UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | WINTER 2011/12

PITTMED

WHAT MAKES GENIUS HAPPEN?

GEOMETRICAL DRAWINGS BY LEONARDO DA VINCI (1452–1519).

OLDEST LIVING ALUMNUS?

On page 40, in your last paragraph of the Last Call ["The Only School of Note," Fall 2011], you make a statement that Paul Caplan is the oldest living alumnus. This may be so, but I might challenge that. My birthday is Oct. 14, 1913. (I believe that a search of alumni records would likely show that century-old members exist.)

I am of the Class of 1937, and I'm 98. I was a Pitt med school faculty member from 1938–1953 with the Department of Physiological Chemistry. Part of that time I served in WWII, and later I received a PhD in biochemistry from St. Louis University. I finally left Pitt by returning to a career in the USAF in aerospace medical research. I commanded three different laboratories.

Incidentally, I found this issue of *Pitt Med* most interesting, since I am old enough to have lived through much of the history and people you reported on. I'm keeping my copy!

Joseph Quashnock (MD '37)
San Antonio, Texas

Dr. Caplan's birthday is Nov. 21, 1912.

LANSING: BOOK WORTHY

I am an alumnus of the University of Pittsburgh School of Medicine, Class of 1960.

The book that I've just published, *The Lansing Effect*, is dedicated to Professor Albert I. Lansing, who was chair of the Department of Anatomy at the time I studied at the medical school. Lansing was well known internationally for his work in many areas, especially the study of the biology and physiology of aging (gerontology). [Simply put, the Lansing effect hypothesizes that the offspring of old parents tend to have shorter lifespans than the offspring of young parents.] Some of the topics that fascinated Lansing—and, because of my friendship with him, also fascinated me—are themes in this new book. They are quite relevant to current-day issues of importance to the medical profession, scientifically and ethically.

By the way, I enjoy the articles in *Pitt Med*. It is a first-class publication.

Donald Malkoff (MD '60)
Centreville, Va.

KEEPING UP WITH DR. HUMPHREY

I have read and reread better than half of the articles you have published in the magazine. Without hesitation, I can say it is one of the many magazines and journals that I look forward to receiving. I have shown certain articles to friends and colleagues who are truly impressed with the overall quality.

In regard to Dr. Tryphena Humphrey, the neuroanatomy teacher in the '50s and '60s: She was a small, white-haired, grandmotherly woman. To be sure I was not exaggerating or hallucinating, I checked with a couple of classmates, who confirmed these impressions: During class, she drew on the blackboard renderings of the brain and spinal cord, including the spinal tracts, ganglia, crossovers, etc. She ordinarily had approximately 10 colors of chalk with which she could write and draw (using both hands) while simultaneously lecturing. It was impossible for the 100 students to even hope to keep pace with her. All students came to class with a box of 10 to 12 colored pencils to duplicate her drawings, which were phenomenal. Heaven forbid that a lead in one of your pencils broke, as you were S.O.L.! There were no textbooks of neuroanatomy that contained diagrams as detailed as hers. She was in the Department of Anatomy with Dr. Davenport Hooker and Dr. Jacob Priman, who were also outstanding.

I believe all in the class (except perhaps those who failed) loved Dr. Humphrey. She would be deserving of recognition in one of your future issues.

Keep up the excellent work.

Lawrence Gilford (MD '59)
Brookville, Pa.

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

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Gold, Periodical Staff Writing

PITTMED

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VOL. 13, ISSUE 4



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Genius! 12

Edison said that genius is "1 percent inspiration, 99 percent perspiration." But where does inspiration come from? Stories and perspectives from folks who might know, including Pitt's newly anointed MacArthur fellow, Elodie Ghedin, and scientific stars like J. Craig Venter.

COVER STORY BY ALLA KATSNELSON, ERICA LLOYD, JOE MIKSCH, AND SHARON TREGASKIS

The Natural 22

For his 12th birthday, Jeremy Berg received a copy of Linus Pauling's *The Architecture of Molecules*. Since then, he has helped scientists understand how DNA binds with proteins, become a department chair at 32, and directed an NIH institute. What's next? The University of Pittsburgh.

BY REID R. FRAZIER

Static 27

Thanos Tzounopoulos has learned that tinnitus is a betrayal of our biology that's rooted in the very strengths that have contributed to humanity's success: memory, learning, and adaptability.

BY ELAINE VITONE

CONTRIBUTORS

A decade ago, ALLA KATSNELSON ["Genius!"] was pipetting her way to a PhD in neuroscience at Oxford, when one day, quite out of nowhere, the experiment she'd been running for months stopped working—and never worked again. When she asked around, everyone kept telling her it could be anything: a new bag of water bath, a changed filter on the water dispenser. Katsnelson troubleshot every wild card she could think of, but still, no dice. "It was a massive method failure that almost undid me," she says. After completing her degree, she made a career change to science writing. This was not because of the (still-yet-unsolved) mystery of her experiment's doom; nonetheless, methods in science has become one of her favorite subjects. Katsnelson is a former news editor for *The Scientist* and former reporter for *Nature*. These days, she's a staff writer for a soon-to-be-launched multiple sclerosis–research site and a freelancer for such publications as *Scientific American* and *Nature Medicine*.

Illustrator STACY INNERST ["Pitt Med Was Here"] spent 17 years on staff at the *Pittsburgh Post-Gazette*. His style, he says, is "sort of painterly and primitive." *The New York Times*, PBS, and children's books are some of the places you might see Innerst's illustrations. For *Pitt Med*, he reimagined the world itself: "I liked the chance to depict a map of the world in an artful way; to represent something people are so academically familiar with and take it in a different direction," Innerst says. He gets a particular kick from his children's book work. His *M is for Music*, with author Kathleen Krull, won a Gold Medal from the Parents' Choice Book Awards. His work was featured at the Art Institute of Chicago's 2011 Picture Book Gallery exhibition, *Artful Alphabets*.

COVER

Geometrical drawings about transformation from curved to rectilinear surfaces and vice versa from *Codex Atlanticus*, Leonardo da Vinci (1452-1519). (Cover: Getty, 2011.)

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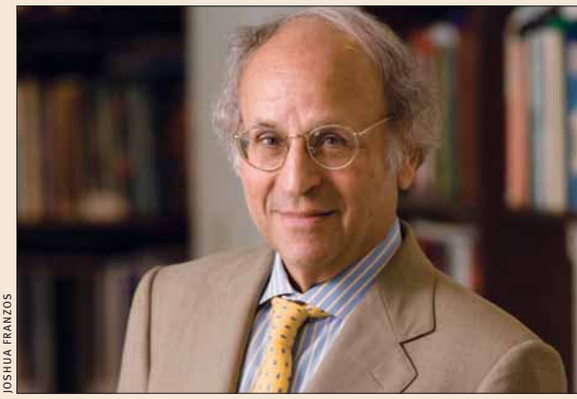
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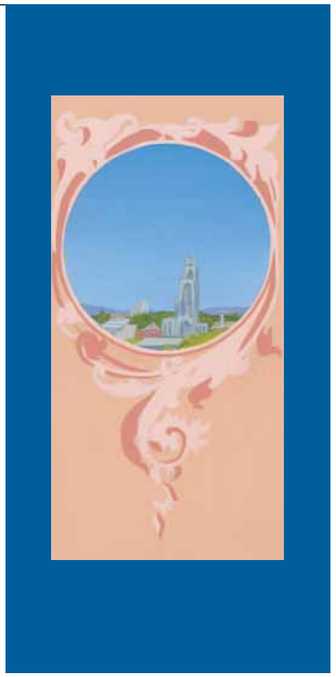
JOSHUA FRANZOS

And no, we don't know where it will lead. We just know there's something much bigger than any of us here.
—Steve Jobs

We live in an era of spectacular advances in medical research. Driven by almost unimaginably powerful technology, we gain further insight into human biology and illness almost by the hour; the momentum isn't slowing. A family of cellular molecules known as microRNAs (miRNA), not even known until the mid-1990s, is able to affect the ultimate expression of many of our genes. Just in the past few months, we have learned that these molecules can be transferred between our tissues and organs and that we can even absorb them by eating miRNA-containing plants. The human benefit may be profound: For example, certain miRNAs can increase our high-density lipoproteins (HDL) and lower our low-density lipoproteins (LDL), thereby potentially reducing the risk of cardiovascular disease. Although the pharmaceutical pipeline is thought to be "dry," with few if any new paradigm-shifting drugs emerging, the fact is that we sit on the brink of extraordinary discoveries based on our rapidly emerging knowledge of druggable cellular targets, the use of molecules like miRNAs as "drugs," the new ability to grow human cells on chips for drug effect and toxicity studies, and the power of computational and systems biology to take us past our knowledge of an individual patient's genome to a rich understanding of how that person's genome is ultimately expressed in a single cell and at an instant in time.

Thus, there is no question that great science today is leading to great medicine tomorrow—faster than ever. Great science is also great business. Every $1 million in research funding is estimated to generate 36 jobs—directly and indirectly. In fiscal year 2010, the University of Pittsburgh, driven by the medical school, received $800 million in research support. That has yielded almost 30,000 jobs! A November 2011 economic analysis estimates that federal- and state-funded research received by U.S. medical schools and their associated teaching hospitals added close to $45 billion to our economy in 2009. Moreover, the $4 billion invested so far in mapping the human genome has yielded an estimated $560 billion in new drugs and other health-related research advances—quite a return! The NIH estimates that the gains in life expectancy in this country since 1970 are worth some $3.2 trillion annually in enhanced productivity. Antiretroviral therapies have turned AIDS from a fatal to a chronic condition, enabling people diagnosed in their 20s to live and work until a normal retirement age. Cancer incidence is now falling at the rate of 1 percent per year, with each percent decline saving approximately $500 billion in otherwise lost productivity. But I've described only the economic impact that research has had in the past, not what we can anticipate for the future. The long-awaited era of "personalized medicine" will be part of routine clinical practice within the next decade; therapies based on a person's specific genetic profile are already used routinely for some diseases. Here, in collaboration with UPMC, we are launching a new Institute for Personalized Medicine to apply our own research to improving disease prevention and the treatment of our patients. Forgive the idiom, but … is great science great medicine *and* great business—or what?

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



Devoted to noteworthy happenings

at the medical school

GETTING CURES TO THE CLINIC

The Clinical and Translational Science Institute (CTSI) at the University of Pittsburgh was founded on the principle that more needed to be done to speed up the process of transforming achievements made in the laboratory into therapies used in the clinic.

The National Institutes of Health seems to think that CTSI is doing a fine job, if one can draw inferences from a recent five-year, $67.3 million grant. Pitt's CTSI is one of 10 such institutes nationwide to have its funding renewed in 2011. Since its founding in 2006 with an $83.5 million grant, CTSI (a collaboration between Pitt, UPMC, Carnegie Mellon University, and the Urban League of Greater Pittsburgh) has had success in creating computer software to improve the diagnosis of melanoma, made advances in the study of sleep disorders, and funded research into the efficacy of low-cost prescription drug programs—to name just a few of the thousands of studies CTSI has supported.

—Joe Miksch

FLASHBACK

On Jan. 14, 1931, the Associated Press reported, "It all started when somebody telephoned that 'two wild men' were running loose on the campus." A wagonload of Oakland police officers was dispatched, capturing Myrlen Morgan and Thomas Wilkins, certain that the two were insane. Not long after, police released the men, quite certain of their sanity! "The whole thing was explained by a member of the faculty later. [For an experiment on respiration,] students Myrlen and Thomas were asked to run about the campus to demonstrate physical exertion."

ILLUSTRATION ROB KELLY (BASED ON PHOTO COURTESY T. KENSLER)



Kensler receives the Friendship Award from Vice Premier Zhang Dejiang

Kensler Lauded Abroad

Thomas Kensler, a PhD professor of pharmacology and chemical biology in the University of Pittsburgh School of Medicine, recently earned the National Friendship Award from the People's Republic of China. According to China's State Administration of Foreign Experts Affairs, the honor is the country's highest given to "foreign experts for outstanding contributions to the country's economic and social progress."

Kensler's research centers on trying to understand how aflatoxins, carcinogens produced by fungi that commonly grow in many dietary staples, contribute to the high incidence of liver cancer in the country's population. He is also testing ways to detoxify our bodies of the carcinogen. Liver cancer is among the three deadliest cancers worldwide. In some regions of China, one in 10 people dies from the disease.

On Sept. 30, on the eve of the National Day of China, Kensler joined other public health advocates, economists, and manufacturers as they were honored in the Great Hall of the People in Beijing.

"I have made the investment of my time and my energy," says Kensler, "and the payback is great friendships. I'm always happy to go to my second home." *—Jessica Titler*



TIM GROEN

A&Q with Aaron Baum on Finance and Health

With a bachelor's degree in mathematics from the University of Chicago, Aaron Baum (Class of '15) worked as an equities trader before entering the University of Pittsburgh School of Medicine's Clinical Scientist Training Program (CSTP). After his first year, Baum took a leave of absence to spend nine months in Haiti. There, he attempted to improve health care access for rural Haitian women and their families by working with Fonkoze, a microfinance bank. Now, he is taking another leave from med school to work toward a PhD in sustainable development at Columbia University.

How a bank improves access to health care

What we were doing was capitalizing on existing infrastructure. The way Fonkoze works is through a network. ... Most of the action, as far as the loans, takes place in the village centers where Fonkoze employees distribute loans and get repayments. The village centers are where women congregate twice monthly in an organized fashion, so you can use that opportunity to provide other services. We trained one client in each center to be able to identify malnourished children using a color-coded upper-arm circumference strip, and then we partnered with Partners in Health to provide care for those children. That was the first project I started doing.

We're piloting a minipharmacy as a social business model where one client per village is trained to distribute essential health commodities (such as oral rehydration solutions, deworming pills, and vitamins) for a small profit. Fonkoze also provides micro-insurance for catastrophe and will soon provide it for cholera. So you can level off your risk as a Fonkoze client.

What a degree in sustainable development offers

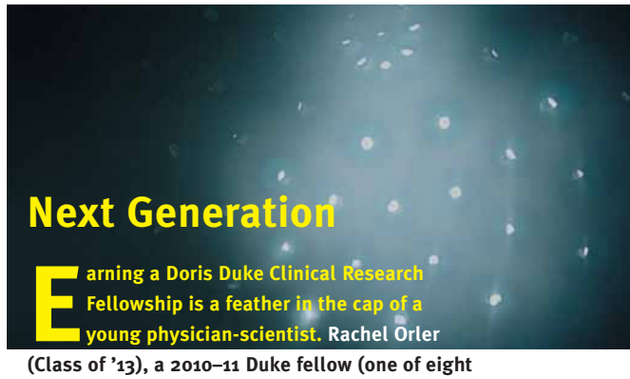
[It's] essentially an economics PhD plus one in natural science. It's great if you are interested in health systems, which by default is a cross-sectoral issue.

What he'll be doing 10 years from now

I don't know. Whatever I end up doing, I hope it will be related to community health systems and will bridge implementation and research. I hope that I have clinical training, but I also hope there is research involved. I also want to be building something concrete.

His question for us

What are your ideas for starting financially viable community health programs via microfinance or other existing rural infrastructures? ***—Interview by Nick Keppler***



Next Generation

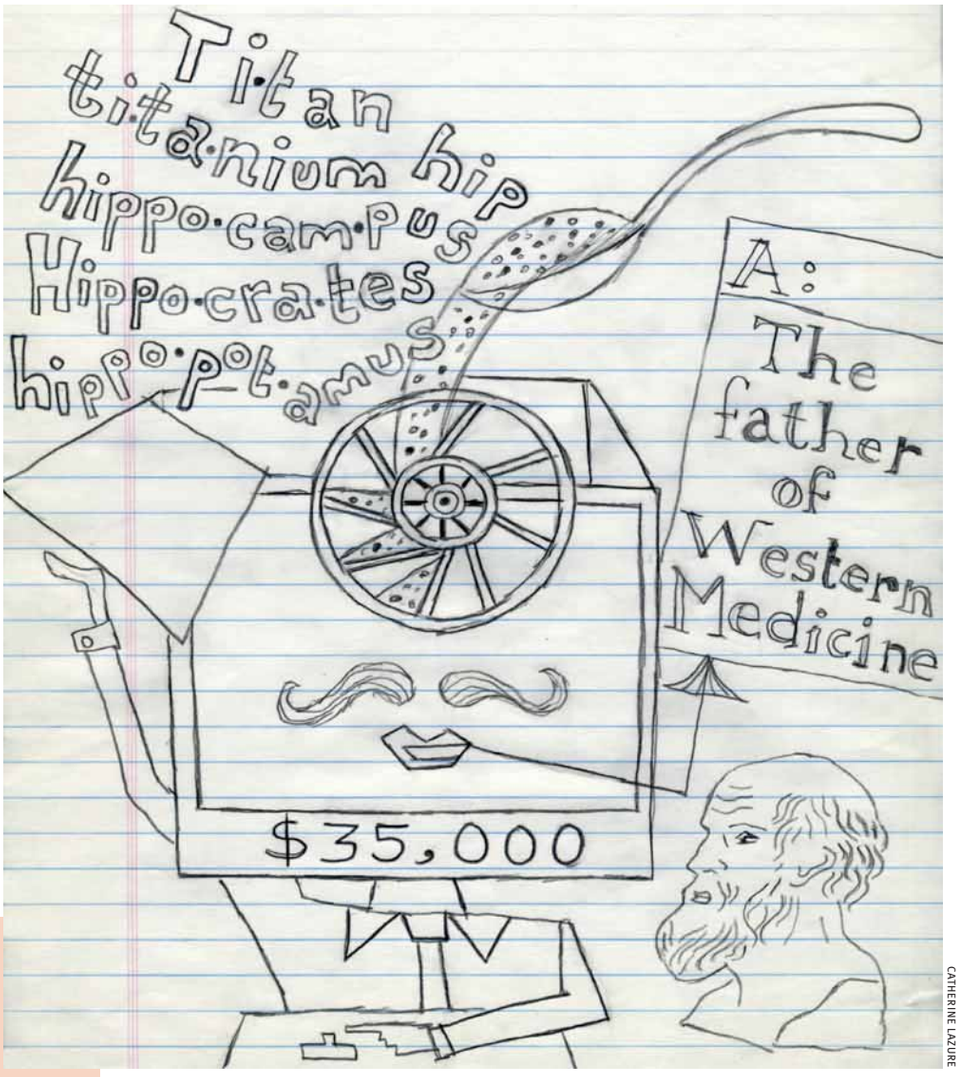
Earning a Doris Duke Clinical Research Fellowship is a feather in the cap of a young physician-scientist. Rachel Orler (Class of '13), a 2010–11 Duke fellow (one of eight from the school that academic year), made the most of her time away from the classroom. Last fall, Reid was the first author on an *Archives of Internal Medicine* paper titled "Associations Between Physician Characteristics and Quality of Care." (The research, done with Ateev Mehrotra, assistant professor of medicine at Pitt as well as a policy researcher at RAND Corp., began as her scholarly research project.) As a Doris Duke fellow, Reid also researched the possible impacts of retail clinic visits on primary care medicine. Oh, and during her Doris Duke year, she earned an MS in clinical research at Pitt. She's spending this academic year at the Center for Medicare and Medicaid Innovation in Baltimore, Md., working on ways to improve health care while lowering costs. Next? "I'm thinking I'll do an internal medicine residency and then probably a general medicine fellowship. And after that, I'll aim to be a physician-researcher doing health policy work."

Pitt med boasts nine new Doris Duke fellows for the 2011–12 academic year. Gillian Harrison is studying the safety and efficacy of modified stromal cells in patients with stable ischemic stroke. Ryan Li is looking to define predictors of osteoarthritis after ACL reconstruction. Rachael Maciasz is researching palliative care communication techniques for cancer patients. Brian Nolan is evaluating tools used to assess response to anti-inflammatory therapy in patients with rheumatoid arthritis. Michael Schowalter is undertaking the proteomic analysis of pure- and mixed-type desmoplastic melanoma, a rare metastatic skin cancer. Ben Sprague is investigating noninvasive cardiovascular imaging. Ryan Stephenson seeks to understand the role of Toll-like receptors—proteins that play a key role in the innate immune system—in head and neck cancer. Lisa Tseng is evaluating the relationship between weight change and physical function at the advent of menopause. And Jacky Yeung is endeavoring to sort out the role of molecular defects related to the rare, and often fatal, brain cancer glioblastoma. ***—JM***

Dr. Watson, We Presume

After about five years of labor, the brainiacs at IBM made a very smart machine called Watson. It understands English (using software to extract meaning from language) and kicks tail at *Jeopardy!* In early October, Dan Cerutti, IBM vice president for Watson commercialization, and Steven Shapiro, former chair of medicine at Pitt and current chief medical and scientific officer for UPMC, met at Science2011 to talk about how Watson could be of service to medicine.

