UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2008

PITTMED

SINGLE CANCER CELL SEEKS MULTIPLE PARTNERS.

AMBITIOUS, HYPER-ACTIVE, UNSTABLE MUTANT WITH NOMADIC TENDENCIES. GOOD AT FITTING IN (FOR A WHILE). INTERESTED IN HAVING LOTS OF OFFSPRING.

REPLY AT YOUR OWN RISK

WARM UP WITH US

In mid-February, baseball fans know that Florida Grapefruit League action is nigh. Alumni and friends of the schools of the health sciences also should think of Florida for another kind of spring training. In Naples, they can come together to learn from all-star researchers about what's new and exciting in science and medicine at Pitt.

Reserve your seats for
WINTER ACADEMY.
Saturday, Feb. 21, 2009
Naples, Fla.

For more information or to request an invitation:
Pat Carver
412-647-5307
cpat@pitt.edu
www.winteracademy.pitt.edu



SHIRLEY, COMPANION OF PITT MED ASSOCIATE EDITOR JOE MIKSCH, AS PHOTOGRAPHED BY HIS WIFE, COLLEEN VAN TASSELL

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

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

For address corrections:

***Pitt Med* Address Correction**
M-200k Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
E-mail: medalum@medschool.pitt.edu

RECENT MAGAZINE HONORS

CASE Circle of Excellence
Gold, Covers (Winter 2007/8)

CASE Circle of Excellence
Bronze, Special Interest Magazines

CASE District II Accolades
Gold, Magazines

IABC Golden Triangle Award of Excellence
Magazines

IABC Golden Triangle Award of Honor
Magazine Design
(E. Cerri)

Carnegie Science Center Journalism Award
Honorable Mention
(J. Miksch)

Pittsburgh Black Media Federation
Robert L. Vann Media Award, Photography
Honorable Mention
(C. Mesa)

PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2008 (AUG/SEPT/OCT)

VOL. 10, ISSUE 3



DEPARTMENTS

OF NOTE 3
A Pitt prof's work helps train SEALs.
"The Change" gets a makeover.
Women make big inroads
in orthopaedics at Pitt.

CLOSER 7
Expert weaves.

INVESTIGATIONS 8
A bionic knee brace.
A new role for old proteins.
Building a researcher's paradise.

ATTENDING 31
Emily Storch's hard-earned comeback.



98.6 DEGREES 34
Scholars Day shines
bright with the help of the O'Malleys.

ALUMNI NEWS 36
What whiskers tell us about brain circuitry.
Theodore Liou knows how to get Reuters to call.

LAST CALL 40
An extraordinary time.





24

FEATURES

Bad Company 12

Understanding cancer's nature may be the only way we can keep it at a distance. Scientists are building a profile of this ne'er-do-well among us—the formative influences, characteristics, and guises that make it so effective. They're even learning how we enable it.

COVER STORY BY JOE MIKSCH AND CHUCK STARESINIC

Diabetes Trials 20

Massimo Trucco and Nick Giannoukakis are attempting to cure type 1 diabetes using an approach that, at first, seems counterintuitive. So far, results are promising.

BY MELINDA WENNER

The Fish and the Med Student 24

Within days of finishing their first-year exams, 15 Pitt med students boarded a plane bound for coastal Maine. During six days of an intense research immersion experience on Mt. Desert Island, the students came to know the ins and outs of the little skate, the South African claw-toed frog, and Maine lobster.

PHOTO-ESSAY BY CHRIS LINDER AND SHARON TREGASKIS

CONTRIBUTORS

Insects are rare in the arctic, but photographer CHRIS LINDER ["The Fish and the Med Student"] says that everyone who approaches the poles gets bit by the "arctic bug." Linder, who freelances and shoots expeditions for Woods Hole Oceanographic Institution, says the experience of walking on the boundless and silent polar ice during a four-hour-long sunset plus sunrise is "like a waking dream." His photographs of an expedition exploring undersea mountains near the North Pole are on exhibit at the Carnegie Museum of Natural History through January. He lives in Seattle with his wife and daughter.

REID R. FRAZIER ["Your Body, Your Juice" and "First Do No Harm"] is a freelance writer and radio producer for WYEP's *The Allegheny Front*. Come assignment time, Frazier morphs into an anthropologist, heading into the unknown in medicine, natural history, or the environment and using what he knows from his own life to make sense of it all. He enjoys the challenge of teasing out an accessible metaphor from lofty, highly specialized subjects, once even comparing the application of mathematical calculations to RNA to working on "a really hard Sudoku." Frazier was drawn to journalism from the start because it gave him the chance to see people in their element and dive in with them. He lives in Wilkinsburg with his wife and two daughters.

COVER

By its very nature, cancer is bad company. That's no surprise, but understanding the character of the disease may help researchers find an Achilles' heel.
(Cover: Typography by Elena Gialamas Cerri. © 2008.)

PITTMED

PUBLISHER
Arthur S. Levine, MD

EDITOR IN CHIEF
Erica Lloyd

ART DIRECTOR
Elena Gialamas Cerri

SENIOR EDITOR
Chuck Staresinic

ASSOCIATE EDITOR
Joe Miksch

PRODUCTION COORDINATOR
Chuck Dinsmore

STAFF CONTRIBUTORS
Meaghan Dorff, Hayley Grgurich, Emily Karam

OBITUARIES CONTRIBUTOR
Macy Levine, MD '43

CIRCULATION MANAGER
Crystal Kubic

CHIEF EDITORIAL ADVISOR
Kenneth S. McCarty Jr., MD, PhD

EDITORIAL ADVISORS
Paula Davis, MA
Susan Dunmire, MD '85, Res '88
Jonathon Erlen, PhD
Joan Harvey, MD
John Horn, PhD
Steven Kanter, MD
Joan Lakoski, PhD
David Lewis, MD
Margaret C. McDonald, PhD
Ross Musgrave, MD '43
David Perlmutter, MD
Kevin Proctor, Class of '09
Gabriel Silverman, Class of '09
Peter Strick, PhD
Gerard Vockley, MD, PhD
Simon Watkins, PhD
Marshall Webster, MD, Res '70
Julius Youngner, ScD

