running today.



Carter

"The legacy that she left was establishing a tradition of having pipeline programs for underrepresented students," says Paula Davis, assistant vice chancellor for health sciences diversity at the University of Pittsburgh.

"But what stands out to me were the things that happened away from Scaife Hall," says Dale Adair (MD '85), one of the dozens of Pitt med students who came to know Carter as a mother away from home. "She treated everybody like family. There were events at her house in Monroeville. Cookouts. Thanksgiving. She helped us build relationships and bond with each other, and she provided support. She was a very warm and inviting soul."

Carter died in September. She was 79.

She earned her RN degree at St. Francis in 1953 and later became one of the first African Americans to serve as head nurse at the hospital. She went on to earn her bachelor's degree in nursing, master's degree in psychiatric nursing, and PhD in higher education administration at Pitt.

The roots of her passion for enhancing opportunities for others ran deep: The daughter of the head of the Mon Valley chapter of the NAACP, Carter joined the massive 1963 March on Washington, bringing her daughter with her.

On April 27, the Pitt chapter of the Student National Medical Association (SNMA) will memorialize Carter at its annual scholarship-fundraiser banquet, which, several years ago, was renamed in Carter's honor. For information about the event or to contribute to the Carolyn M. Carter Scholarship Fund, contact the Office of Health Sciences Diversity at 412-648-2066. *—Elaine Vitone*

BERTRAM R. GIRDANY

MAY 27, 1919–JULY 31, 2012



Girdany

In 1950, when Bertram R. Girdany arrived in Pittsburgh to become the first head of Children's Hospital's radiology department, most pediatric radiology cases were handled at general hospitals. Children were still treated as small adults.

"He was able to bring a special way of treating children that was completely novel," says Girdany's protégé, Shashikant Sane. "He was way ahead of his time."

Girdany died on July 31, at age 93, in his home in Sarasota, Fla.

To minimize radiation exposure, he ensured children's doses were as low as possible and developed alternative procedures. And, as chair, he worked to build a multidisciplinary team, transforming the hospital into one of the giants in the realm of pediatric radiology.

Girdany was a caring mentor. When Sane left to become founding chair of radiology at Minneapolis Children's Hospital, Girdany and his own renowned mentor, John Caffey, checked in on Sane.

"[Girdany] came himself to make sure the job was okay for his boy, making sure the people I would be working with would be treating me appropriately. In 1975, they visited again to make sure I was doing fine, with a standing invitation to come back if I was unhappy," Sane says.

Girdany encouraged his mentor to establish the John Caffey Society, a prestigious group that still meets annually to share new ideas and publications.

Sane and Girdany stayed in touch, even after Sane's departure.

"I became part of the family," says Sane. Girdany encouraged Sane's two children to become radiologists. Both took his advice. *—Em Maier*

JEFFREY A. KANT

OCT. 4, 1946–SEPT. 29, 2012

Jeffrey Kant, the MD/PhD director of the Division of Molecular Diagnostics in the University of Pittsburgh's Department of Pathology, professor of human genetics and pathology, and director of the pathology residency training program, was known as an affable colleague and mentor. His residents honored him as "the residency director with the open door, open appointment book, and open mind."



Kant

Kant died in September. He was 65.

"He always created opportunities where he would take most of the diagnostic load to allow younger faculty to get their research [done] and move forward," says George Michalopoulos, pathology department chair, Distinguished Professor, and close friend of Kant. After Kant's death, Michalopoulos received more than a hundred messages from people inquiring about the beloved vanguard in the field of molecular diagnostics.

Kant helped found and also served as the first president of the Association for Molecular Pathology. As he established his own lab, he strove to engage the field more broadly, sharing his knowledge and expertise in diagnostics. His work led to the introduction of molecular diagnostics components to pathology labs across the country, and Kant continued the expansion of the discipline, discussing the economic and political issues related to the field. His teaching curriculum has been emulated in more than half of the pathology fellowships in the country, says Michalopoulos.