Cerutti and Shapiro say that Watson will be fed just about every scrap of information available to the medical profession and use its speed and unique ability to derive likely answers to complex questions. Watson is expected to be of use in diagnostics and as a way for patients and doctors to work together before they even meet. UPMC's Technology Development Center is in negotiations with IBM to help turn Watson the *Jeopardy!* champ into Watson, MD. Stay tuned. —*JM*



CATHERINE LAZURE

Reilly New Chair of Medicine

John Reilly Jr., an MD, is now the Jack D. Myers Professor and Chair of the Department of Medicine at the University of Pittsburgh, replacing Steven Shapiro, who recently became UPMC's chief medical and scientific officer. He was recruited to Pitt by Shapiro in 2008 to become the department's vice chair of clinical affairs; the two physicians had worked together in Boston.



Reilly

Reilly is known for his studies on the genetic and environmental factors associated with chronic obstructive pulmonary disease (COPD) and the role of alveolar macrophage enzymes in emphysema, COPD, and lung cancer.

"I think medicine is going to change a great deal over the next decade," says Reilly. "What we need to focus on is working with the health care system to put tools in the hands of clinicians so they can measure the kind of care they're providing and can improve systems for delivering care."

On the research front, Reilly says, "We have a lot of scientific talent here, and we need to take full advantage of the patient population that we have through UPMC. Being able to access that clinical data to feed scientific research makes us the envy of most academic department chairs across the country." —*JM*

CLASS OF 2015 CHEAT SHEET

We thought you'd like to meet a few of the med school's new students:

Michael Burrow learned cued language, a type of phonemic signed language, so that he could communicate with his two sisters who are deaf. He later became a cued-language teacher and a certified cued-language transliterator. The 24-year-old entered the University of Utah after taking two years off for a mission trip to Thailand.

Lauren Zammerilla graduated from the University of Pittsburgh in three years but made the most of her time while she was here. The cheerleader and Phi Beta Kappa member was most proud of her sorority's fundraising efforts ($10 million nationally) for St. Jude Children's Research Hospital.

Alexis Chidi entered Pitt's premed guaranteed admissions program at just 16 years old. Since graduating in 2009, she has earned a Master of Public Health degree from Johns Hopkins University, where she was one of a handful of students selected for the Global Health Field Research Award. The award allowed her to travel to Zambia to test the efficacy of using oral fluid samples to monitor immunity to malaria.

Before coming to Pitt, Air Force Academy graduate John Jochum served in the Air Force for 12 years as an F15-C Eagle pilot. The reason for the career change is the same one that first led him to the military: "It's very rewarding to wake up every day knowing that my hard work will be focused on serving others," he says. —*Alexis Wnuk*



"BLADE OF GRASS," COURTESY NIKON SMALL WORLD

(VERY TINY) LEAVES OF GRASS

This photo earned Donna Beer Stolz second prize in Nikon International's Small World Competition. Taken through a confocal microscope, this half-millimeter of grass (magnified 200 times) naturally fluoresces, showing off its blue trichomes and the green and red cells of the blade. How the image came to be is a somewhat convoluted story: Stolz, a PhD, is associate director of the Center for Biologic Imaging and associate professor of cell biology and physiology at the University of Pittsburgh. She met North Side artist Diane Samuels at a bar mitzvah. Samuels was working on a project mapping Sampsonia Way, an effort that included sampling and preserving the alley's flora. After talking with the artist, Stolz decided to put a bit of the grass under the 'scope. And, "Wow!" (Another Stolz image won 19th place, and the entry of her Pitt colleague, Jonathan Franks, was named an "image of distinction.") ***—JM***

Connamacher in Hall of Heroes

Robert Connamacher, whose teaching efforts extend from an inner-city elementary charter school to Pitt's School of Medicine, has been inducted into the Student National Medical Association's Hall of Heroes. The organization, formed to assist medical students of color, bestowed the honor on Connamacher at its annual conference in Indianapolis last April. The SNMA established the Hall just two years ago and has inducted only a few individuals thus far.

"I'm sort of a pipeline by myself," says Connamacher, a clinical associate professor of family medicine at Pitt who earned his PhD in pharmacology from George Washington University in 1966, of his efforts across age brackets. The prof teaches a science program in the Urban League of Greater Pittsburgh Charter School in East Liberty. There, among other things, he orders students in grades one through five to run around the other in configurations that model the parts of atoms. He also is the advisor for Pitt's Medical Explorers, a weekly program sponsored by the med school that gathers for advanced study high school students with an interest in medicine. (Connamacher says they look at autopsies: "There is always a gasp when we pull on a ligament and a finger moves.") In addition, he teaches summer classes for premed undergrads at Pitt, as well as courses at the School of Medicine. He has shepherded thousands of young people in his 45 years of running such programs in Pittsburgh.

Connamacher says he's honored to be inducted into the Hall of Heroes but adds that the "greatest reward for me is the number of students who may not necessarily go on to medicine but find some direction through these classes." ***—NK***



WHILE WAITING

Barb Cozic (shown left) was having some liver trouble. In the morning of Nov. 1, she found out that "trouble" had developed into cancer. Later that day, she and her niece Bree Cooper had a seat in the waiting room of the Frank Sarris Outpatient Clinic at the Thomas E. Starzl Transplantation Institute, where Cozic was to be assessed for a new liver.

A few minutes later, Robert "Bo" Garritano (right) and his wife, Joyce, strode into the room. They had been there before. Many times. On Oct. 9, 2007, Garritano, at age 63—having been diagnosed with liver cancer months before—underwent a liver transplant of his own. For the past couple of years, the Garritanos have volunteered at the Starzl Institute, helping others know what to expect before and after transplantation.

Bo Garritano introduced himself to the dozen or so in the waiting room and then asked Cozic and Cooper where they were from. "Chester, West Virginia," they said. "West-by-God Virginia!" he boomed in response. The voluble Garritano told his story and listened to theirs. "I don't even feel sick," Cozic said to Garritano, "I said to myself, *What am I doing here?"* He replied, "What you have is a compensating liver. When you feel this good, you don't know if you want a transplant. I felt so strong that I was riding my bicycle in the city the day I got mine."

Garritano then wished Cozic and Cooper luck, counseled patience and resilience, and moved across the room to another waiting patient.

"So," Garritano said, "where are you from?" ***—Joe Miksch***

—Photograph by Martha Rial

Explorations and revelations taking place in the medical school



UPCI Summer Academy scholars take a break under the Roberto Clemente Bridge during a bicycling trip. FROM LEFT: Natalie Nash, Matt Miklasevich, Sam Rest (getting horizontal—"planking" in Internet fad-speak), Ishan Chatterjee (crouching behind), Andrew Shin, and program mentor William Buchser.

SMART FUN
IN THE SUMMERTIME

HIGH SCHOOLERS SHINE IN CANCER ACADEMY

BY MARC MELADA AND ELAINE VITONE

On a mid-July morning in 2011, Dilafruz Khakimova wakes up at 5 for her hour-and-a-half commute on the 67 bus from Monroeville to Shadyside. It's a typical workday in a laboratory at the Hillman Cancer Center—you know, interrogating DNA-replication fork progression and the stability of DNA-repair complexes in human cells.

Not too shabby for a 17-year-old, right?

Khakimova is one of 25 high school students participating in the third-annual University of Pittsburgh Cancer Institute (UPCI) Summer Academy. The program was started in 2009 to promote careers in cancer care and research to rising juniors and seniors from both the local area and beyond (students also come from Maryland, Michigan, Indiana, Texas, New Jersey, and California). The students, referred to as scholars, pair up with a mentor researcher at the UPMC Hillman Cancer Center, Pitt's Department of Biomedical Informatics, Pitt's Department of Computational and Systems Biology, or the Magee Womens Research Institute. Each scholar completes a research project during the eight-week program.

Khakimova arrives at her project site, the lab of Chris Bakkenist, Pitt assistant professor of radiation oncology, and opens an incubator filled with petri dishes containing lung cancer cells. With the articulation and enthusiasm of a grad student, she explains their hypothesis: The DNA-repair pathways known as ATM and ATR have a functional relationship and work in tandem. If the hypothesis is right, the popular cancer drug gemcitabine, which targets ATR to stall cancer-cell replication, could be made even more effective, she says.

There's a lot to do: tending to four different cell lines; collecting the cells with a centrifuge and dividing them when they get too crowded; treating the cells with various pathway inhibitors and examining cellular proteins to make sure those inhibitors are working; and, finally, determining whether the inhibitors kill the cancer cells.

"The thing I've learned about lab work is that it's different every day," Khakimova says. Today, she's conducting a western blot, probing for protein expression in lung cancer cells by running them through the shaker (the pink-and-white contraption known around the lab as "the belly dancer").

Lazy days of summer? "Seems like they never existed," says Khakimova. But she wouldn't have it any other way. This is science. This is what she loves. Besides, it takes some doing to outsmart oncogenesis. "My PI always says, 'Remember, Dela, we want to kill the cancer cells without damaging the other cells.'"

In addition to her experimental research, throughout the Summer Academy program, Khakimova's days are filled with traditional classes as well as field trips (to the National Cancer Institute in Bethesda, Md., for example) and events like crab night at program director/instructor Michael Lotze's home in Shadyside. One of Khakimova's favorite experiences was donning scrubs and observing bypass surgery. "It was different than I imagined. They played happy music and were laughing in the operating room."

The scholars are issued security passes. They're given the same intellectual freedom and expected to show the same level of maturity as any med student or MD. Their mentors provide ideas to start with, but, "[The scholars] make the projects work," says Lotze. He adds that these responsibilities inspire the scholars to work hard, be imaginative, and take on meaningful tasks.

Lotze's own Summer Academy mentee (from 2010 and 2011), Ishan Chatterjee, hopes to study at MIT and Pitt med. At the Intel International Science and Engineering Fair in Los Angeles last spring, he presented part of the project he started with Lotze, and he placed second in cellular and molecular biology. Natalie Nash, a fellow Summer Academy scholar, also attended the event.

Before the summer, Khakimova had been thinking about going to med school to become a gastroenterologist. She knows now that she wants to work directly with patients. "My mom says I make connections with people," she says. But lately Khakimova has been thinking it would be fun to be a researcher, too. "They're the ones coming up with all these treatments," she says.

In its first three years, the academy class has already grown from five students to almost 30. Many of the scholars are from economically disadvantaged backgrounds. The program is one of the med school's several mentoring programs for high school and undergraduate students. (It begins accepting applications in January.)

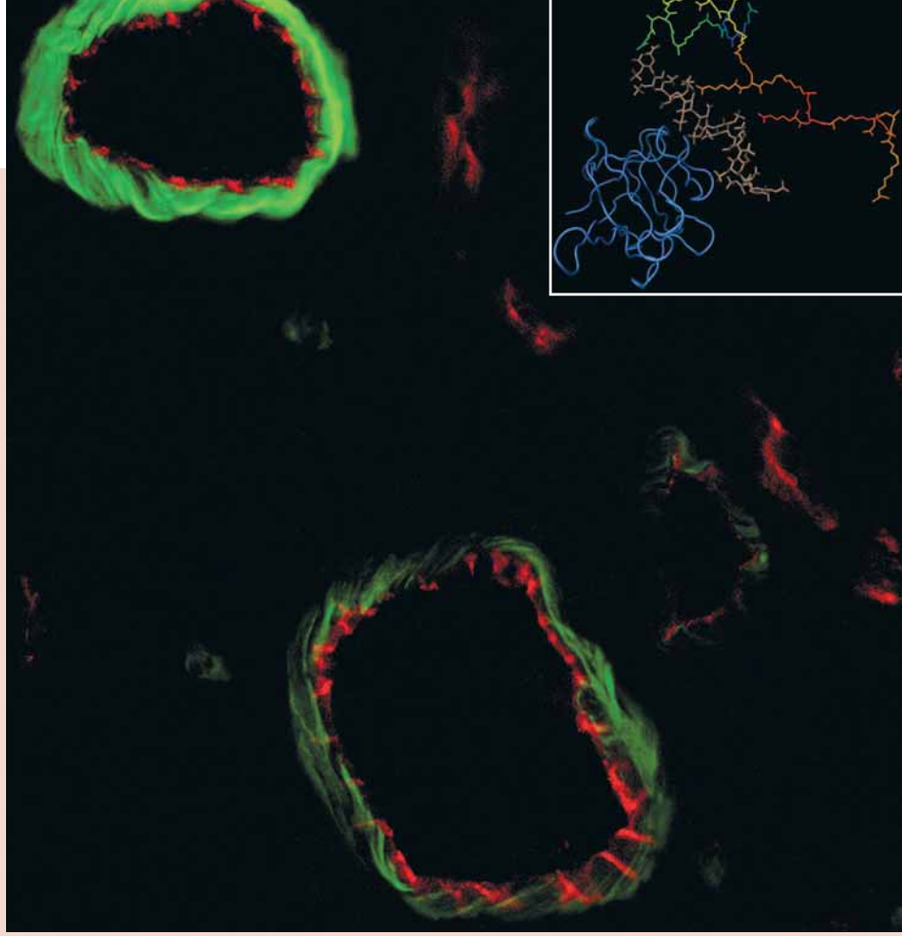
For most 17-year-olds, achieving a leftward shift on an optical-density graph is not the highlight of the summer. But as Khakimova makes her way around the lab, it's clear that there is no other place she would rather be. ■

COURTESY UPCI SUMMER ACADEMY

STRONGER HEARTS

MOLECULE GOES THE DISTANCE TO REGROW BLOOD VESSELS

BY DANA YATES



COURTESY HUNGHAO CHU

Attempts to fortify damaged blood vessels with growth factor have turned out vasculature that quickly breaks down—until a Pitt team concocted a unique compound (inset), which stimulated blood vessel growth in mice. BACKGROUND: The vessels held strong after a month.

A heart attack is a trauma that the body never forgets. In fact, even after an arterial blockage has been cleared, patients are still at risk of heart failure down the road. But Yadong Wang has developed a method that may one day help people heal from heart attacks once and for all.

Wang is a PhD associate professor of surgery in the University of Pittsburgh School of Medicine and of bioengineering in Pitt's Swanson School of Engineering. He is also on the faculty of Pitt and UPMC's McGowan Institute for Regenerative Medicine.

"The body is able to heal itself in many ways. Just look at broken bones," Wang says. "But when it comes to the heart, the body's natural reaction isn't enough."

Specifically, Wang is interested in heart disease, the leading cause of death worldwide. Caused by a buildup of plaque in the arteries, coronary artery disease can slow down or stop blood flow to the heart. Once a heart attack occurs, there's no looking back. Dead muscle is replaced by stiff scar tissue, and the body's healing process actually causes adverse changes in the heart's shape, size, and function.

This process, called pathological remodelling, involves thinning of the damaged ventricular wall, weakening and over-dilation of the ventricles, and enlargement of the heart. Taken together, these changes can lead to congestive heart failure.

That said, Wang is focused on reducing scarring and disrupting the downward spiral of remodelling by spurring the development of new blood vessels. And his weapon of choice in the fight against heart disease? A substance called growth factor.

The body makes use of several growth factors, each targeting various areas and handling different functions, including cell differentiation and cell migration. In light of this potency, growth factor is strictly controlled by the body, which releases the substance only when absolutely necessary.

"It's an efficient system," says Wang. It's also a difficult one to manipulate. Previous research has shown that injections of growth factor are unproductive; the body destroys the substance too quickly for it to take proper effect.

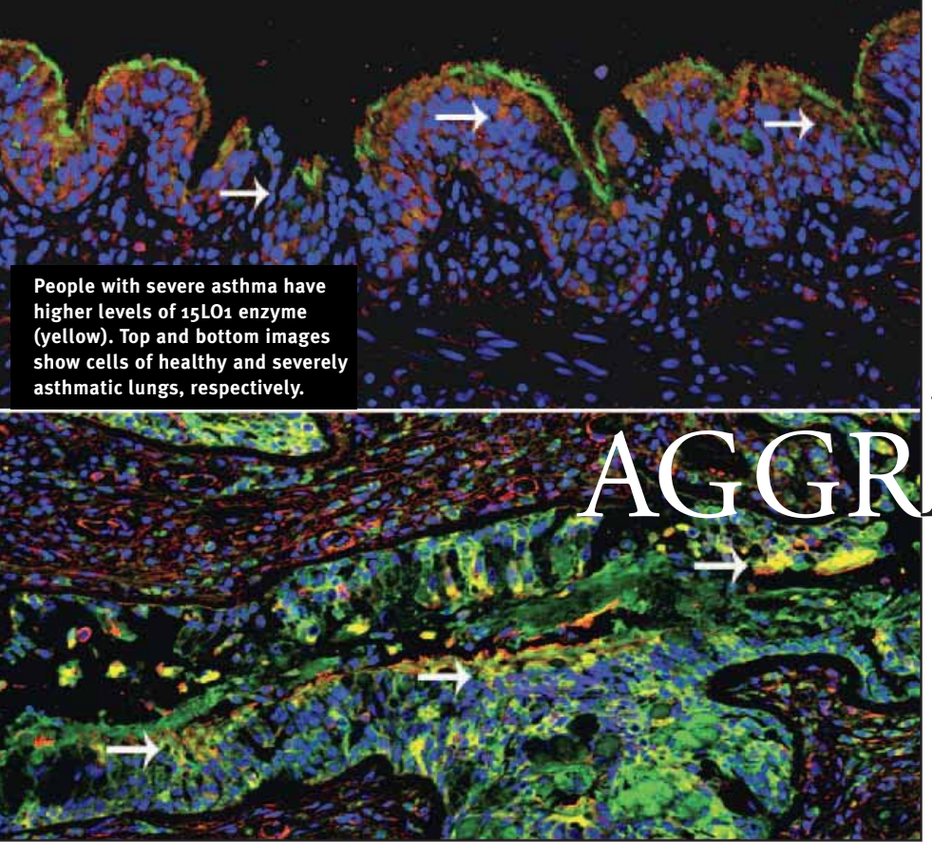
Wang wanted to buy growth factor more time to do its job. So, with his research team, he explored how to control the release of growth factor, bundling and delivering it in a way that enabled the body to harness and use the substance efficiently. The solution: Bond a molecule called heparin to the growth factor. As one of the molecules that binds growth factor to its receptor on a cell's surface, heparin may stabilize growth factor and increase its activity.

After converting the resulting water-soluble compound into a coacervate—a collection of oil droplets—the researchers injected fibroblast growth factor-2 under the skin of laboratory mice. In so doing, the Pitt team of bioengineers and stem cell researchers—which includes Hunghao Chu, Jin Gao, William Chen, and Johnny Huard—became the first to use a coacervate for the controlled delivery of growth factor.

Their findings, which were published in the Aug. 1 issue of *Proceedings of the National Academy of Sciences*, were encouraging. The compound led to the extensive formation of new blood vessels—ones that were robust and resembled arterioles, the small but critical pathways that connect arteries to capillaries. In addition, the new blood vessels were long-lasting. After just one injection of the growth factor compound, the new structures were still intact at least a month later.

The coacervate is not viscous, so it can be injected into the heart using a needle as thin as a strand of hair. The procedure, which could be performed immediately after a heart attack or even a few days later, would be much less invasive than open-heart surgery.

The experimental treatment still must pass muster in clinical trials and be commercialized before it finds its way to patients. In the meantime, Wang is excited about the potential: "We are using nature to help people regenerate and recover," he says. ■



People with severe asthma have higher levels of 15LO1 enzyme (yellow). Top and bottom images show cells of healthy and severely asthmatic lungs, respectively.

COURTESY JINMING ZHAO

ASTHMA AGGRAVATORS

FINDINGS THAT MAY HELP THE MOST SERIOUS CASES

BY MELINDA WENNER MOYER

When people with asthma suffer an attack, the muscles around their airways tighten and their lungs fill with thick, sticky mucus. More than anything else, it is this mucus that makes it impossible for them to catch their breath. "The generation of mucus is considered to be one of the most important pathological changes in asthma," says Pitt professor of medicine Sally Wenzel, director of the University of Pittsburgh Asthma Institute at UPMC. This is what led her to piece together the details of a key signaling pathway that activates mucus production—a pathway that she hopes to dial down so that one day people with severe forms of asthma, an inflammatory lung condition that causes 1.6 million emergency room visits annually in the United States, can breathe more easily.

Some asthmatics can effectively manage their symptoms using existing treatments like corticosteroid inhalers. But a small subset cannot, and research suggests that these patients have a unique biological signature characterized by immune cells that overproduce inflammatory proteins. One inflammatory protein in particular, interleukin-13 (IL-13), has interested Wenzel in part because it is known to play a role in mucus production. In 2010, she and colleagues at a handful of institutions assessed the efficacy of an injected inhibitor of this protein on 243 asthma patients, but they were disappointed to discover that it did not significantly help.