OFFICE OF PUBLIC AFFAIRS
Robert Hill
John D. Harvith, JD

University of Pittsburgh

Pitt Med is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with the alumni and public affairs offices. It is produced quarterly for alumni, students, staff, faculty, and friends of the School of Medicine. PR 6702

The University of Pittsburgh is an affirmative action, equal opportunity institution. © 2008, University of Pittsburgh


JOSHUA FRANZOS

For this is the lesson of science, that the concept is more profound than the laws, and the act of judging more critical than the judgment.

—Jacob Bronowski, *Science and Human Values*

This election season has brought into sharp focus the daunting—seemingly intractable—challenges we now face as a nation: increasing energy demands amid diminishing resources; climate change and other environmental threats; the specter of pandemics; the need to regain a production-based economy, secure a sustainable food supply, and more. All of these concerns must be addressed by science and its derivative technologies, but many fear that this country is on the wane with respect to science literacy. Although it is true that the nation still accounts for more than 40 percent of the world's investment in research and development, new patents, and highly cited research publications, as well as the majority of top-tier universities and Nobel laureates, it is also true that our youth are failing to grasp the notion of science as a uniquely human way to confront and address the issues before us. This country's students continue, on average, to decline in math and science performance.

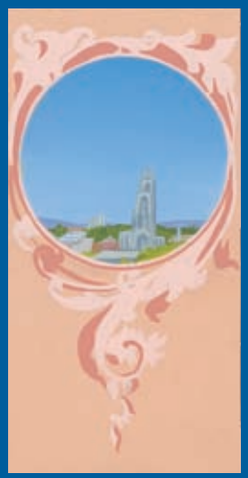
I have thought for a long time that the practice of *the scientific method* might be a remedy for the anxiety that we all experience when confronted with things that make no sense to us. The method is elegant in its simplicity: We observe something that puzzles us. (We should all have the observational powers of Leonardo or Vermeer!) We predict what might be an explanation (i.e., a hypothesis). We undertake an experiment to confirm or refute that explanation. Eventually, the test of time (and examination by our colleagues) validates what we have put forth as the truth.

What an advance we would make as a species if all of us, from childhood on, applied the method to what we observe every day in our lives. Consider, even, the power it might bring to a child in a tormented home. Wouldn't it be a little less frightening and painful for such a child not only to observe the behavior of an addicted parent but also to query others as to what might fuel that addiction, so that the child could then draw the conclusion that he himself is not the cause of that parent's behavior?

Brian Greene, a Columbia University physics professor and author, recently wrote a marvelous op-ed piece in *The New York Times.* He notes that, absent the robust integration of science in our everyday lives, we cannot make rational decisions about any of the trials that condition our future. Science, he says, is a way of life—taking us from confusion to understanding with precision. It is as precious a human experience as is art or music.

All young children explore. They want to know what things are and how they work. However, unless they are applauded as explorers, they lose the urgency to comprehend what's around them, let alone gain an understanding of the universe and its origin, how the brain gives rise to the mind, evolution, and so forth. The brain is most plastic in the early years; that is the time to make scientists of us all. How to sustain our young explorers as practitioners of *the scientific method* throughout the entirety of their lives seems to me to be the greatest challenge to the human condition and to our nation as we rebuild it.

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



Devoted to noteworthy happenings

at the medical school

Super SEALs

During training, American soldiers and sailors might run 10 miles at a clip. They almost never do that during combat. Then they're more likely to sprint in short bursts, climb over obstacles—the kinds of things a football player might do. The University of Pittsburgh's Scott Lephart wondered why the U.S. Navy hadn't considered using the techniques of sports science to train its troops. He recently convinced the military that its special forces should have customized workouts and nutrition plans to maximize performance, prevent injury, and save lives.

Lephart—a PhD who serves as chair of sports medicine and nutrition in Pitt's School of Health and Rehabilitation Sciences, director of the Neuromuscular Research Laboratory at the UPMC Center for Sports Medicine, and associate professor of orthopaedic surgery—runs the new Human Performance Research Laboratory in the SEAL compound in Little Creek, Va. He's using biomechanical analysis to study the physical demands placed on SEALs so they can train like SEALs rather than, say, long-distance runners.

—Katy Rank Lev



U.S. Navy SEALs will train with help from Pitt.

ROBERT BENSON/GETTY IMAGES

FOOTNOTE

Sex, drugs, and rock 'n roll? Try, "Sex and drugs and rock 'n roll, and country, and R&B, and rap, and so on."

Pitt's Brian Primack, an MD assistant professor of medicine and pediatrics, has found that teenage Americans hear about 30,000 references to drugs, alcohol, and tobacco in music annually. Those references are often associated with sex, partying, and general good times. All popular genres were included in the study.

AN ELUSIVE BUG

JoAnne Flynn, a University of Pittsburgh PhD professor of microbiology and molecular genetics, says the greatest challenges facing tuberculosis researchers are the elusiveness of the tuberculosis bacterium and the related puzzle of knowing when treatment has worked.

"In some cases, the drugs take six months to work; in other cases, two months," she says. "By knowing what's happening in a person with tuberculosis, we may be able to shorten therapy, find better combinations of drugs, and reduce the effort it takes to cure the disease."