"More than anything else, he was a very pleasant person. He would take adversity with a sense of sagacity and a smile and say, 'You can turn it around; don't worry about it.' You rarely find that kind of attitude." *—EM*

IN MEMORIAM

'40s

EDWARD J. BENZ, SR.
MD '46
OCT. 26, 2012

'50s

DAVID STEELE
MD '51
JUNE 27, 2012

CARL KLODELL
MD '58
OCT. 18, 2012

FACULTY

ANNE RUSH COOK
MARCH 6, 2012

RICHARD STEINMAN ON VARIABLE GROWING CONDITIONS

BY SHARON TREGASKIS



CAMI MESA

Steinman received the Award for Innovations in Research Training and Education from the Association of American Medical Colleges this fall.

In 1889, a young West London physician investigated more than 700 cases of fatal breast cancer, deploying an agricultural metaphor in his analysis. "When a plant goes to seed, its seeds are carried in all directions," Stephen Paget mused in *The Lancet*. "But they can only live and grow if they fall on congenial soil." The uneven spread of cancer to some organs and not others, he concluded, must owe to variable growing conditions. Scientists, he wrote, must attend not only to the cancer itself, but the "soil" in which it sprouts.

In his laboratory, Richard Steinman (Res '90), an MD/PhD associate professor of medicine and pharmacology at Pitt, puts a twist on that classic metaphor: "Cancer cells on their own are incompetent to cause disease," he says. "What is vital is that they corrupt and engender the collaboration of normal cells around them to generate a local environment that's nurturing for the cancer's growth."

Paget was on to something, says Steinman. But for 100 years, scientists have had limited tools to analyze the dynamic, time-dependent relationship between seed and soil. Think of it, he suggests, more like a stage play. "I'm using some novel approaches to identify that corrupting dialogue," he says. "We assign the words of parts of that dialogue to either the cancer cells or normal cells and then test whether—in the laboratory setting—we're able to make either the cancer cells mute or make the normal, bystander cells surrounding them deaf so they don't hear the corrupting signals."

Cancer disproportionately affects people from underrepresented ethnicities, who are more likely to be diagnosed at a later stage of disease, are less likely to get adequate treatment, and have lower survival rates than others. They are also less likely to be involved in clinical trials and less likely to become physician-scientists, seeking the solutions so desperately needed in their communities. For as long as Steinman has been investigating the molecular signals associated with cancer's spread, he's been tackling those issues, as well.

As an MD/PhD student at the University of Pennsylvania in the '80s, Steinman ascended to the presidency of the Philadelphia chapter of Physicians for Social Responsibility and later to its national executive board. From 1994 to 2000—after finishing his residency and a postdoctoral fellowship at Pitt—he served on the African American Awareness Coalition, a partnership of the American Cancer Society and Pittsburgh medical centers to boost education and outreach regarding cancer detection and treatment within underrepresented groups. This fall, the Association of American Medical Colleges honored Steinman—associate dean and director of Pitt's Medical Scientist Training Program and director of the Physician Scientist Training Program—with its Award for Innovations in Research Training and Education. The award recognizes a partnership he established between the University of Pittsburgh Cancer Institute and Hampton University, a historically Black institution in southeastern Virginia, to introduce undergraduates there to the joys and challenges of oncology research.

Like his labors in the laboratory, says Steinman, his interest in mentoring aspiring physician-scientists and addressing the social correlates of cancer arise from the same root: a desire to amplify his impact. "There is the potential," he says, "to have an effect far beyond what's possible with a set of one-on-one interactions." Not that he doesn't appreciate the one-on-one. Perhaps the most meaningful award he's garnered was Pitt's Donald S. Fraley Award for Mentoring Medical Students, bestowed in October 2012. "It was deeply moving—more so than other past awards," he says, "because the students took it upon themselves to instigate the process."

Mehret Birru Talabi (MD '11), now a resident at UPMC, met Steinman more than a decade ago while an undergraduate exploring career options. Steinman put her to work on a health literacy project. Seeing the joy her mentor took in his research propelled Talabi to medical school and a PhD in epidemiology with an emphasis on disparities. "He's found a lot of creativity and passion and interest in what he's studying in a way that I'd never seen before," says Talabi. "His interests—in disparities, in education, in developing new scientists—are all an extension of how he looks at issues and attacks problems creatively." ■



PLAYING WITH FIRE

If you find it hard not to stare at a flame feeding on a log, you aren't alone. Yet, according to a recent article on the Web site *Life's Little Mysteries*, although this attraction is typical in this culture, it is not universal among adults worldwide.