Part of the problem with blocking this inflammatory protein is that "the levels that you can find in humans are infinitesimally small," Wenzel says—it's difficult to inhibit something that is only present in the body in tiny amounts. Might it be possible, Wenzel wondered, to control mucus production differently, perhaps by targeting mucus-stimulating molecules downstream of this inflammatory protein? Wenzel knew of earlier studies suggesting that the protein activated an enzyme called 15-lipoxygenase 1 (15LO1) and its breakdown product, both of which are present at higher levels in the lung cells of those with severe asthma than in those of healthy people. She also knew that the inflammatory protein turned on an enzyme called extracellular signal-regulated kinase (ERK), which is ramped up more in asthma lung cells, as well. Wenzel wondered whether 15LO1 or its product might somehow help to turn on the kinase and thereby control mucus production in asthma.

To find out, she exposed lung cells taken from 65 asthma patients to the inflammatory protein. Levels of active kinase spiked within minutes. But when she exposed the cells to the inflammatory protein for a week—and then removed the immune chemical and added it briefly again—kinase levels were far higher. This finding suggested to her that perhaps the inflammatory protein stimulates the kinase both directly and indirectly, recruiting other proteins that, over time, take over the activating job. Suspecting that 15LO1 or its product might be one of these recruited proteins, Wenzel performed the same experiment while inhibiting the production of 15LO1 to see what would happen. This time, the kinase was activated in much smaller amounts, which suggested that 15LO1 or its product plays an important role in stimulating it.

Wenzel believes that the inflammatory protein turns on 15LO1 and then that 15LO1 or its product initiates a feedback loop that causes sustained kinase activation (and ultimately mucus production). She published her findings in August in *Proceedings of the National Academy of Sciences.* Ultimately, it may be that "some of these downstream pathways are going to be more important than IL-13 itself" when it comes to making mucus, she says.

So how exactly does 15LO1 or its product activate the kinase? The kinase gets turned on when its activator molecule breaks away from its natural inhibitor. In additional experiments, Wenzel showed that both 15LO1 and its product bind to this inhibitor and pull it away from its activator, allowing the kinase to get turned on.

Ultimately, Wenzel hopes to find ways to inhibit the activity of 15LO1 or its product (or both) in order to slow mucus production and ease asthma symptoms in people who don't have other viable treatment options.

"That is definitely, absolutely our goal," she says. ■

CASE STUDIES:

HOW TO DO MEANINGFUL AND INSPIRED WORK

GENIUS!

Elodie Ghedin, assistant professor of computational systems biology and member of the Center for Vaccine Research at the University of Pittsburgh, runs a pretty small shop. The way she sees it, the most interesting projects are not confined to the four walls of her laboratory. "I used to work on more 'focused' projects—'my own' projects, more 'singular' research," she says, the quotation marks clearly audible in her voice. But since she discovered the power of genomics, the most exciting way forward has been through ambitious collaborations.

Something about her approach seems to be working. In September, Ghedin, 44, was awarded a MacArthur Foundation fellowship–the so-called genius prize bestowed on individuals who show exceptional creativity and self-direction in their field. She initially mistook the cryptic e-mail message from the foundation as spam—she'd been getting a lot in recent weeks—and quipped to a friend that unless there was money involved she wasn't calling this Robert Gallucci guy back. Good thing she Googled him and found out he was the foundation's president.

There was, of course, money involved—$500,000, to be exact, no strings attached. But what made her feel most honored was how recipients are chosen. "It's an anonymous nomination, and then they require multiple letters of support," she says. The recognition from people in her field "was incredibly flattering."

This September, Elodie Ghedin received a MacArthur fellowship, the so-called genius award. What better occasion to delve into the nature of inspiration?

DRAWINGS | LEONARDO DA VINCI

ILLUSTRATIONS OF SCIENTISTS | ROB KELLY

GEOMETRICAL DRAWINGS ABOUT TRANSFORMATION FROM CURVED TO RECTILINEAR SURFACES AND VICE VERSA. FROM *CODEX ATLANTICUS*, LEONARDO DA VINCI (1452–1519). © VENERANDA BIBLIOTECA.



Ghedin

Her colleagues say the award is richly deserved. "Technically, she's outstanding," says Eddie Holmes, a molecular evolutionist at Pennsylvania State University who has worked with Ghedin on sequencing influenza genomes for the past seven years. And yet, he says, "there are many people who work in the technical stuff, but Elodie also has an amazing ability to understand the biology and the evolution and the bigger-picture stuff, as well."

In the early 1990s, for her master's degree in environmental studies at the University of Quebec in Montreal, Ghedin traveled through villages in rural West Africa measuring the bacterial and chemical content of drinking water. "There were tons of parasitic diseases," she recalls. "I saw cases of elephantiasis, leishmaniasis, schistosomiasis." She came back resolved to study the biology behind the ravaging force of these pathogens.

For her PhD research, she developed a potential diagnostic for leishmaniasis—a project that she jump-started in the lab herself, says McGill parasitologist Greg Matlashewski, Ghedin's PhD supervisor. "She would develop these DNA constructs to express things in *Leishmania* and control their expression," he says, and often he doubted it would work. Almost invariably, though, it did.

As a postdoc at the National Institute of Allergy and Infectious Diseases in Bethesda, Md., Ghedin began to delve more deeply into genomics. But her first real taste of leading a genomics-based collaboration came in 2005, when as a research scientist at The Institute for Genomic Research in Rockville, Md. (now part of the J. Craig Venter Institute, or JCVI), she led the effort to analyze the genome of *Brugia malayi*, a parasitic worm that causes elephantiasis. She assembled the world's experts on the worm to do so—about 50 scientists, each spending a week during a two-week period lodged in front of a computer tussling with their favorite genes. "Every day, morning to night, we were just sitting there," says Sara Lustigman, a molecular parasitologist at the New York Blood Center who got to know Ghedin through the experience and remains a frequent collaborator. Surprisingly, says Lustigman, it was really fun. "It was really an example of how she extracts the best from people," she says.

Ghedin's six-member lab at Pitt applies innovative genomic techniques to an array of very small troublemakers, including *B. malayi*, viruses like influenza, and microbes. Ghedin, who maintains a joint appointment at JCVI, credits this mix of systems as a major source of inspiration. In lab meetings, everyone in the group weighs in on the projects under way, and often the best ideas come from people who are working on a different organism. "I think that's creativity, when you see connections that are not obvious," she says. "And for that, it helps to cast a very wide net in your research."

Ghedin plans to use her MacArthur award money to advance her work with *B. malayi*. Finding ways to kill the worm has proven very difficult. It is itself infected with a parasite—an intracellular bacterium that is necessary for its survival—and these symbiotic partners trick the host immune system into overlooking them both. Ghedin aims to identify proteins secreted by the worm and start to dissect their immunomodulatory talents. Because parasitic diseases like elephantiasis don't affect many people outside the developing world, she says, "that's where I always have the most trouble getting funding."

On the flu-virus front, Ghedin and collaborators have most recently been tracking how the composition of strains in a viral population mutates and how the virus is transmitted between hosts. In a virus like HIV, that change is dramatic throughout the many years it inhabits a human host. Influenza, though, generally infects individuals for a week, tops, so much less variability would be expected, but no one knows for sure.

"It's such a basic thing to understand about the dynamics of that virus," she says. "We are designing vaccines with no idea of what's going on." —*Alla Katsnelson*



In 2005, Ghedin led the effort to analyze the genome of *Brugia malayi*, a parasitic worm that causes elephantiasis, the first of her many genomics-based collaborations.

CREATIVE FEARLESSNESS

AND OTHER SIGNS OF LIFE

A CONVERSATION WITH

JEREMY BERG AND GEORGE WHITESIDES

During the University of Pittsburgh's Science2011, we pulled aside George Whitesides and Jeremy Berg, plied them with a couple of beers (courtesy of Pitt's N. John Cooper, dean of the Kenneth P. Dietrich School of Arts and Sciences), and asked for their perspectives on what makes genius happen. Whitesides, who gave the Provost Lecture at the science festival, is the Woodford L. and Ann A. Flowers University Professor at Harvard University. The chemist by training is known for his astonishing breadth of inquiry and ability to contribute to many fields, including nanotechnology, microfabrication, and microfluidics. (He has authored more than 1,100 publications.) Berg, Pitt's associate senior vice chancellor for science strategy and planning and visiting professor of computational and systems biology, is highly regarded for his work in molecular recognition processes and for his scientific leadership. Until earlier this year, he directed the National Institute of General Medical Sciences. (To read more about Berg, see our profile on p. 22.)



Berg

JEREMY BERG: So one thing that we'd like to talk about is creativity, and what leads to creativity. And one thing that I have always admired about your work is the breadth of fields where you've made creative contributions. Clearly it's not the sort of genius where a person has a flash of insight, [but rather where someone] does the same thing over and over again in a clearly intentional, systematic way. So I'd be interested in your strategies and what you think has led to your successes.

GEORGE WHITESIDES: I think there are two thoughtful, well-considered strategies in this, and I would say the first is simply laziness. So, one definition of creativity is doing something that other people don't do. The nice thing about working in areas where other people haven't worked is you don't have to read the literature, … and you can do it according to your own pace. …

I'm a big believer in the notion [of starting from] something that you think is interesting and emotionally engaging and something, ideally, that other people aren't doing. So if you have a problem that has that characteristic—if you look around, and you see evidence everywhere, you can pick problems in health, you can pick problems in the environment, you can pick problems in just phenomenology of nature, and start with something—Where does lightning come from? How do we actually increase the lifespan? What do you do to make pure water? Those are all interesting, good problems that people care about. And the idea of starting from something that's already in the literature strikes me as just an intrinsically bad idea. If it's already in the literature, why are we wasting taxpayers' money doing it?

PITT MED: How do you develop an idea without relying on the past as a foundation?

WHITESIDES: The thing about science that's so wonderful is you don't have to be particularly smart to do good science. If you pick a good problem, nature does it for you. … There are other fields of science where that's not true. You can't be a [standout] mathematician without being a really, really good mathematician. You could be a very good chemist or biologist without being breathtakingly smart.



Whitesides

BERG: Just to push back on what you said: Obviously what you talked about today—protein/ligand interactions and drug design—is something a lot of people have thought a lot about. But what's certainly one of the messages I got from your lecture is "Don't believe everything you think." That, you know, questioning the sort of underlying assumptions that have been made and digging into the fundamentals can lead you in interesting directions.

WHITESIDES: Yes, but there's also another thing about that problem, and that is we know that people have been trying to design ligands to fit proteins for as long as you and I have been in the business. And, you know, it doesn't work. Basically, retrospectively, people will claim success, but it basically doesn't work. And when smart people well equipped with the best tools available try at something for years or decades and it doesn't work, you begin to get the idea that there's something underlying that's wrong. So in that particular area, it's a little bit of a special circumstance because the relation of water and biology is actually a big, important problem, and I don't think that anybody would argue that. And there's been something wrong with our ability to understand how molecules interact in biology—which means in water. And we've tended, because we didn't know how to do

it, to neglect the solvent part of it. ... So, we were, in the [Thomas] Kuhn sense, that is "the nature of scientific revolutions," we were forced to look at water. But not smart in looking at water.

And Kuhn has a notion, which is that revolutions in science occur only in special circumstances, and those circumstances come from the fact that scientists are just as lazy as anybody else. And most scientists … basically make sausage. They repeat work, or extend work, or do whatever they're doing, which is fine. But every once in a while, the theory that's available and the importance of the problem [are] such that you find the theory simply does not explain what's there. You can't get it to work. It won't work. Then somebody has to sit down and try to figure it out. If you can figure it out, if it is figure-outable, and there is a new direction, then that becomes a revolution.

A classic example is quantum mechanics—where, in 1900, physics was regarded as dead because Newton's laws explain mechanics, and the laws of Maxwell, Maxwell's equations, basically explained electricity and magnetism. The only problem was there was a little phenomenon called the ultraviolet catastrophe, where distribution of power radiated by something didn't fit with what was predicted. [So when you did] the simple experiment in which you took a prism and a slit, and you took the solar light and spread it out on a wall and instead of being perfectly continuous, there were these funny black lines. There was nothing in the theory at that point that explained the black lines. And try as you might, you couldn't get a consistent theory to explain the black lines. So what happened in 1925 was this flurry that led to quantum mechanics. Quantum mechanics [didn't say] that Newtonian mechanics and Maxwell's equations were wrong—in fact, they're right—but that there's an underlying story which shows that [there are] other things going on underneath that we hadn't known. And I think there's the same kind of thing in biology. I think we don't have all the tricks, all the basics, of understanding biology.

PITT MED: Is there a way to prepare a mind to notice these things?

WHITESIDES: One of my views is that the way you prepare people to do that is you encourage them when they're in the stage where they can be encouraged not to be timid.

That is, find something that you think is important where the answer isn't actually known. Then the encouragement you can give as a research director is, "Go try it. If it's possible—you're as smart as anybody—then it'll work. …" It won't work every time. But for good people, it basically always works.

BERG: One issue, which I think is really important in thinking about education, is many problems that are interesting and important are at the interface between traditionally separate fields. So the temptation is to work at an interface, but that only works if you actually know a lot of the fundamentals about one side of the fence or the other. In my case, I had just the luck of being completely convinced I wanted to be a chemist then [discovered] biology later on. So I learned a lot of fundamental chemistry, including from people around here, then moved into biology. … So that gets you a leg up on a problem where you can apply a new tool. So the ideal training environment: You don't let people know where they're going to go, train them in one field, and then say, "Now you can look behind the curtain and find out what the new direction is." The danger with [being too] interdisciplinary is teaching people a lot about the border between two fields … is great for the next three or four or five years where that's an interesting frontier, but when that problem gets solved, then they don't know enough to go find a new one.

WHITESIDES: There are things that as a scientist you actually have to know. You have to know thermodynamics. You have to know something about descriptive metabolism and related things. You have to know how catalysis actually works. You have to know the fundamentals of statistical mechanics and quantum mechanics. You have to know something about electromagnetism. These are all hard subjects that require bending your mind. But the laws of electromagnetism in biology are exactly the same as the laws of electromagnetism in physics or in circuit theory or anything else. You get it early, you're then prepared to talk to anybody, for one thing. And [you're able] to do research without doing truly stupid things. My entire career as a consultant has been spent doing one thing, to ask the question—basically, *Does the proposed project violate the second law of thermodynamics?* And, frequently, it does. When it does, you can say with perfect confidence, *You should not do this because it will not work.*

"I think we don't have all the tricks, all the basics, of understanding biology."

BERG: In physics and chemistry, what you need to know is well defined. One thing I learned moving into biology and medicine is that … the same level of information is not quite as fundamental in terms of being able to write it down as facts or equations. … I would come up with these wonderful theories and would talk to a real developmental biologist who would say, "That can't possibly be right because, you know, it wouldn't predict this and this and this—and those are all known to be absolutely true." So there's a base of knowledge in lots of fields you need to master in order to avoid doing things that are just silly.

WHITESIDES: There is another side of this, though. The word that I've come to be very unhappy with is the word "apprentice." We hear this often in science—that a graduate student is an apprentice in the research group, and that he's learning the techniques of the master. It's exactly the wrong way to do it, because the issue is that the master is the master of whatever—the master is master in that time and place—and five years later, it's going to be something else.

I think the master class environment in which [a young person does] something with [a senior person] who really knows how to do it well, and [the senior person] helps you to do it rather than teaches you how to do it, is the right way of doing things. And the great thing about the U.S. system, at least in the past, has been that as a young, independent investigator, as an assistant professor,

you could go do what you wanted to do. I have to say that I'm a little worried right now that there's so much emphasis on getting money that people begin to try to game the system as opposed to doing what they really want to do. That's pretty troublesome to me.

BERG: I would second that. I was also blessed with supervisors and mentors who would give me the freedom to go off and do things and make mistakes. It's a lot like parenting. … You know the mistakes to be made, but you want somebody to feel comfortable exploring … and if they're heading … onto the freeway, you go over and sort of nudge them back away from it.

WHITESIDES: Either that, or if you note they're having problems staying off the freeway, maybe the freeway is the right place.

BERG: I think the fear, and I share [your] concerns, is that if you build cautiousness and timidity into the system, you're going to seriously limit what comes out the other way. … When I was in the NIH, we were involved with developing a couple of programs. And one of the things that was most satisfying about the programs—they were intended for young investigators and highly innovative projects—was I got several e-mails and phone calls from people who didn't get [one] award, saying, *It was so much fun to write about what I really want to do as opposed to what I thought I could get funded to do. And it really helped.*

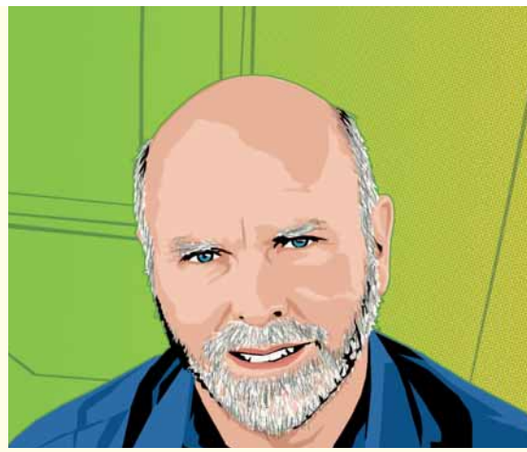
WHITESIDES: What I tell my students is that what I want them to do is to come to me and astonish me. To come with an idea I just never would have thought of myself. And they do it regularly.

—Interview with Joe Miksch

WATCH FOR THE PITTMEDCAST ON ZINIO'S ONLINE NATIONAL NEWSTAND.

ON INSPIRATION

WITH J. CRAIG VENTER



Venter

J. Craig Venter *received the Dickson Prize in Medicine this year at the University of Pittsburgh's Science2011. Venter is founder of the J. Craig Venter Institute (JCVI) and is arguably one of the nation's most productive scientists. His teams at JCVI and elsewhere have developed genomic tools that are transforming medical science by taking on ambitious projects like decoding the human genome, the first human diploid genome (Venter's), and 165 genomes from microbes in the world's oceans. One of his teams has also created organisms from synthetic genomes—he foresees a future in which scientists can "write the computer code of life." Venter set aside some time for* Pitt Med *to share his perspective on the nature of inspiration and how to support inspired people. Edited excerpts follow.*

PITT MED: What do you look for in people you recruit whom you hope will do meaningful and inspired work—will make significant contributions? I suppose we're talking about the scientific level, but if you want to talk about other realms, you can do that, too.

J. CRAIG VENTER: I think the rules are pretty applicable [for all], as far as I can see. Obviously, we start with people who are generally bright people. That shows up in all kinds of ways. Genius is such a relative term. Malcolm Gladwell has looked at all different kinds of intelligence. ...

I've not known too many, if any, really brilliant people who were lazy. So somehow the energy of doing things plays a big role. I know I do much of my learning by physically doing things and by trial and error.

I think [with] people that exhibit genius—other than the kind of genius that shows up with mathematical prodigies or physics prodigies who make their major breakthroughs out of sheer brain horsepower, usually in their early 20s, or 30s at the latest—inspiration comes from a variety of sources. Mainly from people who, you can tell, look at the world a little bit differently than others. I never con-

"I've not known too many, if any, really brilliant people who were lazy."

sidered being an outsider when you come into a new field to be a disadvantage.

If you've read any Sherlock Holmes, you know that he didn't keep a lot of trivia in his head, because he didn't want to clutter up his brain with things. To some extent, that's what happens when going through the school system. We learn how to memorize things, and we clutter things up with lots of memorization versus understanding systems and asking fundamental questions about them.

[He then talks about the fresh perspectives of young scientists like Pitt's Elodie Ghedin (who holds a joint appointment with the Venter Institute) and the Venter Institute's Dan Gibson (who figured out how to assemble and synthesize DNA), and how they used their gifts to contribute to the new field of genomics, a field that "didn't exist long enough for anyone to have any preconceived notions."]

In Elodie's case, she applied [her gifts] to making a big difference in what we're doing in viral analysis. I think just a different perspective has a huge impact.

PITT MED: What about the working environment? Do you put a lot of thought into how to set up things so you don't dampen creativity or inspiration?

VENTER: I put a lot of thought into that.

In part, first off, trying to make it an environment that I find healthy for me. I had this great teacher in high school, Bruce Cameron, who was—when I got back from Vietnam and enrolled in community college—talking about the creative process. Even in writing it's contrary to what people think—[that writers are] inspired by misery, living in difficult conditions… His argument was that people are at their creative best when their pleasure tanks are full. It's hard to think about solving the world's problems if you are hungry or sick or tired or constantly worried about other things.

So I try to keep my pleasure tanks full. [Laughter.]

PITT MED: Do you see missed opportunities where organizations may have had well-intentioned ideas and instead dampen and quash creativity? You don't need to name names.

VENTER: Sure. It's our entire education system. Our university system. And how we construct most businesses. …

The stovepipe academic model … doesn't work very well. I think a lot of my success has been from getting rid of those constraints.