Equipped with $11.4 million from the Bill & Melinda Gates Foundation, Flynn and others at Pitt's Center for Vaccine Research hope to arrive at a better understanding of what makes TB treatments work. They also plan to develop imaging techniques to better monitor the progression of the disease and its treatment. *—Joe Miksch*



CAMI MESA

A&Q

Rethinking "The Change"

Hot flashes. Insomnia. Night sweats. The litany that marks the end of a woman's childbearing years can spark dread. Yet that need not be so, says Judith Balk (shown above), University of Pittsburgh assistant research professor of obstetrics, gynecology, and reproductive sciences. The yoga instructor, acupuncturist, and staff physician at the Women's Midlife Health Center at Magee-Womens Hospital of UPMC describes her vision for the transformation of attitudes toward menopause.

On youth culture

In some cultures, people look forward to menopause because it's the end of menstruation and the beginning of wisdom. Here, we're youth obsessed, and we look at it as the end of youthfulness.

There are so many books and Internet sites that sell hormones as a fountain of youth, women almost feel like if they're not doing [hormone replacement], there's something wrong with them.

On how doctors approach menopause

There are two competing theories: One is that our ideal state is having the hormones of a 20-year-old. When we hit menopause and our ovaries don't work like they did when we were 20, we take estrogen. That's medicalizing—an emphasis on treating.

Is that the ideal state? What we should be mimicking? Or is it the ideal state when we don't have to be slaves to our menstrual cycles, when we can focus on becoming the wise woman?

The second theory is that women do not need estrogen to feel well and be healthy and that the reason we have so much estrogen earlier in our lives is that we need it to reproduce.

Ideally, the focus [as women age] will be on wellness and prevention of disease. And I don't mean prevention of menopause, which is a natural part of life, but some of the conditions like hot flashes, insomnia, osteoporosis, heart disease—conditions we know increase as we get older.

Her question for us

Menopause is a time of life when people say, "I've got to get my act together." This is a group of motivated women who want to improve their health. How do we capitalize on this transitional time to help them do that? *—Interview by Sharon Tregaskis*

Faculty Snapshots

The American Cancer Society has named Jennifer Rubin Grandis (MD '87, Res '93) one of its three new clinical research professors. The honor carries with it a five-year, $400,000 grant. Grandis is a University of Pittsburgh professor of otolaryngology and pharmacology. She studies genetic abnormalities associated with head and neck squamous cell carcinoma. According to *Nature*, she tied for 11th for the most National Institutes of Health grants received by an investigator last year. Her eight grants total $3.7 million.



Grandis

Hans-Christoph Pape develops management techniques for doctors to treat orthopaedic injuries of trauma patients. The American Academy of Orthopaedic Surgeons recognized his contributions with the Kappa Delta Award, its highest honor. Pape, an MD associate professor of orthopaedic surgery, is the fourth Pitt surgeon to win the award in the past five years.



Pape

David Geller serves as president-elect of the Society of University Surgeons. The MD is the Richard L. Simmons Professor of Surgery at Pitt and codirector of the UPMC Liver Cancer Center. Several other Pitt surgeons have presided over the organization in recent history.



Niedernhofer

Geller also is one of three Pitt faculty members newly elected to the American Society for Clinical Investigation, which recognizes physician-scientists who have done innovative work before reaching age 45. Robert Ferris, an MD/PhD associate professor of otolaryngology and immunology, and Laura Niedernhofer, MD/PhD assistant professor of microbiology and molecular genetics, also are now card-carrying ASCI members.



Lakkis

The Association of American Physicians (AAP) recently announced its new members for 2008, including three Pitt profs: Ronald Herberman, an MD who is the Hillman Professor of Oncology, professor of medicine and pathology, and director of the University of Pittsburgh Cancer Institute; Jay Kolls, an MD, the Niels K. Jerne Professor of Pediatrics and Immunology, and chief of the school's Division of Pediatric Pulmonology; and Fadi Lakkis, an MD, the Frank and Athena Sarris Professor of Transplantation Biology, a professor of surgery and immunology, and scientific director of the Thomas E. Starzl Transplantation Institute. *—JM*

Orthopaedics is Women's Work

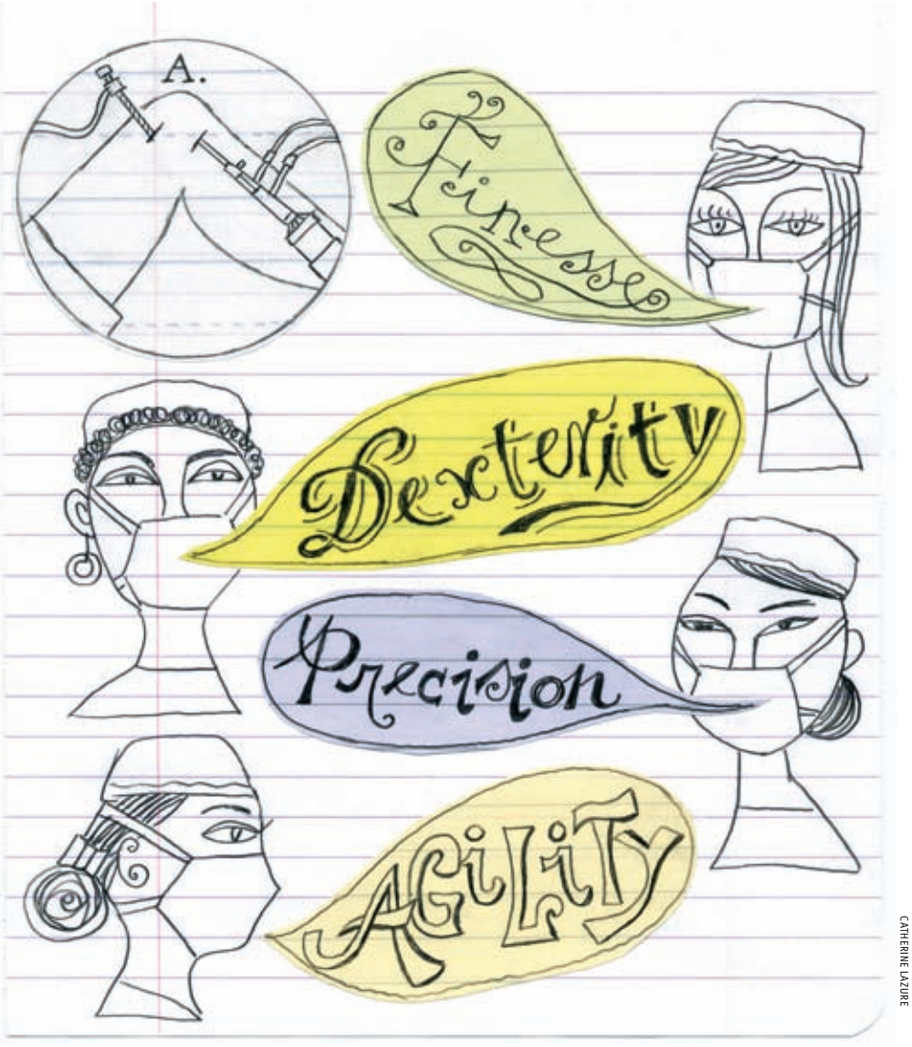
The percentage of women graduating from American medical schools increased from 8 in 1970 to 43 in 2001. The percentage of women filling orthopaedic residency posts, according to a comprehensive study published in 2003, rose from .6 to 9 during that time span. The perception of the strength required for the job may have kept some women from pursuing such training (and kept some men from encouraging their female colleagues to do so).