However, it is natural for young children to be drawn to fire, regardless of where they live. Kids want to master it. And—as the Web site and a new evolutionary anthropology argument explain—in societies where fire is an everyday tool, children are given opportunities to do so. By age 3, they start experimenting with fire. (These kids really do cook their mud pies.) They are gradually given more responsibility with larger fires as they age, and by 7 they're able to control a blaze. That's about the age when they become less interested in it.

In the industrialized world, most of us never get to that point. UCLA's Daniel Fessler, an evolutionary anthropologist, told *Life's Little Mysteries*, "The motives that drive fire learning are only incompletely satisfied, with the result that, throughout life, fire retains greater allure or fascination than would normally be the case."

This doesn't mean it's a good idea to toss your kiddo a Zippo: Fire fascination has serious and deadly consequences in our world. And half of the cases of arson in this country are attributed to children. Pitt's David Kolko, PhD professor of psychiatry, psychology, and pediatrics, says that in a study he conducted of children between the ages of 6 and 13, 31 percent of nonpatients and 51 percent of psychiatric outpatients had set a fire before the initial study interview. What can a parent do to keep things cool? First and foremost, Kolko says, control access to lighters and matches. And make sure you have smoke detectors and fire extinguishers around, just in case. *—Erica Lloyd*

***When kids have an unusually strong attraction to fire, Kolko's SAFETY team can help. To find out more*: www.wpic.pitt.edu/research/safety/**

DUSICA PARIPOVIC/GETTY IMAGES

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

MEDICAL ALUMNI WEEKEND 2013
MAY 16–20

Reunion Classes:

2003	10th Reunion
1998	15th Reunion
1993	20th Reunion
1988	25th Reunion
1983	30th Reunion
1978	35th Reunion
1973	40th Reunion
1968	45th Reunion
1963	50th Reunion
1958	55th Reunion

SENIOR CLASS LUNCHEON (ALUMNI WELCOME)
MAY 17
11 a.m.
Connolly Ballroom, Alumni Hall

ALUMNI WEEKEND OPENING COCKTAIL RECEPTION
MAY 17
5:30 p.m.
Ballroom, Pittsburgh Athletic Association

ALUMNI WEEKEND NIGHT AT THE SYMPHONY
MAY 17
8 p.m. curtain
Heinz Hall

ALUMNI WEEKEND CHAMPAGNE BREAKFAST
MAY 18
9 a.m.
11th Floor, Scaife Hall

ALUMNI WEEKEND REUNION DINNER GALA
MAY 18
6 p.m.
LeMont Restaurant

CLASS OF 2013 COMMENCEMENT
MAY 19
10 a.m.
Carnegie Music Hall

ALUMNI WEEKEND SCOPE AND SCALPEL PRODUCTION
DATE TBA
Pittsburgh
For information:
www.scopeandscalpel.org

PALM BEACH HEALTH SCIENCES ALUMNI RECEPTION
FEBRUARY 13
Palm Beach, Fla.

WINTER ACADEMY
FEBRUARY 15
Ritz-Carlton
Naples, Fla.
www.winteracademy.pitt.edu

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS
DATES TBA
Los Angeles, Calif.
Phoenix, Ariz.

Unless otherwise noted, for more information: Pat Carver 412-648-9059, cpat@pitt.edu

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ALL TOGETHER NOW

Peaches and Herb reunited because it felt so good, because they understood. You, Pitt med graduate, can reunite for these or other reasons from May 16 to 20 at the Medical Alumni Association's Alumni Reunion Weekend. Come see the newest gaggle of grads off into the world of doctoring at the Senior Class Luncheon. Take in the tip-top tones of the Pittsburgh Symphony Orchestra. Dine on fine food and drink in the view from Mt. Washington's LeMont restaurant. And espy the latest installment of the proud tradition that is Scope and Scalpel. (We're told that the choreography has advanced quite a bit from the rehearsal pictured above.) For more information on Medical Alumni Weekend, look on the other side of this cover. Or visit www.maa.pitt.edu.