I find most people really like working on teams and on projects that are much bigger than anybody but where their unique expertise is actually required and makes a difference.

… I think the environment is a very, very key part of creativity. I think people probably have even more creative ideas than even they realize, [but the environment might not be] conducive for their expression.

PITT MED: What sorts of ways does the academic environment quash creativity?

VENTER: Well, rote memorization versus comprehensive understanding. Why? Because you can quantitate it. The same way universities, for faculty promotions, want to count publications and citations. …

I've often joked that people prefer those systems because they can count and they don't have to read. So if you have to actually read somebody's study and understand it and decide whether it has value, that's totally different from just saying, "Well, 300 other people have cited it, [so] it must have value." Even if 300 other people are citing it and saying, "This is a great example of crap."

[Also], this is a nonscientific notion for someone who is a geneticist and who sequenced the human genome—but bright people have bright eyes. It looks like there's a light on in there. [Laughter.]

… I think being in the Vietnam War from a very young age had a huge impact on the rest of my life. Because you learn in war, certainly the biggest thing you have to lose is your life. And once you get past that … It certainly changed my risk outlook on things. I've not been afraid to fail or walk away from things. I've rebuilt my career a few times. [Laughter.] I think that it's really amazing in science the number of people who are actually afraid to do the experiment. Whether it's fear of failure or fear of success, a lot of people in science can't bring things to closure. They will drag on a six-month study for 10 or 20 years.

PITT MED: Think about what it must have been like for someone like Thomas Starzl, a surgeon who cared about his patients, to take the risk. Of course, these [patients consenting to experimental procedures] are usually people who have no other alternatives. But it must be scary to be the one who could immediately end a life because of trying something new.

VENTER: But how much worse is it to not try?

It looks like optimism and pessimism are probably genetic traits. I think I've been quoted on this before: It's usually the optimists that accomplish things. You have to have that life-affirming energy.

—Interview with Erica Lloyd

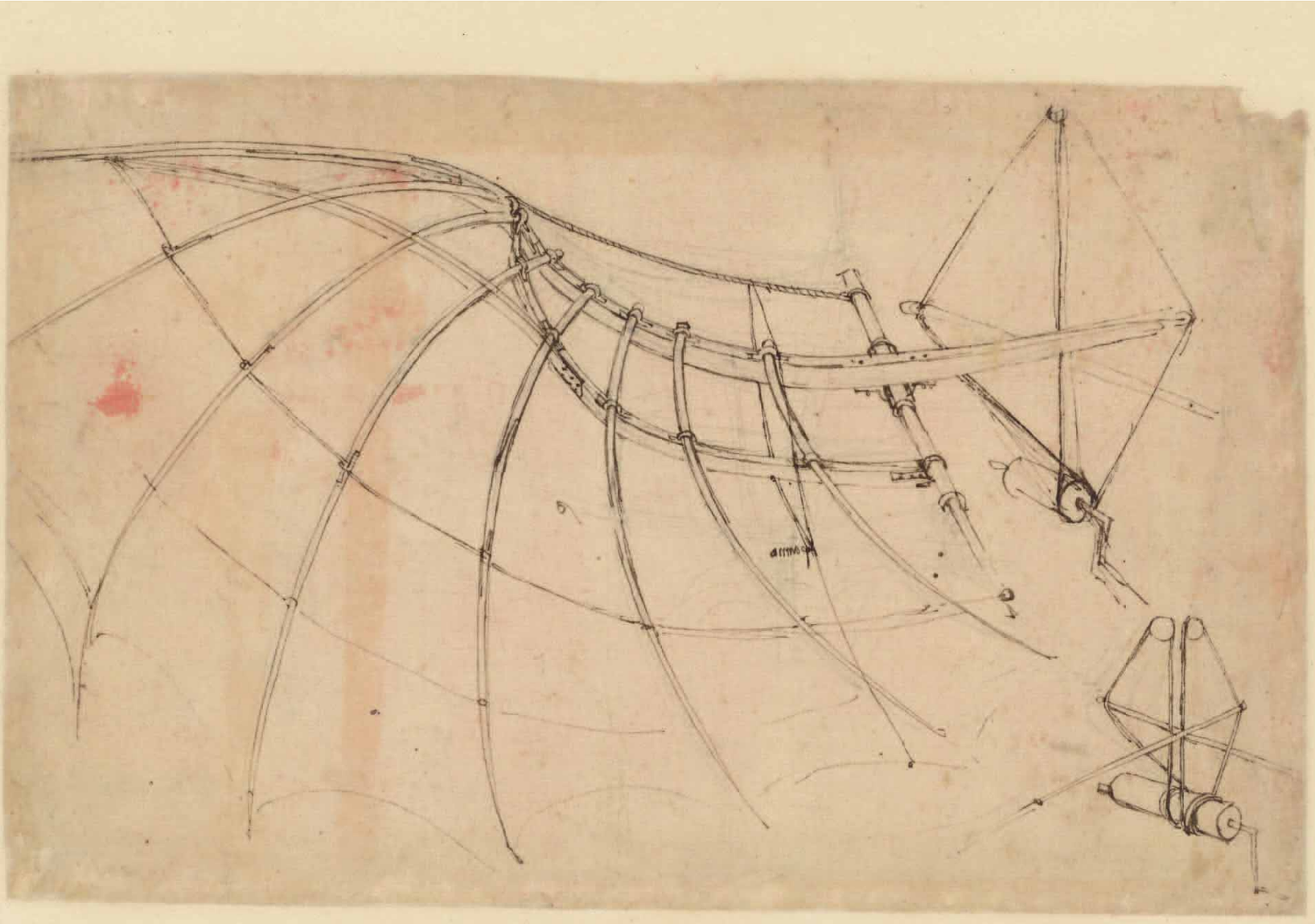
THE FIX FOR FIXATION

To boost creativity, beware the psychological phenomenon of fixation, warns innovation expert Christian Schunn, a PhD and Pitt professor of psychology, learning sciences, and intelligent systems who studies problem solving and creativity as a senior scientist in the University's Learning Research and Development Center. "The first idea that comes to mind can block your ability to come up with other ideas," he explains. "One answer can get stuck in your mind, even when you know it's a bad solution."

He offers these tips to avoid fixation:

■ **Put a twist on the classic brainstorming scenario where a group gathers in front of a whiteboard as a facilitator scrawls the ideas each person calls out. "That way is pretty much guaranteed to produce fewer ideas," says Schunn. "Once people see someone else's ideas, they get stuck on them." Instead, have everyone jot down suggestions first by themselves, then compile and review them together.**

■ **Likewise, when doing a literature review, instead of having everyone**



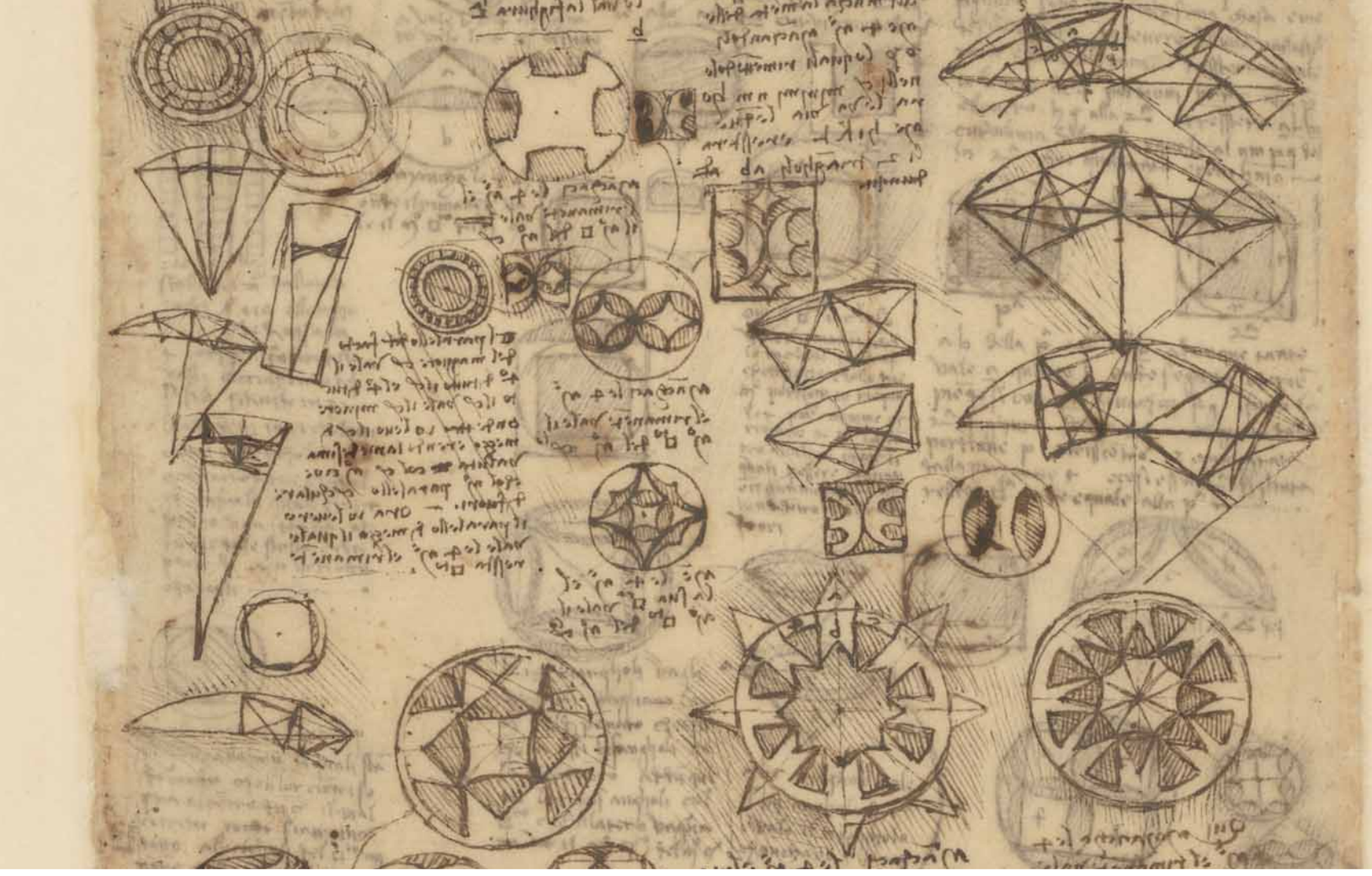
WING COVERED WITH A CLOTH AND MOVED BY MEANS OF A CRANK WINCH; BELOW RIGHT, DETAIL OF THE WINCH. *CODEX ATLANTICUS*, LEONARDO DA VINCI. © VENERANDA BIBLIOTECA.

on the team read everything, divide into subgroups that develop expertise in a particular realm of the problem. When the groups come back together, they'll enrich one another's thinking. "When you have people drawing from a broader pool of analogies, there's more you can draw on," he says. "Spreading the literature review around is a way of not getting the core thinking stuck on one similar path."

■ Try new metaphors. For example, if the problem is viral infection, consider re-framing the problem as "how things get in," opening your mind to such concepts as keys in locks, basketballs thrown through hoops, and even groundwater seeping into a well. "If you think about the problem in very specific ways," Schunn explains, "the problems that are already associated with it come to mind. By categorizing your work as a more general problem, it frees up associations to more general solutions."

■ Don't go in too deep too soon. For example, Schunn points out, computer modeling can demonstrate briskly whether a research approach is headed in the wrong direction, saving time and money. Yet simulations demand a level of detail that can pull a scientist deep into the weeds early in the process. "You can get stuck thinking about the details and prevented from thinking in more general ways," Schunn cautions. "Go back and forth between a very detailed model and just sketching it out on paper or some way that's purposefully sloppy so you can think in more general ways. People can get very attached to the specific thing they built on the computer and lose the forest, as it were."

—Sharon Tregaskis



GREATER THAN THE SUM

PITT PEOPLE: BETTER TOGETHER

Murat Can Cobanoglu, who trained as a computer scientist in Istanbul, applied to graduate school with the intention of one day upending the drug discovery process.

Now, as a PhD student in the joint University of Pittsburgh School of Medicine/Carnegie Mellon University computational biology program, he seems to be off to a good start. Cobanoglu is certainly energized by the weekly lab meeting in Room 3065 of Pitt's Biomedical Science Tower 3, where he muses over microscopic goings-on with a crew of disparate members that includes engineers, chemists, and physicists.

"When a chemist looks at a drug compound, he has insights someone else might not have," says Cobanoglu, who has been developing *in silico* models to predict drug-protein interactions. "[I] look at the computational methods. And the physicist looks at the interactions between the molecules in a molecular dynamics simulation and again has a valuable insight.

"When you combine each of these different people with their different backgrounds, it makes for an excellent and very fun environment and super-creative lab meetings."

The spirit of what's happening in Room 3065 can be found across campus. When speaking with new Pitt med recruits, as well as longtime faculty members, what often comes up is how extraordinarily welcoming the environment is to collaboration. Some have suggested it's a Pittsburgh thing—the task-oriented bent of people who choose to live and work in a rust belt/near-Midwest city.

"[In some academic towns], they don't even talk to each other in their own departments. They take it as a point of pride," says Christian Schunn, a PhD professor of psychology, learning systems, and intelligent systems, who studies problem-solving and creativity as a senior scientist in Pitt's Learning Research and Development Center. He says Pittsburgh thrives on a "help-your-neighbor, talk-to-people-on-the-street sensibility."

Schunn may be on to something, but there's also strategic thinking behind the culture that has arisen.

A collaborative ethos seems to have seeped into the soul of this medical school at least since the late Thomas Detre, who oversaw Pitt's health sciences from 1984 to 1998, began breaking down territorial strongholds by building institutes and centers. Observers say that the academic environment has become optimized in the last decade in a number of ways, from the "open lab"

design of new facilities to deciding who will lead programs. "There's a great deal of thought invested here to build the best teams and build an environment where there are no barriers," says Joan Lakoski, associate vice chancellor for science education outreach, health sciences, and professor of pharmacology and chemical biology.

"We never worry here at Pitt about where someone is housed. We just say so-and-so is the best, and we pick up the phone and talk to them."

She says that Arthur S. Levine, senior vice chancellor for the health sciences and dean of the medical school, delights in his work as a talent scout. "He gets the best minds and brings them together."

When Simon Watkins joined Pitt's faculty in 1991, advanced imaging was considered technically demanding but not much more. The young scientist, now a professor of cell biology and physiology as well as of immunology, intended to establish the intellectual rigor of his field.

"I had this vision of building a center that would be at the edge of what you can do with optics and microscopes and computers," says Watkins, who founded the Center for Biologic Imaging shortly after he arrived and has overseen its growth into a 20-person research staff that works with scientists from across campus and around the world. "I was always given the resources to build that dream."

Early in his own tenure, Watkins was integrated into multiple investigations that continue to this day by senior faculty who already had established projects and funding streams. "We tend, generally, to cut the pie into thinner slices and get more people involved," he says.

Watkins is a scientific partner in an astonishing number of studies—he himself is "very active" in 60 or 70 at the moment, and his group is contributing to perhaps 250. His is a special case because other labs rely on Watkins for cellular imaging expertise, yet, Lakoski notes, the University has made the financial piece for him and others "virtually seamless, which offers tremendous flexibility."

"No one is bean counting," she says. If faculty get together to apply for a grant, the collaborators themselves agree on the division of labor and the money follows that plan.

"In fact, you are rewarded for taking risks," Lakoski says, pointing out pilot programs and bridge funding pools that reward collaborative activity. "A number of funds are designed to bring clinicians and basic scientists together."

Watkins says it's important to think about synergy when bringing in new people, too. "We look at how [prospective hires] fit or fill the needs of the larger medical campus," says Watkins, comparing the mindset to that of a landscaper choosing new plants to enhance an existing garden.

"Because we know where people will fit, we know whom they're going to collaborate with when they come here. There's nothing worse than bringing in [junior scientists] and then isolating them in their own lab."

As medicine and science get more complex, investigators and physicians need to be able to turn to sophisticated colleagues with differing expertise. And with federal funding getting sparser, they will have even more incentive to partner. That said, even with support from on high at Pitt, there's plenty to finesse on the ground.

Cobanoglu's mentor, PhD scientist Ivet Bahar, traveled from Turkey to Pittsburgh to establish a Center for Computational Biology and Bioinformatics in 2001. Her first few years here weren't exactly a walk in the park.

"When I joined this university, I was frustrated about not being able to speak the same scientific language with many people here," says Bahar. So she proposed, with the encouragement of Levine, that the school form what is now the Department of Computational and Systems Biology (systems biology being the field that uses modeling to investigate how the whole—whether a molecular system or an organism—is bigger than the sum of its parts). The department would bring together faculty with expertise in biology, chemistry, engineering, immunology, math, and physics. A year after the founding of the department, she campaigned successfully for the formation of the school's joint PhD program in computational biology with Carnegie Mellon (Cobanoglu's program)—another step in the process of building a common vocabulary among scientists from different fields.

Bahar requires that each member of her group develop a fluency in the language of computational biology: Imagine the United Nations conducting business exclusively in Klingon instead of using translators to bridge the chasm.

"It makes for super-efficient communication and collaboration," says Cobanoglu.

"What brings us together is the great opportunities in this field right now … in the post-genomic era," says Bahar, the John K. Vries Professor and Chair of Computational and Systems Biology. "We are all excited about our ability to solve some longstanding problems."

"The literature shows that teams composed of diverse individuals with different technical backgrounds—backgrounds in terms of where they trained, different outlooks—outperform individuals every time," says Lakoski.

Yet, the hazards of miscommunication among those trained in different fields are substantial.

"If you have a way of dealing with the process of getting to common ground, the overall diversity is helpful," says Schunn. "But a lot of smart teams go down in flames because they can't resolve their differences."

To head off probems before they start, Schunn advocates face-to-face meetings early in a collaboration. "You need to be able to draw, point, and follow up on quizzical looks in ways that the telephone or Skype just aren't great for," he says.

Such contact also builds trust. "If you hang out with people and get to know them, you can come to a different ability to understand why they did something differently from the way you might have done it."

Lakoski, who gives the first lecture in an annual course on team science (yes, there's a course) for clinical and research faculty from all of the health sciences schools, says, "Team science takes longer because you have arguments, people don't understand each other's perspectives, and, until recently, people haven't had training. It's not like you swallow a pill, and suddenly you're a team scientist. It takes practice."

Pitt is educating its future clinicians along these lines, as well.

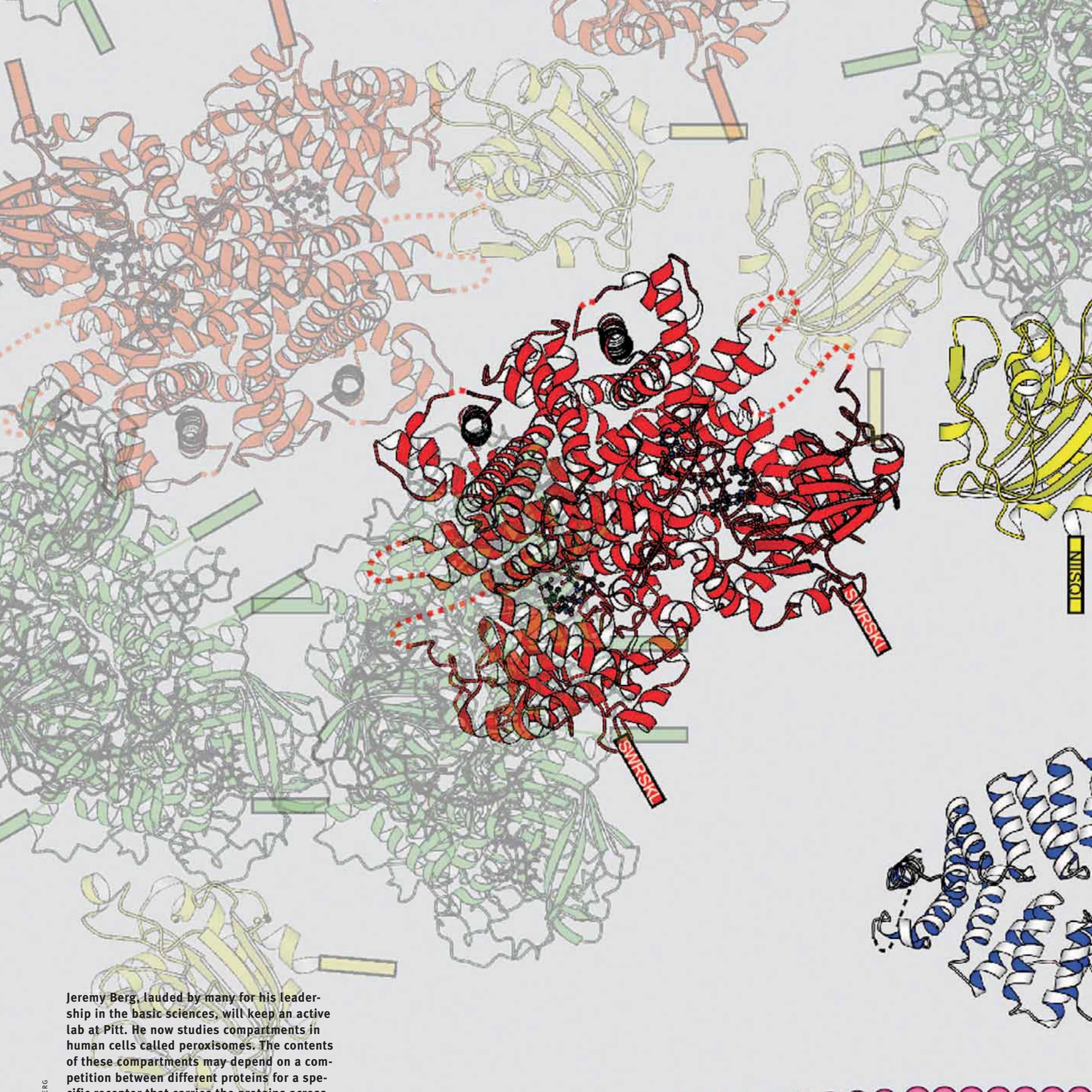
Like research, caring for patients is a joint effort more than ever today. So the University's health sciences schools have been building awareness of the importance of cross-disciplinary communication as part of the curricula. In 2010, a team of students from the schools of pharmacy, nursing, and medicine trained together to compete in an interprofessional competition at the University of Minnesota. It was Pitt's first time sending a team. In the contest, the Pitt students spent hours on a fictional post-mortem. Then, before a panel of judges, they presented their analysis of what led to the death and a proposal for how to avoid similar outcomes. Groups from nine institutions competed.