Things are changing. Especially in the University of Pittsburgh's Department of Orthopaedic Surgery. Of the eight-member residency class accepted in 2008, says department chair Freddie Fu, five are women. And all five scored in the 99th percentile on their USMLE exams, Fu adds.

"Twenty percent of the people in our program are women," says Fu, including seven of the department's clinical faculty members. Having a significant female faculty presence, says Fu, helps attract highly qualified women residents.

Robin West, MD assistant professor of orthopaedic surgery, says that women are drawn to Pitt because of the environment Fu has created. "He loves children and is very supportive of family obligations," says West, a mother of two.

West predicts orthopaedics will continue to draw more women into the fold. "With arthroscopic surgery, finesse is more important than strength," she says. ***—JM***



CATHERINE LAZURE



RENEE ROSENSTEEL

GUNS 'N HOSES

Undoubtedly, there are less painful ways to raise money than this. Still, in February, 18 city police, firefighters, and paramedics donned boxing gloves, entered the squared circle, and duked it out in front of 250 people at the Hilton Pittsburgh for departmental bragging rights. (They also raised more than $12,000 to help build a program to screen city emergency workers at risk for heart disease.)

The screening program began in May. It was created by UPMC's Cardiovascular Institute, directed by Barry London, an MD/PhD who serves as Pitt's Harry S. Tack Professor of Medicine and chief of the Division of Cardiology. *—JM*

BRUSSELS SPROUTS AT PITT

The University of Pittsburgh is now a repository for archival material the European Union has accumulated since its formation in the 1950s. This is the most complete collection of the material anywhere, though constituent elements can be found in Europe, according to Phil Wilkin, the University's curator for the collection. The materials consume 3,400 feet of shelf space and 300 feet of microfiche.

Jonathon Erlen, history of medicine librarian for the Health Science Library System at the University, says the archive is a boon for Pitt med students and faculty.

Erlen notes that the collection includes documents on the progression of HIV/AIDS in Europe and Africa, health policy material in fields ranging from maternal health to immigrant health, five decades of demographic data, and medical research on myriad topics.

"A nearly endless supply of material for our students doing their scholarly projects," he says. *—JM*



COURTESY ROBERT WAGNER

FALCON FYSICALS

Pediatricians may face some pretty uncooperative tykes in the exam room, but at least they don't have talons.

Robert Wagner, chief of surgical veterinary services at Pitt, faces frenetic raptor offspring each year when he performs annual physicals for peregrine falcon chicks born atop the Cathedral of Learning. The baby birds manage to endure throat and rectal swabs, avian phlebotomy, and a chilly stethoscope on their chests before they're cleared for takeoff. *— Hayley Grgurich*

Name Dropping

The School of Medicine is home to its share of scientific superstars, but on Oct. 2 and 3 it will welcome the following standouts from out of town as part of Science 2008, its annual celebration of research in medicine, engineering, computation, and basic science.

The University of California, Berkeley's Randy Schekman, PhD professor of cell and developmental biology and Howard Hughes Medical Institute investigator, will deliver the Dickson Prize in Medicine Lecture. Schekman's lab focuses on the processes of membrane assembly, vesicular transport, and membrane fusion among organelles of the secretory pathway. He has received the Eli Lilly and Company Research Award in microbiology, the Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Science, the Gairdner International Award, and the Albert Lasker Award for Basic Medical Research.

Peter Walter of the University of California, San Francisco, will give the Mellon Lecture. Walter, a PhD, is professor and chair of UCSF's biochemistry and biophysics department. He's also a Howard Hughes Medical Institute investigator. Walter studies the endoplasmic reticulum (ER). The ER is a gateway for proteins leaving cells, keeping misfolded proteins in its grasp rather than letting them run amok. ER malfunctions are thought to contribute to the progression of diseases such as cancer, diabetes, cystic fibrosis, and vascular and neurodegenerative conditions. Walter also has won the Searle Scholar Award, Eli Lilly Award in Biological Chemistry, Passano Award, Alfred P. Sloan Jr. Prize, and the Wiley Prize in Biomedical Sciences.

Marcus Raichle is this year's Klaus Hofmann Lecturer. An MD, he is a professor of radiology, neurology, neurobiology, and biomedical engineering at Washington University in St. Louis. Raichle has helped lead advances in the development and use of positron emission tomography and functional magnetic resonance imaging to study the living brain. His work resulted in the first integrated strategy for the design, execution, and interpretation of functional brain images. He is a member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences, as well as a fellow of the American Association for the Advancement of Science. ***—JM***



EXPERT WEAVES

Paul Bigeleisen trod a colorful path on his way to the anesthesiology department at the University of Pittsburgh.

As an undergraduate at Oberlin College in Ohio, Bigeleisen studied physics and built electronic violins. At the University of California, Berkeley, he embarked upon a graduate degree in theoretical physics. But then he injured his neck wrestling and, upon recuperating, opted to go to the medical school at the University of California, Davis. "A lot of the physics work seemed esoteric and lonely," he says. He trained as an anesthesiologist, entered a private practice, started a pharmaceutical software company, sold the company, and, following the lead of his grandmother and mother, began to design rugs. Eventually his rugs were sold internationally.

(Bigeleisen was inspired to design the crocodile rug shown above because the animal is a symbol of strength among African people who live along rivers—"though the indigenous people of these regions don't make woven rugs," he notes.)

Bigeleisen left private practice for university life. Then the rigors of academic medicine at the University of Rochester demanded that he abandon his rugs. But Bigeleisen could not abandon creativity. He began to study three-dimensional animation and, with his medical knowledge and the help of students, designed a virtual reality simulation to teach physicians the anatomy of the peripheral nervous system and how to perform ultrasound-guided nerve blocks. In 2004, the software won recognition in a visualization contest sponsored by the National Science Foundation and the journal *Science*.

The nerve block simulator is nearly ready for production.

In 2005, Bigeleisen arrived at Pitt, where he started an artificial intelligence lab in the Department of Anesthesiology. The Peter M. Winter Institute for Simulation Education and Research then asked him to create a virtual reality trainer for the airway, which the institute is testing.

—Joe Miksch

—Photo by Renee Rosensteel

Explorations and revelations taking place in the medical school



BETTMANN/CORBIS

It comes too late for Steve Austin, but the bionic knee brace could be part of the next generation of neuroprosthetics.

YOUR BODY, YOUR JUICE

HUMANS AS A POWER SOURCE

BY REID R. FRAZIER

Douglas Weber, a PhD assistant professor in the University of Pittsburgh's Department of Physical Medicine and Rehabilitation, is a biomedical engineer interested in neuroprosthetics, which may explain why he has a squeeze toy shaped like a human brain lying on his desk.

Weber, a self-described "gadgets guy," looks for something to show how his bionic knee brace, known as a biomechanical energy harvester, generates electricity based on the same principles as a Toyota Prius. Lacking anything that looks like a car, Weber grabs the squishy brain instead.

"That linear motion of a car carries a bunch of energy with it," says Weber, "driving" the squeeze toy down a straightaway on his bookshelf. "To slow that vehicle down, you have to get rid of that kinetic energy," he adds, then parks the little gray brain near the end of the shelf.

In a normal car, the kinetic energy of a car's motion dissipates into the brake pads, in the form of heat created by friction. Hybrid cars use that energy to spin a turbine, generating electricity.

Weber, who holds a secondary appointment in Pitt's Department of Bioengineering, helped create a device that does essentially the same thing with the human leg. After a 10-minute walk, the device generates enough juice to power a cell phone for a half-hour.

"All we're doing is we're taking energy from one form, and we're converting it to another," says Weber.

Instead of brake pads, the harvester uses the hamstrings as its unwitting power source. The hammies, it turns out, act a lot like brake pads when we walk. They slow the leg down, just as it straightens out at heel strike. (Otherwise, the knee would hyperextend with every step.)

The device Weber and his collaborators created offers resistance on the knee when it "brakes." The resistance turns gears and a motor, which, in turn, generate electricity. The brace provides resistance only at the moment when the leg is trying to slow itself down. If "turned on" during the entire step, the harvester would feel like a shackle.

"The elegance of the design is being able to harvest energy without the metabolic cost, so the person doesn't feel it," says Yad Garcha, the CEO of Bionic Power of Vancouver, British Columbia, which is marketing the brace. (The company's motto: "You're the Juice.")

"A lot of the device was built over beers at Doug's kitchen table," says Max Donelan, a collaborator of Weber's who is now an assistant professor of kinesiology at Simon Fraser University in Burnaby, British Columbia.

Weber and Donelan were both postdoctoral fellows at Edmonton's University of Alberta in 2002. Weber worked in the Centre for Neuroscience, studying ways to record brain signals for use in neuroprosthetics. Donelan, a physiologist, approached Weber about a question he had been kicking around: Could a knee brace generate electricity?

Weber headed to a local hobby shop to pick up gear sets and electric motors normally used in remote-control cars. The harvester was later born in his Edmonton home.

Weber and Donelan affixed the gears and motor to an orthopaedic knee brace with screws, tape, anything they could find. The result was more *MacGyver* than *The Six Million Dollar Man*, Weber says. (For the record, Weber was "absolutely" a fan of Lee Majors' character Steve Austin when he was growing up in the '70s.)

"It wasn't chewing gum and duct tape, but it really wasn't far from it," he notes.

The pair took the clunky brace and tested it in Donelan's lab. When they registered 1 watt of electricity pulsing out of the brace with every stride, "We knew we had something," says Weber. A few years later, they had a prototype, and in February, they published test results in *Science*.