Guess whose team took home the top prize.

—Sharon Tregaskis and Erica Lloyd

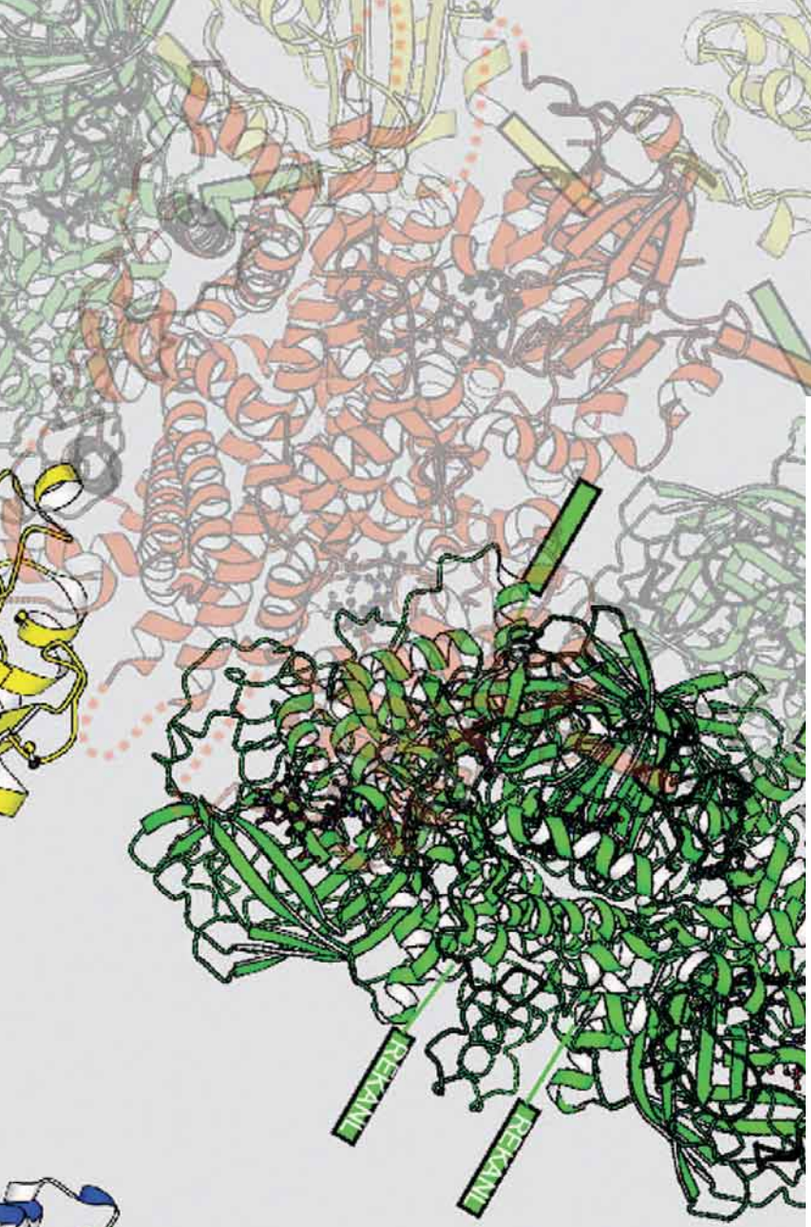


RULES FOR THE CREATION OF THE GEOMETRICAL GAME (LUDO GEOMETRICO) FROM *CODEX ATLANTICUS*, LEONARDO DA VINCI (1452–1519). © VENERANDA BIBLIOTECA.



Jeremy Berg, lauded by many for his leadership in the basic sciences, will keep an active lab at Pitt. He now studies compartments in human cells called peroxisomes. The contents of these compartments may depend on a competition between different proteins for a specific receptor that carries the proteins across a membrane (shown here as pink-and-green-layered ribbon) into the interior of the peroxisome.

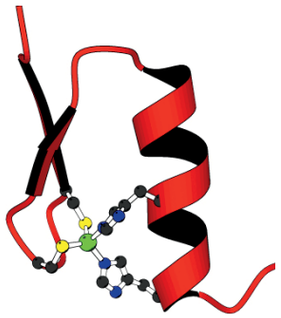
COURTESY J. BERG



JEREMY BERG, A RISING STAR AT NIH, COMES TO PITT | BY REID R. FRAZIER

THE NATURAL

When he was a young assistant professor at Johns Hopkins University, Jeremy Berg's grad students could hear him coming before he walked in the door. So eager was he to start the next activity, the scientist made a habit of running between meetings. John Desjarlais, a PhD student in Berg's lab, remembers hearing the elevator door open and the sound of the 6'2", wide-shouldered scientist bounding toward him. "You'd hear this freight train coming down the hall. He would literally sprint down the hallway," says Desjarlais, now vice president of research at Xencor, a California biotech company that engineers proteins. "We all knew not to open any doors when we heard this."



COURTESY J. BERG

Berg predicted the structure of zinc fingers, which are now customized by scientists to "knock out" DNA sequences.

Berg's haste could be forgiven. He was busy making eye-popping discoveries about the structures of transcription factors, proteins that activate DNA. Berg pioneered the study of zinc fingers, molecular tools used by transcription factors to identify binding sites on DNA. He was extremely curious. He was enthusiastic. He'd spend hours in his office bending a wire model of a protein structure to get the shape just right. He'd do experiments with proteins just to see what happened. (He once asked Desjarlais to add cobalt to an insoluble zinc-finger analog—just to confirm that it would turn blue. It did.)

What propelled him down the halls of Johns Hopkins sustained him during a run to the upper ranks at the National Institutes of Health (NIH). At the age of 45, he was named director of the National Institute of General Medical Sciences.

In his eight years as head of NIGMS, Berg became a leading thinker in how to fund scientific research, spread grant money to more labs, and encourage creativity in science. He championed high-risk research, young investigators, and diversity. "He was one of the best hires I ever made," says the man who brought him to the agency, former NIH director Elias Zerhouni.

This year, Berg made a quick turn in his run as he came to Pitt to become the University's first associate senior vice chancellor for science strategy and planning for the health sciences. Berg will continue his research as professor of computational and systems biology. In general terms, Berg's job will be to think deeply about biomedical science at Pitt. How to do it better, how to do it creatively, and how to get young scientists the training and resources they need.

"I see his role being very similar to the role that he had at NIH, which is to participate with me in the planning and strategizing inherent in science," says Arthur S. Levine, Pitt's senior vice chancellor for the schools of the health sciences and dean of the School of Medicine. "He'll help me make our institution as competitive as it can possibly be."

Levine first learned of Berg's interest in Pitt in late 2010, when he got a letter from him. *Was there any work for him in Pittsburgh?* Berg wanted to know.

"I would have to admit I was surprised," Levine says. "Dr. Berg is a terrific scientist and a terrific scientific leader. He is seen almost heroically by the national scientific community."

It is rare for an NIH director to knock at your door. But Berg's situation was unique. His wife, the influential radiologist Wendie Berg, was being recruited at a number of different universities around the country. Could any of them find a job for her trailing spouse? "A lot of other places were kind of not sure what to do with me," Berg says.

Levine's answer to Berg's query? "Of course."

Who wouldn't want Berg's help? A quick scan of his CV reveals a stellar career. But really the proof is in the respectful tone former colleagues, bosses, and students get when speaking of Berg.

Zerhouni first met Berg when the two men worked at Johns Hopkins, where Zerhouni was vice dean for research. The two men worked together when Berg headed Johns Hopkins' Institute for Basic Biomedical Sciences, which coordinated scientists from across disciplines.

"In that position, he really was a leader—you could tell," says Zerhouni.

"He was open to understanding the dynamics of research outside his own field."

At NIH, Berg drew attention for his frank and open discussions about the agency's challenges. He started its first blog. Earlier this year, he made waves as the lone dissenter on a vote that, among other implications, would likely close NIH's National Center for Research Resources, a home for basic and translational science for decades. Berg thought NIH hadn't thought the decision through enough and said so. The vote was 12-to-1 in favor.

Berg nonetheless gained respect from scientists for speaking his mind. "He has great integrity to stand up for his convictions," says Stanford's Suzanne Pfeffer, president of the American Society for Biochemistry and Molecular Biology.

GOING UP, IN A HURRY

Berg began this life of curiosity as a Stanford faculty brat. His father, Paul Berg, was a mathematician, and his mom, Judy Nadell, a hematologist. For his 12th birthday, Berg's father gave him *The Architecture of Molecules*, an illustrated book coauthored by Nobel laureate Linus Pauling and artist Roger Hayward. The book portrayed molecules in pastel ball-and-stick drawings. It was chemistry made visible, and the young Jeremy Berg understood just enough of it to get hooked.

As an undergraduate at Stanford, he migrated toward chemistry. Among his teachers there were structural chemist Keith Hodgson, biochemist Lubert Stryer, and inorganic chemist Richard Holm. He learned X-ray crystallography from Hodgson. Holm was interested in modeling the active sites of metal-containing enzymes, particularly those containing molybdenum. (This element allows enzymes to promote key reactions such as the conversion of nitrogen gas to ammonia and the conversion of xanthine to uric acid.)

"He was extremely skilled in determining 3-D structures of molecules using X-ray defraction," Holm says. "Mind you, this guy was a freshman or sophomore; and this is the kind of technique that graduate students, some of them, don't learn very well, ever.

"He was a brilliant student, one of the most outstanding undergraduates I've ever seen, anywhere," says Holm, now a professor of chemistry at Harvard. Working with Hodgson and Stryer, Berg, at 21, coauthored a paper in *Nature*.

Berg got a PhD in chemistry at Harvard, working with his old Stanford professor after Holm moved his lab to Cambridge, Mass. Holm asked Berg to create molecules that would simulate the reactivity in addition to the structural properties of the catalytic sites of some molybdenum-containing enzymes. Berg developed such a system, one of the first reactivity models in bioinorganic chemistry.

Pure chemistry wasn't Berg's primary interest—he wanted to work in biology, too. So he chose a postdoctoral fellowship in the department of biophysics at Johns Hopkins, where his soon-to-be wife, Wendie, was getting her MD/PhD. (They met in quantitative analysis class

Berg asked a colleague at Hopkins how many times someone had predicted a protein structure. "If yours is correct," his friend told him, "that would be one."

at Stanford. His parents also met in college, in quantitative analysis class.) At Hopkins he worked in the lab of Carl Pabo, a young scientist studying the structures of DNA-binding proteins.

Berg landed a faculty position in Hopkins' chemistry department. As he was preparing to start his own laboratory, a group of scientists led by Nobel laureate Aaron Klug of the MRC Laboratory of Molecular Biology in Cambridge, England, discovered "zinc fingers," small domains organized around bound zinc ions within a protein that binds to specific sequences of DNA. They proposed that the zinc fingers determined the DNA sequences to which the protein binds.

This discovery got Berg wondering: What did those zinc fingers look like? If scientists could understand how zinc fingers were made, they could conceivably make their own. "I had time to stare at the sequence and think about what it might mean," says Berg. "It was sort of like Tinkertoys. Once you had the building blocks, then it was a question of how can you put these together in a way that made sense to the overall structure."

Berg proposed a structure in which the zinc ion organized each zinc finger into a unit well-suited to bind DNA. This model would allow the fingers to slide inside the double-helical tube of DNA at precise positions. This would explain the structures' ability to bind with such specificity and affinity.

Berg asked a colleague at Hopkins how many times someone had predicted a protein structure. "If yours is correct," his friend told him, "that would be one."

He published his prediction in 1988. Berg waited. A year later, a group of scientists at Scripps used nuclear magnetic resonance spectroscopy to determine the structure of the zinc finger. There it was; just as he'd predicted. (Pabo's lab, where Berg had done his postdoc, later became the first to develop the crystal structure of a bound zinc-finger protein.)

In tandem with other technologies, zinc fingers are now used in the creation of "knockout" rats and mice—scientists now design fingers that recognize a sequence on the genome they want to exchange.

Berg's zinc-finger prediction got the young scientist noticed at Hopkins. Among those impressed was Thomas Pollard, chair of cell biology. He saw Berg give a presentation. "He'd done something brilliant, and the way he conveyed it really gave you confidence that he was on top of things," Pollard says.



MARTHA RIAL

Berg at his new home, the University of Pittsburgh. To learn about his thoughts on building an inspiring research climate, see his conversation with George Whitesides (p. 15.)

Pollard was on the search committee for a chair in the biophysics department, where Berg had been a postdoc. Berg was 32, almost preposterously young for the position, but Pollard put his name up for the post anyway. (Pollard was 34 when he became chair of his department.)

"I think I literally said, 'Why would I want to ruin my career at such an early stage by getting into administration so early?'" Berg says now, with a chuckle. Berg thought it might slow down his research career. But every morning, heads of other departments would stop by his office, nudging him to take the job. He did. He was among the youngest department chairs in the history of the university.

ASKING HARD QUESTIONS

Jeremy Berg met Elias Zerhouni through Wendie, Zerhouni's colleague in radiology. He worked closely with Zerhouni on various intramural committees, and Zerhouni was impressed by the "ecumenical" way Berg treated other disciplines. When Zerhouni was named director of NIH in 2002, he had to fill several leadership positions. A search committee forwarded him several names for the NIGMS job. One of them was Berg's.

NIGMS holds a special place in the hearts and minds of basic scientists around the world. "It's probably one of the most critical institutes, because it funds science at the edge," says Zerhouni, who is now president of global research and development for Sanofi. "It's where the frontier of knowledge is created." Unlike most NIH institutes, NIGMS has no disease focus. Along the continuum of bench to bedside, it is the most "bench" of all institutes.

For the position, Zerhouni wanted someone who was committed to what he called "transformational" research—high-risk, high-reward science. When he interviewed Berg, he got an earful about some of the agency's shortcomings in this regard. NIH didn't invest heavily enough in risky science or lesser-known

and younger scientists, Berg told him. "He felt the NIH peer review was somewhat conservative and that it should truly encourage breakthrough research," says Zerhouni. On this the two men agreed, and Zerhouni eventually convinced Berg to take the job in 2003.

It didn't take Berg long to make his mark on the agency. In 2004, NIH launched the Pioneer Award, a pet project of Zerhouni's. Zerhouni had wanted to fund innovative research, especially from scientists who may not score as highly along traditional NIH guidelines. When the first batch of awardees was unveiled, Berg was disappointed.

"I was really looking forward to Googling a bunch of people I'd never heard of and trying to figure out what they were doing and why they were chosen," Berg says.

The nine awardees were all excellent scientists, Berg says. But they were also well-established, and almost all were older, white men.

"I was mouthing off to the deputy director [Raynard Kington, now president of Grinnell College] that I thought this was a lost opportunity," Berg remembers. Kington told him to, essentially, go tell it on the mountain. Berg wrote a long e-mail to Zerhouni spelling out why he thought NIH could take bigger chances with the Pioneer program.

"A day or two later," Berg recalls, "I walked into a meeting, they pointed over to me and said, 'How would you like to run the Pioneer program?'"

Berg accepted the challenge and asked colleague Judith Greenberg to help administer the award. The following cycle, NIH did more to advertise its intention to award high-risk projects and a diverse pool of applicants. Among the next year's recipients was Nathan Wolfe, a young public health scientist at Hopkins who was interested in tracking down novel animal viruses in Asia and Africa before they "made the jump" to human populations. (Wolfe's work has since been featured in *The New Yorker* and *Time*; he founded and directs the Global Viral Forecasting Initiative.) Approximately half the recipients were women, and several were from underrepresented groups.

There was another problem with NIH, Berg had told Zerhouni. Many weren't sure why it supported some investigations but not others. "I said, 'What will you do about it?'" Zerhouni says. "He said, 'I'll be more transparent. I'll tell people, *Here's the funding we have; here's what we're funding and why.*'"

Berg then became the first blogger in the NIH administration. The Feedback Loop, begun in 2009, is a blog that Berg and others in his institute used to communicate their methods to scientists. Berg has blogged about how the institute rates and debates grant applications. He published his own studies on the correlation between peer-review scores and the likelihood a grant gets funded.

"None of the rest of us do that," says Story Landis, director of the National Institute for Neurological Disorders and Stroke. "How big should a lab be to get the maximum productivity, per person or per dollar? We all talk about that, but Jeremy actually did the analysis."

In the spirit of transparency, Berg has studied how well the peer-review process correlates to quality, as measured in publications, citations, and patents. And he's illustrated the results with Lorenz curves, Gini coefficients, and histograms.

"These are things that people at NIH hadn't been doing or sharing," says Greenberg, now director of NIGMS. "After he started doing it, more and more of these kinds of analyses are coming out from other parts of NIH."

Pollard, Berg's champion at Hopkins and now dean of the graduate school of arts and sciences at Yale University, wasn't surprised about Berg's innovations at NIGMS.

"He's absolutely curious about how things work, whether it's zinc fingers or whether it's teaching or whether it's how the NIGMS runs. And if you're curious about how they work, you can try to figure out how to make them work better."

WHAT CAN BERG DO FOR YOU?

The next chapter in Berg's career began this summer, when he moved into his office at Pitt's Scaife Hall. Berg will continue his own research, which in recent years has turned toward the targeting of proteins to peroxisomes. These are organelles that have several vital functions, including breaking down long-chain fatty acids and synthesizing certain lipids. Berg is attempting to decode the system that determines the appropriate composition of proteins within peroxisomes that leads to proper function.

Wendie Berg, meanwhile, will continue her work on techniques to improve breast cancer screening. She has led multicenter investigations into the efficacy of the techniques. (See "Lessons in Survival" in the Summer 2011 *Pitt Med*.)

In his science strategy and planning position, Levine envisions Berg working on some of the same topics that interested him most at NIH—looking for ways to improve diversity, encourage breakthrough research, and help refine bioscience graduate training.

Berg's experience at NIH will also be of use at a time of economic uncertainty in science funding. His arrival at NIH coincided with the end of its "doubling" period, in which the budget increased from $15 billion in 1998 to $28 billion in 2002. Since then, the budget—currently at $31 billion—has been held essentially flat.

How do you get the most bang for the research dollar? How much funding is too much? These are the kinds of questions Berg asked at NIH.

How do you get the most bang for the research dollar? How much funding is too much? These are the kinds of questions Berg asked at NIH, and they are very relevant in the current funding climate, says Pfeffer, president of the biochemistry and molecular biology society. (Berg was elected to succeed her as president in 2012.) "It's probably time to ask, 'Are we spending that money as wisely as we should be?'" Pfeffer says. "Berg has some really good ideas about that."

Berg is also putting thought into how to foster bold, high-risk science at the University.

"That's one of the things that's attractive about Pitt," he says. "There seems to be a fairly strong culture of that boldness.

"There's still so much we don't understand," he says.

"There's still a lot more to be discovered. There are just many, many examples over time of people who are working on one problem who then make an observation that didn't make any sense at all at the time, and then had the good judgment to decide it was potentially something really important."