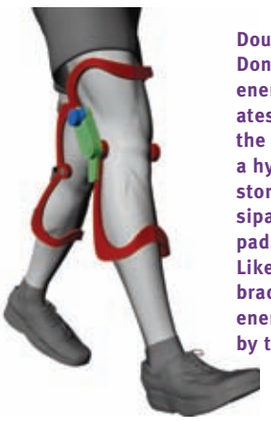
The first market for the device will be the military, whose forward-most personnel lug upwards of 30 pounds of batteries for various navigation, night vision, and communications equipment. Bionic Power will ship a batch of energy harvesters to the Canadian military next year.

Hikers and first responders are other potential users.

Weber hopes the device will dovetail with his research into the next generation of neuroprosthetics. Bionic sensors and motors currently in development require power.

His lab is researching ways to "tell" the brain about a limb's position, speed, and contact with objects.

"We're trying to send signals to the brain to create sensations of touch and limb position for artificial limbs, enabling amputees to literally feel the prosthesis as if it were their native limb," Weber says.



Douglas Weber and Max Donelan's biomechanical energy harvester generates electricity using the same principles as a hybrid car. A hybrid stores rather than dissipates energy into brake pads when it slows down. Likewise, this bionic knee brace harvests the kinetic energy normally absorbed by the hamstrings.

His research group is one of the first to test this somasensory technology. (*Soma* is Greek for "body.")

Donelan says of his friend and collaborator, "The way Doug thinks, the place where the person ends and the machine begins becomes kind of a gray area." ■

COURTESY BIONIC POWER

SHOCK TREATMENT

A NEW USE FOR OLD PROTEINS

BY CAROLE BASS



JOSHUA FRANZOS

Robert Binder is exploring the use of proteins known to protect cells from heat to instead protect us from cancer.

If Robert Binder were in advertising, his first assignment would be a new branding campaign for his pet subject: heat-shock proteins.

But Binder, a PhD assistant professor of immunology at the University of Pittsburgh, spends his days in the lab, not on Madison Avenue. So he is spared the task of devising slogans like, "Heat-Shock Proteins: They're not just for heat shock anymore." Instead, Binder can devote himself to understanding what these ubiquitous proteins do and how they do it.

Sure, HSPs protect cells against damage from heat and other stresses. But they appear to do even more—like fight cancer.

Binder is one of a growing number of researchers attempting to develop cancer vaccines.

Conventional cancer therapies typically poison healthy dividing cells along with cancerous ones. Binder and his colleagues envision using patients' immune systems to shrink tumors while sparing healthy cells. The trick is getting the immune system to recognize a cancer as an undesirable.

Like conventional vaccines, cancer vaccines use a tiny bit of the target for an antigen, which stimulates an immune response to the tumor. Binder's lab—and recent clinical trials building on his work—creates personalized vaccines by using antigens derived from heat-shock proteins in individual tumors.

Russia has approved selected use of such a therapy for kidney cancer—the first such sanction anywhere for a therapeutic cancer vaccine.

"These proteins are very abundant, and they're present in all cells," Binder says. And though HSPs are named for their first-discovered ability, protecting against heat damage, "there's no reason they should be limited to one function," he adds.

In fact, in 1986, a team led by the University of Connecticut's Pramod Srivastava discovered that heat-shock proteins can trigger a powerful immune response. Binder did his graduate work with Srivastava at Connecticut, delving into the question of how HSPs work.

Srivastava, an immunologist, calls his former student "a superb experimentalist."

Binder discovered that a protein known as CD91 is a receptor for heat-shock proteins. He now routinely creates cancer vaccines by purifying HSPs from a mouse tumor that binds to CD91 on the surface of specialized immune cells. The HSP is able then to get inside the cell and kick the immune system into gear.

"In mice, it works across the board," Binder says. "We've used over 15 different kinds of tumors."

When he vaccinates a healthy mouse, then injects tumor cells, the mouse stays cancer free. When he vaccinates a mouse that already has cancer, "the tumors shrink but they don't go away. But when we surgically remove the primary tumor, we're able to treat the metastatic disease," Binder reports.

But does the therapy work in people?

Binder experimented with the vaccine in mice for 10 years. Then Srivastava and colleagues—including John Kirkwood, director of the melanoma program in Pitt's Division of Hematology/Oncology—began clinical trials in human cancer patients. One study, a phase III trial involving 322 people with advanced melanoma, was published in February in the *Journal of Clinical Oncology*. (The vaccine goes by the trade name Oncophage. Antigenics, a company that Srivastava cofounded and of which he owns a small share, makes Oncophage and funded the clinical trials.)

"When you look at patients who actually got the vaccine, then you see that patients who had diseases of the lymph nodes, skin, or lungs did much better," Srivastava says.

Specifically, the median survival—the point at which half the patients had died—was about 900 days for the vaccinated group, compared to less than 400 days for the control patients, who received chemotherapy.

Another recent phase III trial involved 728 people with kidney cancer. In the July 5 issue of *The Lancet*, Srivastava and his coauthors reported no overall difference between patients who received Oncophage and those who didn't. But they are further exploring "possible improvements in recurrence-free survival in patients with early-stage disease."

After that trial, which was funded by Antigenics, the treatment got the okay from the Russian government for use in the treatment of kidney cancer patients at intermediate risk for disease recurrence.

Binder now plans to investigate how heat-shock proteins might fuel vaccines for infectious diseases as well as for autoimmune disorders. ■



COURTESY RIMED

Construction of the Biomedical Research and Biotechnology Center of Sicily is slated to begin next year.

DON'T KNOW MUCH ABOUT SICILY

A PARTNERSHIP WILL PUT REGION ON SCIENTIFIC MAP | BY ELAINE VITONE

Admit to Sicilian Filippo Pullara that you don't know much about his native Palermo, Italy, and he'll sigh with pity. It's a blue-skied paradise, he'll tell you—a place where anything below 50 degrees Fahrenheit is considered a cold day.

"Palermo is perfect," he says.

The catch, however, is that for almost anyone outside of the tourism and hospitality industries—and especially for a young physicist like Pullara—jobs are hard to come by.

Fortunately, that's about to change.

Pullara is one of six young Italian scientists who arrived at the University of Pittsburgh this summer as the first recipients of a new annually awarded postdoctoral fellowship. (Three more fellows will arrive by year's end, and 12 per year are expected thereafter.) The scientists' living stipends and research are funded by RiMED, a foundation created in 2006 to receive government and other funds to build the Biomedical Research and Biotechnology Center of Sicily.

Construction of the $398 million center, which will be located in Carini, a quick drive from Palermo, is slated to begin next year. Planners expect it to be completed in 2011. The center will be managed by UPMC. Arthur S. Levine, Pitt's senior vice chancellor for the health sciences and dean of the School of Medicine, serves as RiMED's scientific director.

While the design plans are in the works, the office of Academic Career Development for the Health Sciences is grooming the RiMED fellows to staff it, supplementing their research efforts here at Pitt with training in ethics as well as communication, presentation, and management skills.

Instead of applying for positions in specific laboratories, as postdocs generally do, RiMED fellows spend the first month at Pitt rotating through several labs that match their interests, looking for the best fit. When Pullara completed his rotations, he chose to work in the lab of Guillermo Calero, PhD assistant professor of structural biology. Pullara is putting his physics background to use studying protein interaction in DNA and RNA repair—and loving every moment of it.

"It's more than just a job—it's a passion," says Pullara.

"In the evenings we often stop working just for a quick dinner. Then we come back to the lab, saying, 'Ah, I have an idea!'"

RiMED's momentum comes on the heels of the 10th birthday of ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione), a hospital in Palermo that provides transplants and other specialized services. ISMETT was founded by UPMC and the Italian government in 1997. The hospital is now at full capacity—70 beds—and performs 150 transplants per year, with some of the highest transplant survival rates in all of Europe.

ISMETT filled a dire need for Sicilian patients. Prior to its opening, the region had no transplant facility of its own and was forced to pay high costs to send patients abroad for such surgery.

"Our public-private partnership model was so successful that the government wanted to use it to start a research center, as well," says Bruno Gridelli, medical and scientific director of ISMETT and UPMC International. Gridelli also is a professor of surgery at Pitt.

In its short history, ISMETT has amassed an abundance of gadgetry that makes this small hospital seem anything but. Case in point: its telepathology lab.

"We're a small hospital, so we don't have a full staff of pathologists covering 24-7. In fact, we only have *one*!" Gridelli says. "But through this connection, we can count on the competence of pathologists in Pittsburgh and their round-the-clock availability."

ISMETT's 255-square-meter regenerative-medicine lab, dubbed the Cell Factory, was funded by a €5.3 million grant from Italy's Ministry of Technological Innovation in 2005. Last year, ISMETT added Web cameras and specialized microscopes, turning the site into a rare breed of laboratory known as a *collaboratory*.

"Many of the instruments can be connected to other labs around the world," says Gridelli.

"It's a great tool for training and for quality control. … We also have microscopes that can be controlled from any place that has a Web connection."

If the runaway success of ISMETT is any indication, Pullara and the other RiMED fellows can look forward to one day working in a researcher's paradise. In the meantime, they are ever eager to hear the latest on the planning stages of the building.

"This is a great opportunity for me, for Sicily, and for the region," Pullara says. "Building this center is a huge opportunity for research in general." ■

SINGLE CANCER CELL SEEKS MULTIPLE PARTNERS.

AMBITIOUS, HYPER-ACTIVE, UNSTABLE MUTANT WITH NOMADIC TENDENCIES. GOOD AT FITTING IN (FOR A WHILE). INTERESTED IN HAVING LOTS OF OFFSPRING.

It might be helpful to think of cancer as a ne'er-do-well among us. The one your doctor warned you about.

INSIGHT INTO THE NATURE OF A KILLER

BY JOE MIKSCH AND CHUCK STARESINIC

BAD COMPANY

In 1971, President Richard Nixon declared war on cancer.

This nation has spent billions of dollars to contain the enemy since that day. Cancer is expected to cause about 565,650 deaths in the United States in 2008. On the plus side of the ledger, effective treatments and even cures have been developed for leukemia, prostate and breast cancers, and other forms of the disease. We have learned much. And we have learned that much more escapes our grasp.

Ronald Herberman—director of the University of Pittsburgh Cancer Institute (UPCI), associate vice chancellor for cancer research, Hillman Professor of Oncology, and professor of medicine at the University of Pittsburgh School of Medicine—was at the National Cancer Institute when war was declared.

Herberman says the strategists of the War on Cancer envisioned a series of concentric circles, with the outside ring representing the state of knowledge about cancer at the time. If they could solve the first ring, the second, the third, then they'd be homing in on the enemy and its mysteries— and hit the bull's eye.

No one has hit the bull's eye. It's likely, considering the growing number of known variables associated with the onset and progression of cancer, that there isn't just one to aim for.

TYPOGRAPHY | ELENA GIALAMAS CERRI

Cancer is more complex and cunning than that. Today, scientists have gleaned a much better sense of its nature—which should translate to better care for patients. Rather than thinking of cancer as a foreign enemy on a battlefield, it's probably more helpful to think of cancer as a ne'er-do-well among us. The one your doctor warned you about.

Cancer is a bit like a predatory character in a thriller. Imagine someone who, lacking any virtue, tries to seduce others to let him hang around. He adds nothing of value and yet will do anything—hide, temporarily change his character, even behave like a bully—for some companionship. But if he succeeds, he'll end up corrupting everyone around him. The more he gets to know you, the more dangerous he becomes. Not the kind of character you want to get involved with.