If these types of observations and researchers aren't supported, he says, "you're going to end up not knowing about whole areas of science that are going to be more relevant in the long run." ■



ANDREW LAMBERT PHOTOGRAPHY/SCIENCE PHOTO LIBRARY

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TINNITUS IS ONE WAY OUR BRAINS LEARN AT THE CELLULAR LEVEL

BY ELAINE VITONE

The Ebers Papyrus, one of the oldest surviving medical texts, describes a mysterious condition the ancient Egyptians called "bewitched ears." Throughout the centuries, its characteristic ringing, buzzing, hissing, static, or other noises have cursed such notables as Charles Darwin and Ludwig van Beethoven—some historians speculate they're what drove Vincent van Gogh to cut off his own ear. Today, 10 to 15 percent of the population experiences tinnitus, as it's now called, chiefly older people and those who've been exposed to loud sounds, from machinists to musicians. For some, it's an occasional nuisance, but for up to 10 percent of sufferers, it's debilitating. With its consequences of fatigue, cognitive impairment, and depression, tinnitus is finally getting its due attention. It's the most prevalent service-associated disability for veterans of the wars in Iraq and Afghanistan.

There is no surefire cure, though some find relief in masking their tinnitus with other sounds. "I don't know what silence sounds like anymore," said Will.i.am of the Black Eyed Peas in an interview with *The Sun* last winter, in which he repeatedly wiggled his finger in his ear and shook his head. "Music is the only thing which eases my pain. . . . There's always a beep there, every day, all day. Like now. I don't know exactly how long I've had this, but it's gradually gotten worse."

In spite of their prevalence, historically, these phantom sounds have remained just that. As recently as 20 years ago, we were looking for their source in the wrong place: the ear. (Tinnitus *is* associated with hearing loss, after all.) Then came the reports that people whose sense of hearing had been completely dismantled—cancer-surgery patients whose auditory nerves had been cut—also suffered from tinnitus. This was the ultimate proof that it wasn't the ears that had been "bewitched" at all; it was the brain.

Thanos Tzounopoulos, a PhD assistant professor of otolaryngology, recently became the first to watch tinnitus in action at the cellular level, finally uncovering exactly how some brains turn on themselves in this way. He's learned that tinnitus is a betrayal of our biology that's rooted in the very strengths that have enabled humanity's success: memory, learning, and adaptability. Ironically, the cellular savvy that made Beethoven arguably the greatest composer the world has ever known also drove him to despair, his mind caught in a loop of "rushing, roaring sounds."

Tzounopoulos speaks with a Greek accent (he hails from Athens) and an easy laugh. In his jeans, Converse All Stars, and sideburns, he looks a bit more like a guy on his way to a rock concert than an international expert in the molecular aftermath of exposure to deafening decibels. The young investigator has been pushed to the main



COURTESY T. TZOUNOPOULOS

ABOVE: Thanos Tzounopoulos found that the brain centers that govern our senses are plastic just like those that enable learning and memory. RIGHT: Principal neurons of the dorsal cochlear nucleus—the first nucleus that ushers sound signals into the brain. This area is more active in mice with tinnitus than in healthy mice.

COURTESY M. RUBIO

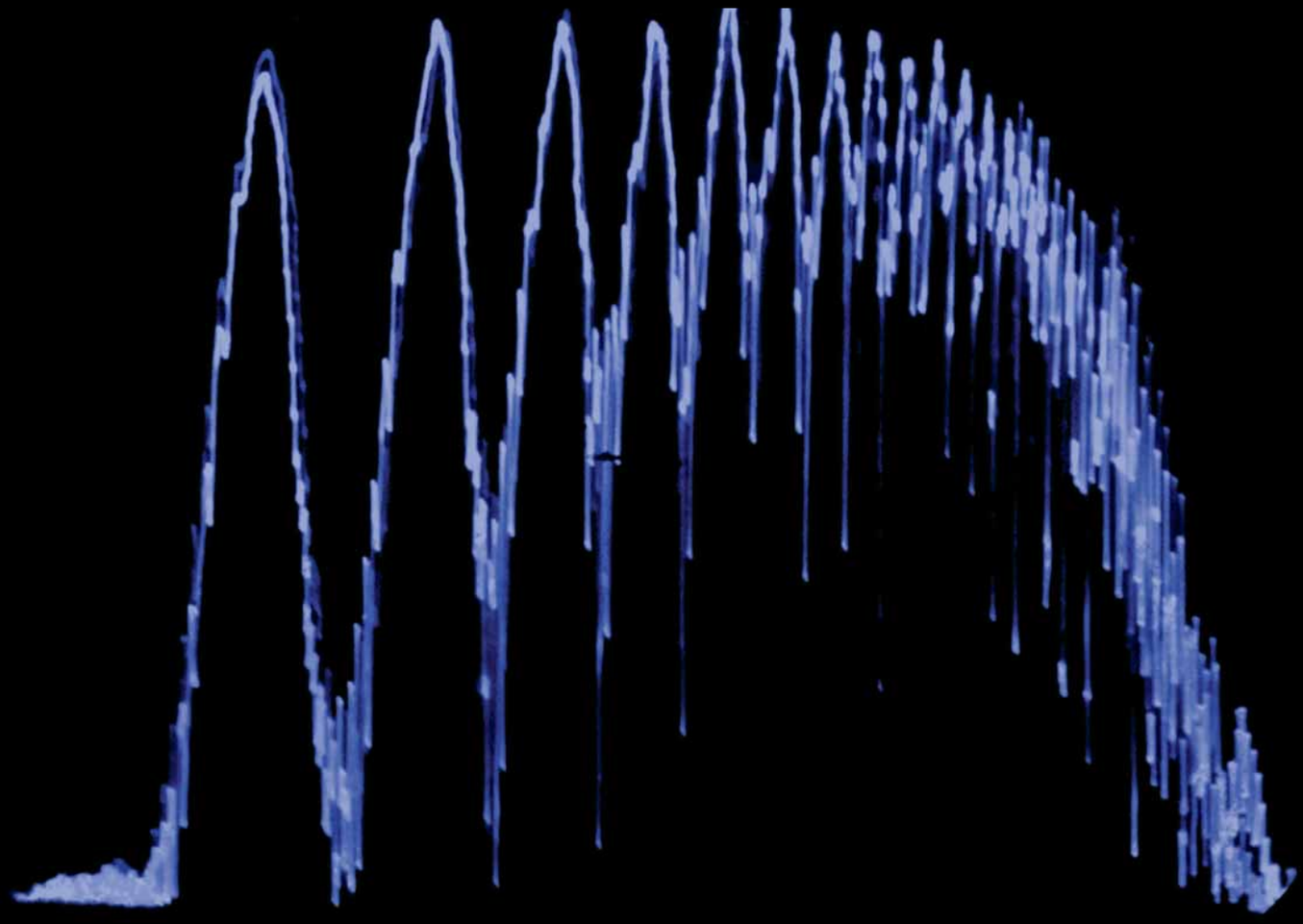


PHOTO RESEARCHERS

When loud sounds damage the hairs in the ear that turn sound-wave vibrations (such as these from a musical instrument) into a signal for the brain, hearing is lost. Yet people with tinnitus (associated with hearing loss), find loud sounds unnerving. Tzounopoulos saw this hypersensitivity as a clue that their brains had adapted, trying to make up for what their bodies now lack.

stage in recent months, finding his decade-long study of sensory processing suddenly of interest to the likes of *The Wall Street Journal* and NPR. "Whenever my research has direct implications for disease, it's as good as it gets for me," he says.

Tzounopoulos cut his research teeth studying the hippocampus (the brain center for memory and learning) as a postdoc in the lab of Roger Nicholl and Robert Malenka, trailblazers in the field of brain plasticity at the University of California, San Francisco. It was the 1990s, and the field was ripe with promise. Experts were buzzing over something called long-term potentiation (LTP), a phenomenon in which stimulating individual synapses causes the strength of their responses to increase. "It's a kind of training," Tzounopoulos says. Though LTP was first described in the late 1960s, its exact molecular mechanisms had remained elusive, but now, they were finally coming into focus. Scientists were becoming more and more confident that LTP was exactly what they'd hoped: a mechanisms of plasticity. Learning, at the cellular level.

A few years later, when Tzounopoulos began his second postdoc, he was eager to carve out his own niche. He knew he was going to stick with memory and learning—he wanted very much to understand the mechanisms of this training. But he decided it would be best to center his studies further upstream from the hippocampus, which gets involved very late in the process of learning. He settled on the brain's sensory processing—specifically, the very first structure in the auditory-processing chain, the auditory brain stem. "Because there you know what the information is about: sound."

At the time, no one believed the structure was plastic. The hearing portion of the brain was just the messenger, everyone assumed—it leaves the fancy work to pros like the hippocampus.

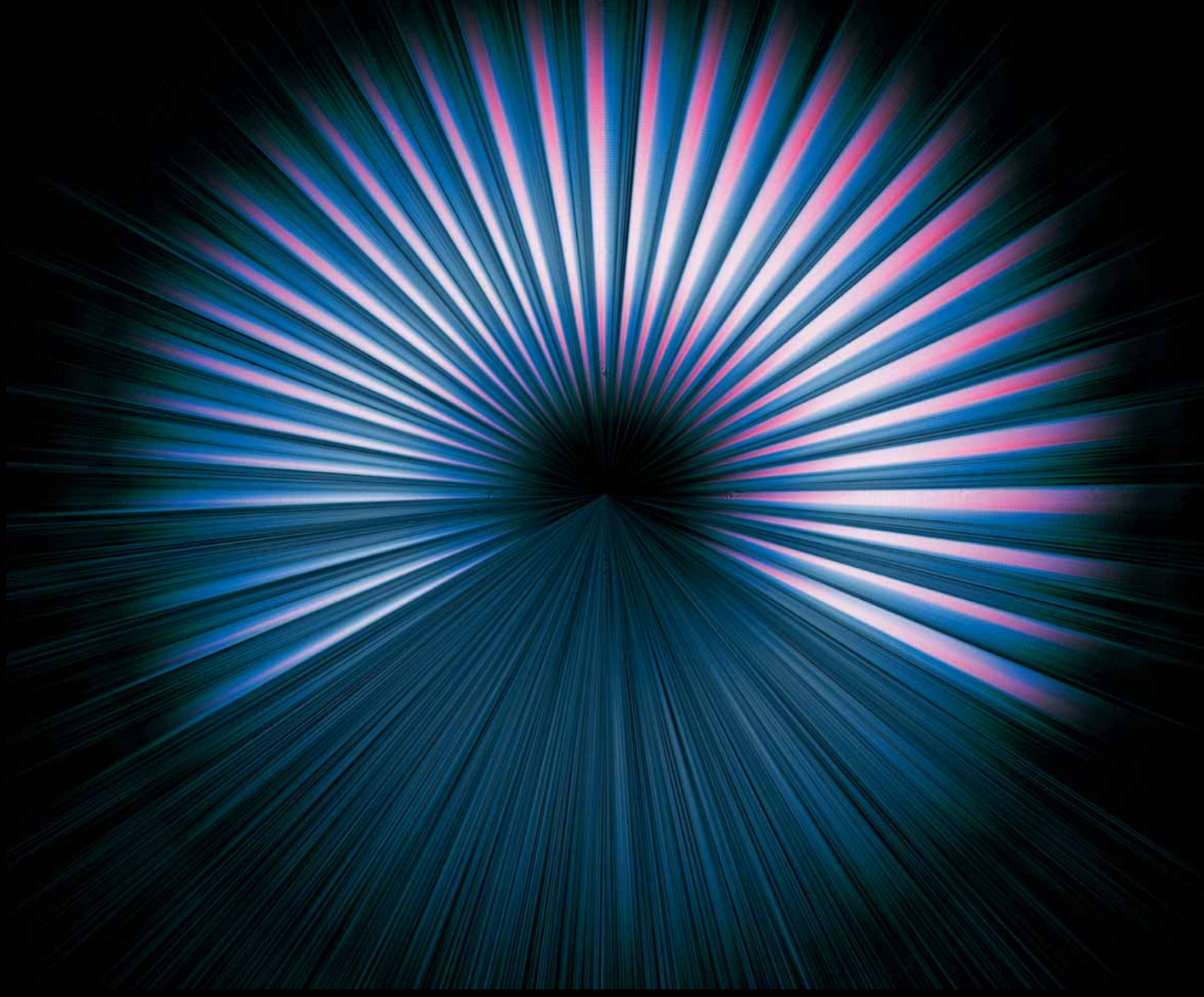
But Tzounopoulos noticed that the auditory brain stem had the same sort of wiring and organization that characterizes the cerebellum, the site of motor coordination.

"It was a gamble," he admits. But it worked. He stimulated individual synapses in the auditory brain stem and found LTP there, too. In 2009, he published a review of his findings in *Neuron* at the journal's invitation.

Next, as a great many scientists before him, Tzounopoulos sought to further understand healthy brain functioning by observing what happens when it's not so healthy. In the '50s, scientists discovered what the hippocampus was for by talking to a brain-surgery patient who was incapable of making new memories, Tzounopoulos recalled. So, about four years ago, he decided to study plasticity in the auditory brain stem by observing what happens when plasticity mechanisms misstep and the plasticity of the brain bends out of control.

As far as he could tell, that's what tinnitus was.

When hearing is damaged, the central nervous system must sense it, he figured. Wouldn't it stand to reason that the brain would want to maintain a certain level of activity? Could it be that it was trying to fill the silence on its own? It had been well documented in imaging studies that in people with tinnitus, the auditory circuitry's response to sound is far more pronounced. The system



PAGES 30-31: PHOTO RESEARCHERS

is fundamentally different in people with the disorder—perhaps because it's been trained to be, he thought. Just as auditory synapses in a petri dish can be trained to rev up. Just as a healthy hippocampus can be conditioned to recall the lyrics to "Ode to Joy."

"Nature, in a sense, is conservative," he says. "Once it's found solutions, it keeps using these solutions."

Sound travels in waves, vibrations that are picked up by the hairs of the inner ear. These hairs convert the vibrations to a chemical signal, then pass them to the brain through the auditory nerve. Inside, the auditory nerve stimulates the dorsal cochlear nucleus (DCN), the first nucleus in the auditory brain stem. The portal to the hearing brain.

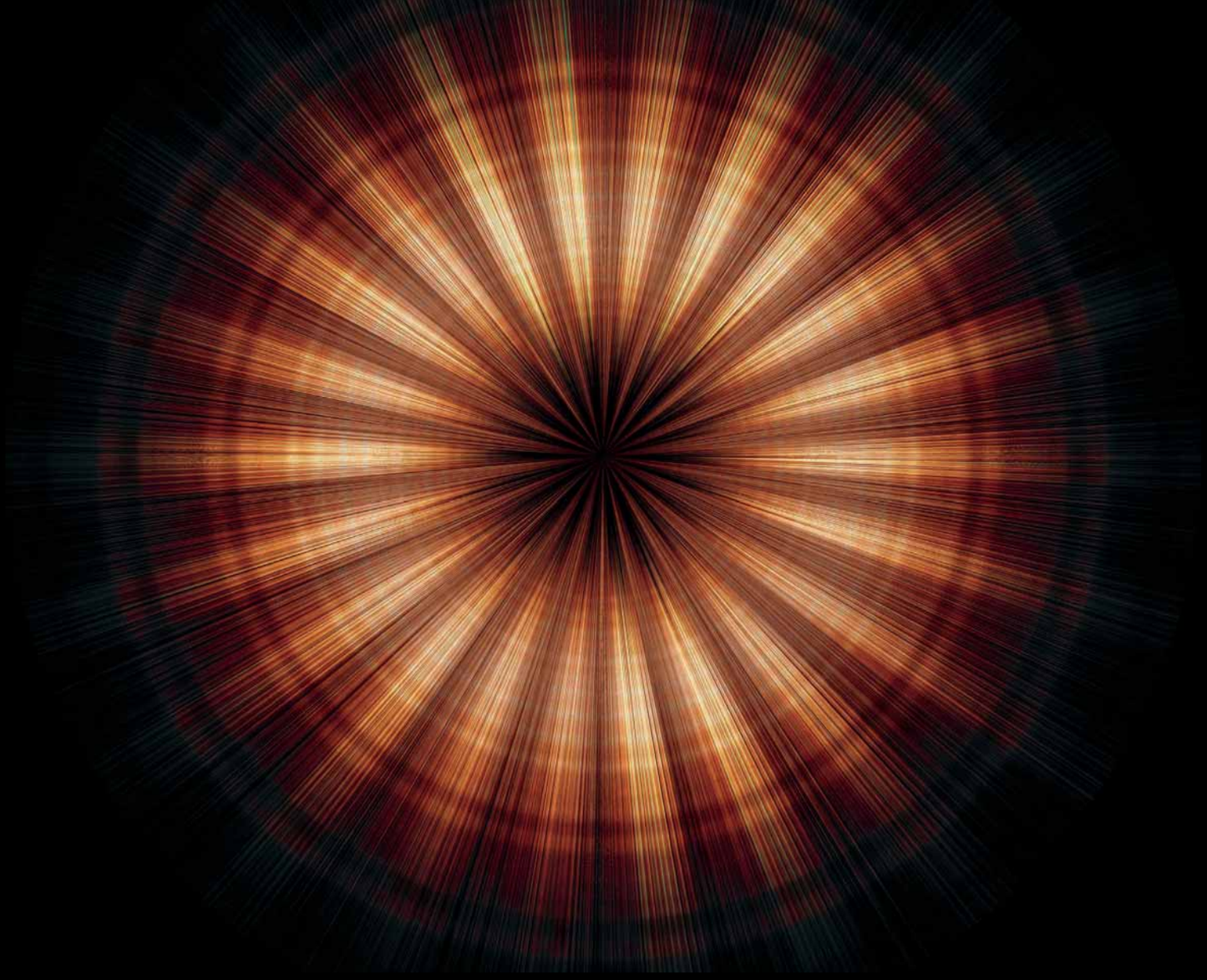
Once inside, the signal becomes part of the constant balancing act that is synaptic function: Excitatory forces move to increase signal activity on the one hand, and inhibitory forces decrease activity on the other. With the stimulation of a sound, the excitatory force increases, and a neuron fires. The process continues duplicating along the neurological chain, and, eventually, the person perceives sound. But in tinnitus, the neurons fire without the sound, which Tzounopoulos figured could be happening for one of three reasons: Either they're exposed to more excitatory force, less inhibitory force, or both.

To find out which, Tzounopoulos' team used a mouse model of tinnitus. Under sedation, the rodents were exposed to sounds about as loud as an ambulance siren (116 decibels) for 45 minutes. Weeks later, the team confirmed which mice had tinnitus by conducting startle experiments: The team played for the mice a 70-decibel tone, then interrupted it, and then resumed it before sounding a much louder pulse. The healthy mice perceived the gap and jerked with surprise; in the mice with tinnitus, however, their internal noise masked the silence in that gap.

The team then studied brain slices of the mice, watching how the synapses responded when they tweaked the balance of excitatory and inhibitory forces. As it turned out, amping up the former had no effect. But blocking inhibition did. Specifically, they found, deficiency in the inhibitory neurotransmitter GABA is the culprit in tinnitus.

On a fall afternoon in 2011, in his office in Biomedical Science Tower 3, Tzounopoulos cracks open his laptop and pulls up two movie files side-by-side on the screen: one with an outline of a dorsal cochlear nucleus of a mouse with tinnitus, and the other with the DCN of a healthy mouse. The cells are rendered with flavoprotein autofluorescence (FA), a technology he mastered while a fellow at the Marine Biological Laboratory in Woods Hole, Mass. Within the mitochondria—the powerhouse of the cell—are proteins called flavines, which fluoresce when oxidized with use. The brighter the glow, the stronger the activity.

Tzounopoulos clicks PLAY on the healthy mouse reel, and a small portion of it flashes red, then dissipates into orange and yellow. "But if you do the same thing in tinnitus,



Some tinnitus sufferers experience their phantom frequencies as buzzing or chirping sounds, like the song of a cricket (opposite page, converted mathematically into graph form) or cicada (above). Author and radio personality Garrison Keillor finds that cicada serenades mask his tinnitus perfectly. *Medicine has no remedy*, he wrote in 2007. *My only alternative, I guess, is to wander the planet in search of cicadas.*

look what's going to happen," he says, hitting PLAY on the diseased mouse model's movie. This is no small, localized response. "The whole area lights up." (Tzounopoulos published his findings in *Proceedings of the National Academy of Sciences* in 2011; he presented these movies at the international Tinnitus Research Initiative Conference last summer in Niagara Falls. See our Web Extras at pittmed.health.pitt.edu.)

Tzounopoulos is excited about the road ahead as he continues to sort out the story of tinnitus: What are the intrinsic, molecular properties of cells that dictate how adaptable they will eventually become? What exactly causes the decrease in GABA? Is less of it released? Are there fewer GABA receptors in play? Or has the circuitry reorganized itself so that there are fewer GABA-simpatico neurons? And just what exactly separates those who develop tinnitus from those who don't?

And then, of course, there are the therapeutic possibilities. Based on some very preliminary data, Tzounopoulos hopes he has a lead. In recent years, his team discovered that a certain neuromodulatory system—the cannabinoid system—is central to all forms of brain plasticity, sensory and otherwise. Further: "This system is very dominant in the auditory brain stem, and it mediates these ups and downs of synaptic strength," he says.

It's a target that's worked well in the past. The cannabinoid system—so named because its receptors are what cannabis binds to when the brain is exposed to marijuana—has also been linked to numerous physiological processes, including appetite, mood, and the sensation of pain. Hence, medical marijuana has been useful in treating chronic pain, which is now considered an apt parallel to tinnitus. Chronic pain is a similar story of the body betraying itself. "There is some peripheral damage that leads to a central response," Tzounopoulos says. "And this response then goes out of control."

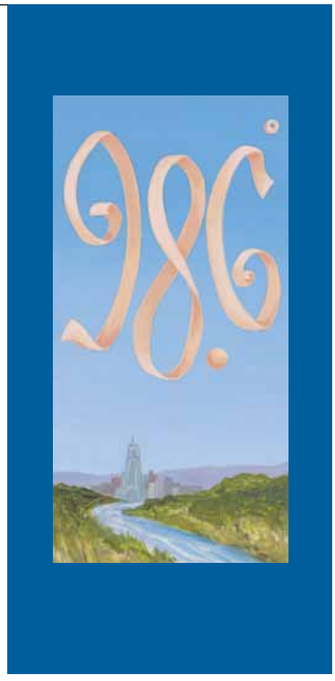
In addition to chronic pain, mechanisms of plasticity have been found to be a driving force in addiction, Tzounopoulos points out.

"It's the same mechanisms that wire the reward systems. You get a reward—you feel good for doing something, so you want to do more of it. Constant abuse messes up these mechanisms. It's this learning route induced to an extreme. The addicted brain gets stuck in that state."

Nature is conservative, Tzounopoulos has noted. Rather than coming up with a whole new song and dance for every occasion, it tends to run through a familiar playlist. ■

WATCH FOR THE PITTMEDCAST THIS JANUARY ON ZINIO.

People and programs that keep the school healthy and vibrant



BEHIND CHILDREN'S SMILES

Lisa Vecchione (DMD '00, MDS '03) dedicated her career to the care of children with cleft palate and other craniofacial abnormalities. In fact, at the time she died in an auto accident last August at the age of 44, she had more than 3,000 active cases.

Vecchione "became very close with her patients," says Joseph Losee, a friend and chief of the Division of Plastic Surgery at Children's Hospital of Pittsburgh of UPMC. "She really became almost part of their families."



Vecchione

After earning her master's degree in dental science and doctorate in medical dentistry at the University of Pittsburgh, Vecchione completed a fellowship in cleft-craniofacial orthodontics at New York University. In 2004, she returned to Pittsburgh as the first director of orthodontics at the Cleft-Craniofacial Center at Children's and clinical assistant professor of surgery in Pitt's School of Medicine. Over the last seven years, Vecchione built a hospital-based orthodontics program that includes naso-alveolar molding, presurgical orthodontics, and ear molding. She also led or co-led several studies on cleft and craniofacial conditions in children.

In her honor, Children's Hospital of Pittsburgh Foundation is establishing the Lisa Vecchione Memorial Lectureship—"an annual recognition of her energy and her dedication and her commitment to those children," says Losee.

—Jessica Titler

RACE TO ONE MILLION

The Class of 1961 is inching up to one million—$1 million in lifetime donations to the School of Medicine. At the class's 50th reunion during Alumni Weekend in May, it was announced that the class had, at that time, donated more than a combined $875,000, establishing the Class of 1961 as among the highest-donating classes in the School of Medicine's history. The class gave more than $117,000 in the last fiscal year alone.

Richard Paul (MD '61), a reunion co-chair, notes that Pitt's telethon program, which he and classmate David Katz were heavily involved in for many years, helped the cause. When calling up former classmates to request donations, he and Katz stressed that a large portion of the donations would support Medical Alumni Association scholarship funds. "Nobody could really object strenuously … to scholarship funds for needy students," Paul says.

The class now seeks to increase its total to $1 million. One class member, who wishes to remain anonymous, provided even more incentive for the class to reach this grand goal: He pledged to bequeath $25,000 to the School of Medicine upon his death if that would bring the class's lifetime giving total to $1 million or more.

The anonymous donor notes, "I was moved by the fact that we're very close to $1 million." *—Alexis Wnuk and Jessica Titler*

BOOSTER SHOTS

ADVOCATE FOR INTERNISTS

As they graduate with growing debt burdens (the national average was nearly $144,000 in 2009), fewer U.S. medical students are going into internal medicine and family practice, opting instead for more lucrative specialties. Fewer still plan to pursue internal medicine research, an area of study that investigates key questions about the pathophysiology of disease.

Hoping to bring budding physicians into his fold, **Frank A. Anania** (MD '88) recently made his first gift to the School of Medicine, a five-year pledge worth a total of $15,000. Anania's gift will support Pitt med students who have expressed an interest in internal medicine and plan to pursue careers in clinical, translational, or public health research. Anania, professor of medicine who directs the Division of Digestive Diseases at the Emory University School of Medicine, is both an internist and a physician-scientist. "I don't want us to become extinct," he says. "I want to encourage students to go into internal medicine and … retain them in academia." *—AW and JT*

NEW ON BOARD

A native of Pittsburgh's North Side, **Eric White** is the new director of development for the University of Pittsburgh School of Medicine. His earlier career found him working as an officer for PNC Bank and at the Manchester Craftsmen's Guild as founder Bill Strickland's assistant. One of his goals is to help Pitt "attract and support the best and brightest through scholarships. Paying back loans is a huge burden for medical students," says White. *—AW and JT*

To find out how you can help: emw61@pitt.edu

PITT MED WAS HERE

Throughout Western Pennsylvania, it seems you can hardly flip a chart without seeing a Pitt med student nearby. It's no secret that our emerging physicians are getting their feet wet all over this region and beyond. But did you know many of our students are also crossing oceans to make a splash?

Through senior electives, summer enrichment experiences, and scholarly research projects, our students are diving into clinical and research work in both urban and rural settings throughout Asia, Africa, the Americas, Europe, and Australia, often in underserved areas. In the last decade, students have brought medical supplies to hospitals and clinics; made house calls in Honduras; scrubbed for transplant surgery in Sicily (at the UPMC-affiliated ISMETT); and confronted such global-health threats as HIV, malaria, TB, malnutrition, and chronic noncommunicable diseases, often amid the challenges of a resource-limited setting.

"I appreciated how much waste there is in the U.S. as I saw many patients diagnosed simply by clinical exam, basic labs, plain X-rays, and ultrasounds," says Corinne Rhodes (MD '10), who completed a rotation in the Southeastern African nation of Malawi in her fourth year.

"Often the complicated tests and procedures that we utilize to determine diagnoses are not necessary to bring the patients back to their former state of health," she says.

Last summer, second-year student Jeremy Kauffman traveled to China with funding from the Medical Alumni Association. In his eight weeks abroad, Kauffman brought care to people still living in tents more than a year after the devastating earthquake in Yushu; to orphaned children with special needs in Kunming; and to villagers in rural Nang Qian—"Rural in the sense of a six-hour drive from Yushu along dirt roads over 15,000-foot mountains," he adds. He also assisted a surgeon in Xining for three weeks, an experience that inspired him to consider a future in pediatric surgery, as well as a relevant scholarly research project.

"I heard about the summer enrichment program," he says, "and I was really encouraged by the fact that part of the mission was to broaden the horizons of the medical students and give them opportunities to grow professionally and personally. Both of these were achieved in my case."

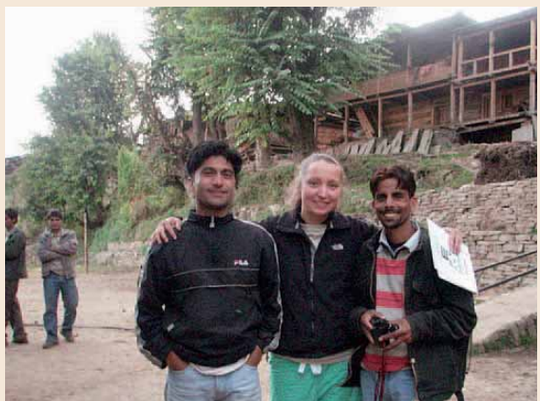
In the past decade, some 350 Pitt med students have traveled to 67 countries to learn about medicine from other perspectives. The map on the next page charts travels from 2002 to 2011. —*Elaine Vitone*











COURTESY J. KAUFFMAN AND A. GUSHCHIN

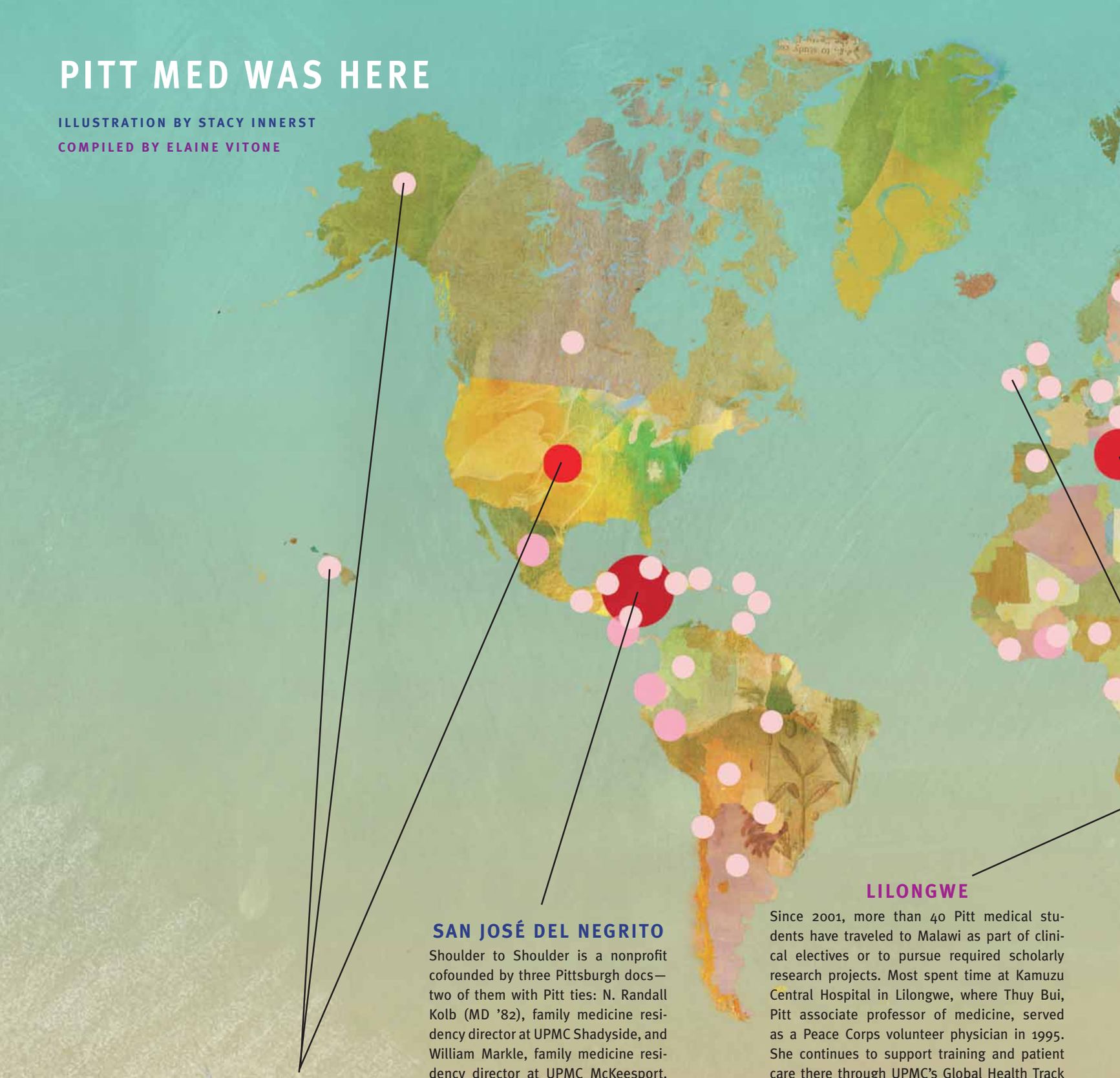
Jeremy Kauffman (Class of '14) worked with patients last summer in several settings across China. BOTTOM LEFT: Kauffman (second from the right) helps pull his mobile clinic out of the mud in Nang Qian, China. TOP LEFT: Teaching English to Tibetan children in Yushu.

In her Pitt med days, Anya Gushchin (MD '09) volunteered at eye clinics in Nepal and India. TOP MIDDLE: Visiting the Taj Mahal after a month-long medical trek in the mountains. BOTTOM MIDDLE: With the village chief and schoolteacher (holding an ophthalmoscope) of Dodra, India. ABOVE: At a seminar on antibiotic resistance Gushchin organized for Kathmandu Medical College and Shigan Health Center in Nepal.

PITT MED WAS HERE

ILLUSTRATION BY STACY INNERST

COMPILED BY ELAINE VITONE



NATIONS WITHIN A NATION

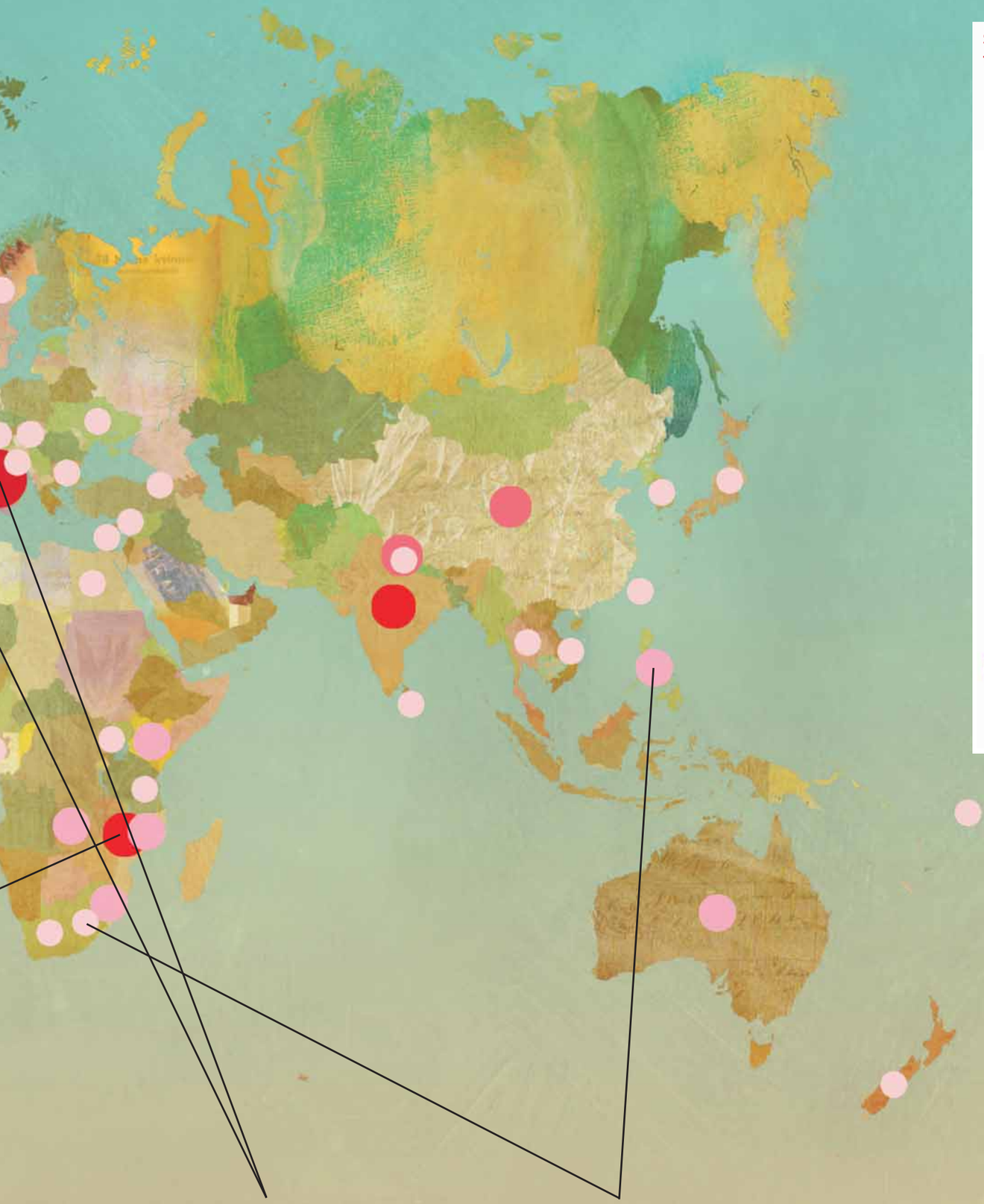
Thirty-four students have worked with indigenous peoples in North America, including members of the Navajo, Yavapai-Apache, and Hopi nations. They've also served with native Alaskan and Hawaiian communities.

SAN JOSÉ DEL NEGRITO

Shoulder to Shoulder is a nonprofit cofounded by three Pittsburgh docs—two of them with Pitt ties: N. Randall Kolb (MD '82), family medicine residency director at UPMC Shadyside, and William Markle, family medicine residency director at UPMC McKeesport. The organization has brought some 150 students to San José del Negrito, Honduras, in the last decade to provide preventive, primary, and acute care and help with public health initiatives. On their most recent trip this fall, Pitt med students gave well-child exams to 600 kids in the area and provided many other services.

LILONGWE

Since 2001, more than 40 Pitt medical students have traveled to Malawi as part of clinical electives or to pursue required scholarly research projects. Most spent time at Kamuzu Central Hospital in Lilongwe, where Thuy Bui, Pitt associate professor of medicine, served as a Peace Corps volunteer physician in 1995. She continues to support training and patient care there through UPMC's Global Health Track Internal Medicine Residency Program. By the way, in 2000, Bui and Pitt assistant professor of biomedical informatics Gerry Douglas (PhD '09), her husband, cofounded Baobab Health, a nonprofit that uses technology to improve health care in developing countries. So far, Baobab has helped bring antiretroviral therapy, HIV testing and counseling sessions, imaging studies, and lab tests to thousands of Malawians.



STUDENT CLINICAL AND RESEARCH TRAVEL EXPERIENCES (2002–2011)

1–3 STUDENTS: Argentina, Armenia, Austria, Belize, Bolivia, Bosnia, Brazil, Bulgaria, Canada, Chile, Colombia, Cuba, Dominican Republic, Egypt, England, Gabon, Germany, Guatemala, Haiti, Hungary, Ireland, Israel, Japan, Lebanon, Lesotho, Liberia, Mali, Nepal, New Zealand, Nicaragua, Nigeria, Paraguay, Saint Lucia, Samoa, Scotland, South Africa, South Korea, Spain, Sri Lanka, Sweden, Taiwan, Tanzania, Thailand, the Virgin Islands, Togo, Trinidad and Tobago, Uganda, Ukraine, and Vietnam

4–10: Australia, Costa Rica, Ecuador, Ghana, Kenya, Mexico, Mozambique, Peru, Swaziland, the Philippines, and Zambia

11–20: China and the Himalayas

21–40: India and the United States

41–99: Italy and Malawi

100 PLUS: Honduras

SOURCE: OFFICE OF STUDENT AFFAIRS

PALERMO AND DUBLIN

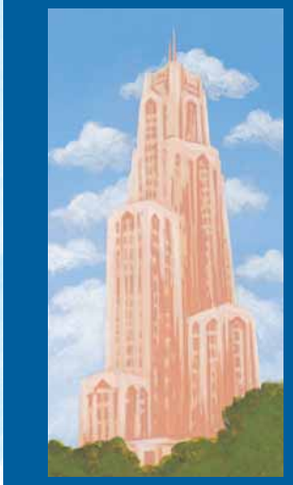
Italy has been super simpatico to Pitt meders. Since 2003, 57 have made the trip, most of whom based their clinical and research experiences at Palermo's UPMC-affiliated transplant hospital, ISMETT. A similar student program is in the works at UPMC Beacon Hospital in Dublin, Ireland.

SCHOLARS AT LARGE

Based on their experiences abroad, students have completed scholarly research projects ranging from mass drug administration for elephantiasis in the Philippines to predictors of infant malnutrition in Lesotho.

HOW DO THEY GET THERE?

Students often do their own fundraising to cover their travel expenses, many of them garnering support through Medical Alumni Association Summer Enrichment Scholarships and Travel Grants from the University of Pittsburgh Center for Global Health. ■



CLASS NOTES

'80s

Though he modestly claims he's "just doing administrative work," **Frank Castello** (MD '82) is anything but your average administrator. Recently named Physician of the Year by *NJ Biz Magazine*, he has been medical director of Children's Specialized Hospital, the country's largest pediatric health-care rehabilitation system, for 11 years. During that time, the Mountainside, N. J.–based hospital has grown substantially, from treating 3,000 patients in 2000 to six times as many today. Castello says, "The most rewarding aspect has really been the ability to help grow programs, recruit physicians, and expand the services that we can offer to kids." Those expanded services include a sophisticated pharmacy system that significantly reduced the hospital's error rate, a new method for priming IV tubes that resulted in 18 bloodstream-infection-free months, and the Chronic Illness Management Program, an inpatient program that teaches adolescents with chronic illnesses how to manage their health.

Byers Shaw (Transplantation Surgery Fellow '83), one of many Thomas Starzl protégés who've gone on to lead transplantation programs of their own, has a new title to add to his CV: prize-winning essayist. In August, Shaw—professor of surgery and cofounder of the liver-transplantation program at the University of Nebraska—was presented with a $5,000 check at a packed public reading in Pittsburgh's Garfield neighborhood, which was attended by Starzl and other members of the Pitt transplant team from the 1980s. Shaw's essay, "My Night With Ellen Hutchinson," tells of a liver transplant Shaw performed late one winter night in 1983—one of his first without his mentors by his side. The contest was sponsored by the Salt Institute for Documentary Studies, based in Portland, Maine, and judged by *The New Yorker*'s Susan Orlean of *The Orchid Thief* and *Adaptation* fame. The essay was published in the summer 2011 issue of the literary journal *Creative Nonfiction*.

Alakananda Basu (PhD '85) pours a lot of effort into grant writing—to fund her research in signal transduction and chemotherapy resistance, certainly, but also to support another pleasure: mentoring. She's been shepherding teen scientists since her Pitt days; as a postdoc she took an 8th-grader under her wing. Now at the University of North Texas Health Science Center in Fort Worth, Basu is a professor of molecular biology and immunology and graduate advisor for the cancer biology program, which she launched in 2007. Through the school year, her plate is full teaching and mentoring grad students. She spends summers mentoring high schoolers in her lab, too—"especially minority students," she says. This summer, one of her charges, 17-year-old Shree Bose, won the grand prize—a $50,000 scholarship and a trip to the Galapagos—at the first Google Global Science Fair for a cisplatin-resistance project she completed with Basu's guidance.

When pain specialist **Mark Hashim** (MD '89) volunteered to coach his son's soccer team in 2010, he didn't expect that it would lead him to practice medicine in a Third World country. As it happened, one of his son's teammates' fathers was Leo Vieira, cofounder of People for Haiti, a nonprofit that provides basic necessities and medical care on the island. Hashim has since traveled to Haiti on two of the organization's five-day medical mission trips, during which medical volunteers treat up to 1,500 patients. The ailments they treat range from severe infections to physical deformities to vision loss. It's the Haitians' spirit and thankfulness that Hashim says he misses most after a trip. "After a while of practicing back in the U.S., you go, 'God, I really need to go back to Haiti again.'" He's planning to do that in January 2012.

Hashim (right) in Haiti





Arnold

WE KNEW YOU WHEN: JAN D. SMITH

Jan Smith (Critical Care Fellow '67, Pulmonary Diseases Fellow '69, Internal Medicine Resident '71), an MB ChB, originally came to Pitt to complete a fellowship in critical care medicine with Peter Safar in his burgeoning program. Under Safar's leadership, Smith experienced a revolution in resuscitation and critical care medicine. He describes Safar as "extremely dynamic" and admits that he "had to run to keep up." But it can be hard to keep up with Smith himself.

As a White youth growing up in South Africa under apartheid, Smith knew he had a privileged life. But in 1961, he was the odd man out. He was working at McCord Hospital in Durban, South Africa, which at the time was still a racially segregated hospital. He was the only White intern. "It was a tremendous social experience," he says—one that has remained with him in his decades of work as a professor of anesthesiology, internal medicine, and critical care medicine at Pitt and in his travels.

And travel he does. Smith, a Pitt anesthesiology clinician emeritus (he still teaches part-time), has regularly served as a volunteer physician in several African countries. In South Africa, Smith has helped set up educational programs and works with the University of Pretoria on HIV medicine, TB, and critical care programs. He has also worked in Tanzania at Kilimanjaro Christian Medical College, helping to train medical professionals in the delivery of anesthesia care and serving as an external examiner

JIM JUDKIS



COURTESY UPMC

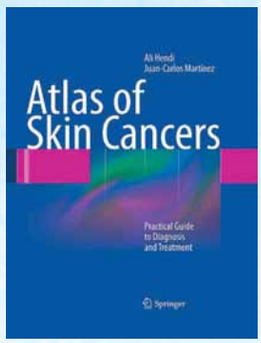
In September, Pitt celebrated the 30th anniversary of the emergency medicine residency program. Among those who helped celebrate (from left): Susan Dunmire (MD '85, Res '88); Michael Turtorro (Res '90); Walt Stoy (PhD '90); Robert Whipkey (MD '81, Res '84); Pitt's academic EM program founder Ronald Stewart; Dave Ellis (behind Stewart) (MD '82, Res '85); former EM department chair and the residency program's first director, Paul Paris (MD '76); Sandra Schneider (MD '75, Res '78); Kevin O'Toole (behind Schneider) (MD '83, Res '86); Mike Plewa (Res '88); Pitt's current chair, Donald Yealy (Res '88); Vince Verdile (Res '87); and Ronald Roth (MD '82, Res '85).

'00s

Prostate-cancer hormone treatment tends to follow an unfortunate yet predictable pattern, explains **Nima Sharifi** (MD '01), assistant professor of internal medicine at University of Texas Southwestern Medical Center: The patient is given medication to block testosterone, the staple food of prostate-cancer cells, but within a year, the cancer returns. The cancer cells' workaround, we've long assumed, is to use a particular pathway to make their own testosterone, which they subsequently use to produce DHT (dihydrotestosterone), an even more potent superfood. In recent years, new drugs have been deployed to block this pathway, but many patients' cancers have proven resistant to these second-line therapies, too.

Recently, Sharifi found what appears to be the reason why—a discovery even he didn't believe at first. "We looked at this in six cell models," he says, "and all six showed the same thing." (The same was true in patient biopsies, he'd later find.) Turns out that late-stage prostate-cancer cells use an additional, completely separate pathway to produce DHT directly—no testosterone required. The study was published in *Proceedings of the National Academy of Sciences* in July. A multicenter, Prostate Cancer Foundation–funded effort is now in the works.

When television producers first asked **Jen Arnold** (Pediatrics Resident '03, Neonatal/Perinatal Fellow '07) and her husband, Bill Klein, who both have spondyloepiphyseal dysplasia resulting in short stature, to star in their own reality show, the couple was skeptical. Then something happened while she was out shopping. "A little girl came up to me and said, 'You're a little person like in *Little People, Big World*,'" (another reality show) Arnold recalls. In the past, children had often pointed or used derogatory terms. The experience helped her see the educational possibilities. Says Arnold, "I've always been happy to share awareness." Now entering its fifth season, *The Little Couple* follows Arnold and Klein through their daily lives, from searching for a home to considering their options for starting a family. The show also depicts Arnold's work at Texas Children's Hospital in Houston, where she's a neonatologist and medical director of the Pediatric Simulation Center, a program she helped build after training at Pitt's WISER Center.



Hendi's 2011 book

While working at the Mayo Clinic in 2005, **Ali Hendi** (Dermatology Resident '03, Mohs Micrographic Surgery Fellow '04) noticed a gap in medical literature. As a skin cancer specialist and Mohs surgeon, Hendi often received referrals from general practitioners for lesions that mimicked skin cancer but were not. "There was really no atlas of skin cancers geared toward primary care physicians," he recalls. It also occurred to him that he had access to high-quality images of every tumor treated at the Mayo Clinic, which "were not being utilized to their maximum potential." So with Juan-Carlos Martinez, Hendi wrote *Atlas of Skin Cancers, Practical Guide to Diagnosis and Treatment* (Springer, 2011), which details skin cancers in their many forms, as well as conditions that commonly mimic them.

Jill Hagenkord (Pathology/Oncology Informatics Fellow '07, Molecular Genetic Pathology Fellow '08) recalls facing criticism for how she saw the future of medicine before she came to Pitt. Genomic technologies were too expensive—totally impractical for clinical use, her instructors told her. That changed when she began her training in informatics and molecular genetic pathology here. The directors of these programs—Michael Becich and Jeffrey Kant, respectively—had each "defined their fields," she says. "To have access to these two pioneering guides who actually got what I wanted to do was amazing." Hagenkord, who was recently named chief medical officer of Complete Genomics, a human-genome-sequencing service company, hopes to continue her mentors' tradition of innovation. "Whole genome sequencing as a diagnostic tool breaks the mold in so many ways. It's really utterly game changing."

—Jessica Titler and Elaine Vitone



Smith

for the local Tanzanian anesthesia board examinations. And Smith has served on medical missionary trips to many other countries.

"Jan is one of a handful of physicians I know who has truly dedicated his entire life to medicine," says John Williams, an MD, the Peter and Eva Safar Professor, and chair of Pitt's anesthesiology department. "I know very few physicians who will take their vacations and continue to work in a foreign country."

Smith is quick to point out that he feels he gets more than he gives in his volunteer work. "You appreciate what your medical colleagues are doing with minimal resources. You learn from them, because their physical examination skills and their clinical acumen are so great. We have a lot to offer them with things like TB testing and malaria vaccination. It's a true collaborative spirit," he says. *—Maureen Passmore*

ELSIE R. BROUSSARD

JAN. 30, 1924–SEPT. 12, 2011

As a pediatrician in the late 1950s, Elsie Broussard noticed that when mothers brought infants in for their well-baby visits, they brought a range of perceptions to the exam table. "Some mothers would see their babies in a positive light—active, energetic—while others would describe [babies who were just as active] as out-of-control difficult," explains Broussard's daughter, Jude Cassidy, a PhD professor of psychology at the University of Maryland. Curious as to how those perceptions would influence their parenting—and in turn, their children's development—Broussard pursued a master's and a PhD in maternal and child health at Pitt. In the ensuing decades, she helped legitimize the newly emerging field of infant mental health as her hunches about the roots of mental health in parent-child relationships bore out.



Broussard

In September, Broussard, professor emeritus of public health psychiatry and clinical associate professor of psychiatry in the School of Medicine, died of a heart attack while driving in Shadyside. She was 87.

In 1963 Broussard launched a longitudinal study called the Pittsburgh First-Born Project, and for nearly 40 years, Broussard worked with families to determine what stood in the way of positive parenting behaviors and developed interventions that proved successful in improving children's outcomes. Recalls Broussard's son, Francis Cassidy (MD '79), "She told us many times you can never spoil a baby. You can never love them too much."

—Elaine Vitone

BERNARD I. MICHAELS

DEC. 26, 1917–JULY 22, 2011

There are few people who can claim to enjoy going to work every single day. Bernard I. Michaels (MD '42, Res '48), clinical professor of pediatrics at Pitt and former president of the medical staff at Children's Hospital of Pittsburgh of UPMC, who practiced there for almost 60 years, was one of those rare people, says his son, Robert Michaels. "He loved being helpful, liked making a difference in the well-being of families, and adored watching children grow up." The elder Michaels cared for many of his patients from birth into adulthood and many families through multiple generations. He also took pride in the "huge number of patients of his who became pediatricians," adds Robert Michaels, who pursued the same path himself.



Michaels

Bernard Michaels died of a heart attack in July. He was 93.

When Children's Hospital of Pittsburgh of UPMC installed a historical timeline mural in its new location two years ago, Michaels was one of the few physicians to be included in the painting, notes Andrew Urbach, medical director for clinical excellence and service. "He had a passion for pediatrics and for his families," Urbach explained. "He had a level of excellence that set a standard for Pittsburgh." *—Jessica Titler*

FÉLICIEN M. STEICHEN

OCT. 13, 1926–JUNE 27, 2011

Since Félicien Steichen, professor emeritus of surgery at New York Medical College, died in June, it's been difficult breaking the news to his mentees, says long-time colleague Jean-Michel Loubeau (Res '77). One said he felt like he'd just lost a second father. Steichen was known to join his residents on call even late into the night. "He always said, *We have to teach these young people not how to do an operation but how to operate*," Loubeau recalls, adding that many of Steichen's pupils went into academic surgery.



Steichen with his grandson Adrien.

Steichen was professor of surgery at Pitt and associate chief of surgery under Mark Ravitch at UPMC Montefiore in the 1970s. Together, they developed a course in surgical stapling at Pitt, instructing hundreds of surgeons from all over the world on "how to operate" as a new surgical paradigm emerged. Ravitch and Steichen worked with U.S. Surgical Corporation to create these instruments, as well as several of the first miniaturized staplers, trocars, and other devices that ushered in the era of minimally invasive surgery. Ever wary of a conflict of interest, they did all their consulting gratis.

Years ago, Steichen's son, François Steichen, happened to meet one of his father's trainees. The younger Steichen was at an appointment for an insurance physical when the doctor realized François was his mentor's son and sheepishly offered a hug, recalls François. "I told him, 'Yes, it's okay. I've heard this before.'" *—EV*

IN MEMORIAM

'40s

THOMAS R. SARACCO
MD '43A
JULY 19, 2011

CONSTANTINE Z. MORAITIS
MD '47
OCT. 10, 2011

'50s

MELVIN L. COHEN
MD '53
SEPT. 4, 2011

GEARY EICHER JR.
MD '54
SEPT. 10, 2011

MICHAEL LADO
MD '55
AUG. 11, 2011

JOSEPH TANNENHAUS
RES '56
MAY 24, 2011

STEPHEN A. STEVENS
MD '58
JULY 15, 2011

RICHARD DIETRICK
MD '59
AUG. 6, 2011

ROBERT G. O'BRIEN
MD '59
JUNE 3, 2011

NICHOLAS N. VASILOPOULOS
MD '59
AUG. 19, 2011

'60s

JOHN L. MINARD
MD '61
AUG. 20, 2011

THEODORE M. TABACHNICK
MD '61
SEPT. 2, 2011

'70s

JUDITH E. ORIE
MD '78
NOV. 5, 2011

FACULTY/STAFF

GEORGE THIERS
JUNE 9, 2011

JULIE MAGARIAN BLANDER IMAGINES A NEW KIND OF VACCINE

BY KRISTEN COSBY



FRANK HARRIS

Magarian Blander solved the mystery of why vaccines based on live bacteria outperform their killed-pathogen counterparts.

When the American embassy in Lebanon was bombed in 1983, the immigration paperwork of Julie Magarian Blander's family went up in flames—along with their chances of escaping the civil war that had been raging since 1975.

Blander was 9 when the war began. "You'd be in school, and all of a sudden, there would be bombs falling," she says. "You would have to be picked up under great danger."

By the time her family was able to escape to the United States, she was a year away from completing her bachelor's degree at the American University of Beirut. She made the decision to see it through and keep her scholarship—she was used to living in danger, she says.

Now, Blander (PhD '97) faces grave threats of a different sort—deadly microbes—as an associate professor of immunology and director of the Innate Immunity Research Program at Mount Sinai in New York City. In July, Blander received the 2011 Burroughs Wellcome Fund Award in Pathogenesis of Infectious Diseases.

As a postdoc at Yale, she worked with the late Charles Janeway Jr., a founder in the field of innate immunology. He'd put forth the "far-fetched" proposal that the cells that make up our immune systems have receptors that can tell the difference between cells that make up our own tissues and the cells of foreign infectious agents; therefore, there must be identifiable structures on foreign microbial cells that provoke our immune system to react. When Blander joined Janeway's lab in 1997, he and postdoc Ruslan Medzhitov had just confirmed the existence of such a mammalian cell receptor.

Blander was eager to learn more about the immune system—in particular, why vaccines made of living, attenuated strains of a pathogen are more effective than vaccines made of dead pathogens. She proposed her own far-fetched hypothesis: Not only can our immune systems tell the difference between our own cells and foreign cells, but also between living foreign cells and dead foreign cells.

Blander studied immune-cell reactions to live bacteria and found that the immune cells' receptors responded to a certain kind of messenger RNA molecule that is structured very differently from our own messenger RNA molecules. But when the invading bacterial cells died, their load of RNA molecules was rapidly lost. The messenger RNA molecules served as signatures of microbial viability. They were missing from dead vaccines, hence the weaker immune response to them, and adding them back augmented dead vaccines to perform as well as live vaccines. Blander's findings were published in *Nature* in May 2011.

Blander imagines that in the future we will be able to take molecules made from dead pathogens and supplement them with these signature molecules. "So you can combine the best of both—what's good in a live vaccine and in a dead vaccine—and it's safe," says Blander. "You can vaccinate people without having the fear of being injected with a viable strain of microorganism."

If Blander is successful in synthesizing these signature molecules, her efforts could lead to the creation of a universal vaccine, one that could be adapted to fight any microorganism—or even tumor cells, she says. (Her research applies only to bacteria, yet she is confident that similar signature molecules indicative of microbial viability will be found in viruses, parasites, and fungal infections, too.) Such a vaccine would greatly reduce the time it takes to launch immunization efforts against new microbial contagions. It would also make it easier to vaccinate populations in disaster zones and developing nations, where it is difficult to administer the multiple doses dead vaccines require.

"It seems like a simple idea," she says, "but it has tremendous implications for the development of vaccines for infectious disease, or even for cancer immunotherapy." ■

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STOLEN MOMENTS

Living within gurney-rolling distance of the School of Medicine is "addictively convenient," says Sarah Ramer (Class of '12), who has lived at the University of Pittsburgh's Darragh Street Apartments, located just two blocks from Scaife Hall, since the complex opened in 2007.

There's the sense of community one would expect when med students share walls. Ad-hoc study groups. Walking next door in socks to borrow sugar to make cookies for a potluck. Impromptu cornhole tournaments on Darragh's courtyard (a hot spot for student group functions, as well as personal gatherings). Benjamin Cobb (Class of '13) says he first met many of his classmates at a party in the courtyard. A year later, after the construction of a new patio, he recalls, "During the summer, me and my friends would get together on the patio, grill some stuff, and just chill out on the grass and eat burgers."

Darragh has, quite literally, optimally positioned Cobb to get the most of his evenings. He has been known to stop by when he sees a professor's light on in Scaife after hours. Stolen moments with busy profs can be hard to come by otherwise.

And, Cobb says, "Sometimes, after I leave the hospital, I'll throw some regular clothes on, walk across the street to the hospital, and see my patients." He recalls one patient who was flat and unresponsive during his rotation; she brightened up at night when her family was able to visit.

"At night, I can sit down and talk to them. And when I'm done, just go right across the street and go back to sleep." *—Jessica Titler*

—Photography by Cami Mesa



Ramer (top) and Cobb.

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

MEDICAL ALUMNI WEEKEND 2012

MAY 18–21, 2012
Reunion Classes:
2002 1997
1992 1987
1982 1977
1972 1967
1962 1957
For information:
medalum@medschool.pitt.edu.
Or go to www.maa.pitt.edu.

ERIE HEALTH SCIENCES ALUMNI RECEPTION

DECEMBER 6
6 p.m.
Courtyard by Marriott
Ambassador Conference Center
Garden Atrium
Erie, Pa.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

CLEVELAND HEALTH SCIENCES ALUMNI RECEPTION

DECEMBER 8
6 p.m.
MYXX Restaurant
Fairmount Business District
Cleveland Heights
Cleveland, Ohio
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

WEST PALM BEACH HEALTH SCIENCES ALUMNI RECEPTION

FEBRUARY 15
6 p.m.
Esperante Corporate Center, Atrium
West Palm Beach, Fla.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu

NAPLES 2012 WINTER ACADEMY

FEBRUARY 17
Ritz-Carlton
Naples, Fla.
For information:
Pat Carver
412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS:

DATES TBA
Los Angeles, Calif.
Phoenix, Ariz.
San Francisco, Calif.
For information:
Pat Carver
412-647-5307
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TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu

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DON'T PLAY THE GOAT COME BACK FOR REUNION

Billy, here, and his white-clad friend were best buddies at the School of Medicine in the mid-1930s, but they lost touch. Never attended any of their Pitt med reunions—don't that bleat all?

Don't mutton to yourself over missed opportunities. Take time—Friday, May 18 to Monday, May 21, 2012—to reconnect with the people and places that made your medical education special. It'll be fun.

Classes whose years end in 2 and 7 will be recognized throughout the weekend. Figuring out if your cohort is one is so easy a kid can do it. (Or you can just look at the calendar list on the other side of this cover.)

So goat for it, and join your classmates at Medical Alumni Weekend 2012.

Register at www.maa.pitt.edu/reunionweekend/

PHOTO COURTESY FAMILY OF EDWARD J. CARROLL JR. (MD '34)