Pitt researchers give us insight into this bad seed and how we might take advantage of cancer's own nature to do away with it.

FORMATIVE INFLUENCES

Before the War on Cancer, there was the Special Virus Cancer Program, which was launched by the NCI (National Cancer Institute) in 1964. The goals of this well-funded, high-profile program were to isolate human cancer viruses and develop a human cancer vaccine or antiviral magic bullet. As it turns out, however, viruses aren't behind most human cancers.

Why then, decades later, is molecular virology such an integral part of cancer research? At UPCI, it is one of four basic research programs, housing some 28 scientists. For virus hunters Patrick Moore, who leads the program, and Yuan Chang, his wife and close collaborator, it all goes back to the virus they discovered in 1993. (Seven viral precursors to human cancer have been discovered since the 1970s—two by Chang and Moore, both MDs who are Pitt professors of pathology and of microbiology and molecular genetics, respectively.) Moore has been known to say of this virus—KSHV, or Kaposi's sarcoma herpes virus—that it looks like it was made by a demented tumor biologist, because it contains all the human genes you would want to make a tumor. Over eons of infecting human cells and hijacking our cellular machinery, KSHV has pirated human genes related to cell-cycle control, cell proliferation, programmed cell death, and immune system modulation.

Cancer viruses like KSHV and the polyomavirus responsible for Merkel cell carcinoma, which Chang and Moore revealed on the pages of *Science* in 2008, can point scientists toward the human genes and, therefore, the cellular mechanisms involved in cancer progression.

This way, researchers are learning the biology behind cancer's deviousness.

TURN-ONS AND TURNOFFS

Sometimes, relationships can go too fast and spiral out of control. Other times, it seems like the parking brake is always engaged, and you're dragging a heavy load. Oncogenes and tumor-suppressor genes are the accelerators and brakes of cancer.

To put the brakes on cancer, you'll want to know about a protein called p53. Its job is twofold. When things are going well genetically, p53 keeps cell growth in check by helping kill cells that are heading out of control; it initiates apoptosis, or programmed cell death. And when cells are functioning normally, the protein works to prevent apoptosis, permitting a cell to live out its normal life cycle.

The gene that produces p53 is a tumor suppressor gene, meaning its regular functioning helps curtail cancer. When the gene that codes for p53 is inactive or malfunctions, cancer results. About half of all cancers are related to disruption of the p53 gene.

Conversely, genes that when turned on become hyperactive and produce proteins that encourage cellular overproliferation are called oncogenes.

So in the case of p53, cancer results when a gene fails to do its job right. With oncogenes, it's a matter of the gene doing its job too well.

"To put it in a user-friendly way, the formation of cancer and the progression of cancer are probably the end result of an imbalance between the regulation and deregulation of the accelerator, which would be the oncogene, and the brakes, which would be the tumor suppressor gene," says Jennifer Rubin Grandis (MD '87, Res '93), a professor of otolaryngology and pharmacology in the School of Medicine.

Grandis' colleague Robert Ferris says that 60 to 70 percent of head and neck cancers are related to a mutation in the p53 pathway. The human papillomavirus (HPV) can cause such mutations. An HPV viral protein called E6 chops up and degrades the p53 gene, rendering it unable to produce the tumor-suppressing protein. Smoking, says the MD/PhD associate professor of otolaryngology and immunology, can also disrupt p53.

Oncogenes, reports Grandis, represent a more complex problem. In most human cancers, she says, there is no discrete mutation of the oncogene. Instead, there's a higher level of activity and an increased production of problematic proteins. The causes of this increased activity are manifold, among them: the swapping of unrelated chromosomes on genes, exposure to carcinogens, and viruses.

Ferris says that understanding the mechanisms that account for these errors is key to developing new treatments.

UNSTABLE MABEL

We've all encountered a few unstable characters. As a general rule, they are bad news, and that is certainly true of cancer. Genetic instability is something all cancers have in common, regardless of whether that instability is attributed to a virus, cigarette smoke, unfortunate inheritance, environmental exposure to carcinogens, ultraviolet light, or inexplicable bad luck. Whether cancer is in the blood, the brain, or the bladder, a population of cells in the body has lost its way and begun to proliferate out of control to the point where it interferes with normal body functions.

There are myriad ways for the genome to become unstable. DNA constantly breaks down. Cell division gone awry can leave a cell with extra copies of genes, including genes responsible for proliferation. Another cell may be incomplete, perhaps lacking genes that limit proliferation.

Living things, through millions of years of evolution, have evolved a whole host of genes associated with maintaining genomic integrity. Scientists are now attempting to identify these genes and understand how they are involved in cancer.

A tumor, by definition, is all of those cells that are genetically unstable in the worst possible ways—able to both escape destruction and proliferate.

SURVIVAL OF THE FOULEST

Being unstable has its advantages. Genetic instability allows a tumor to evolve, just like random mutations have allowed living organisms to evolve through the ages.

Cancer cells experience natural selection. Those that don't proliferate aren't successful. Same goes for those that are so unstable they self-destruct. Some are killed by the immune system or chemotherapy. The survivors are a bad bunch—they are able to evade the immune system, survive chemotherapy, and rapidly proliferate.

"The major limitation in the approach of immunology, but also in the approach of chemotherapy, is the ability of tumor cells to develop escape mechanisms because of genetic instability," says Soldano Ferrone, an MD/PhD Pitt professor of immunology who is an expert in molecules manufactured to turn the immune system against cancer. He and other Pitt immunologists are working on a two-pronged immunotherapy for melanoma as well as breast, head, and neck cancers. By combining antibodies with stimulation of the immune system's killer T cells, they believe they can counteract any escape mechanisms the cancer may evolve.

THE BAD SEED

Remember when you were a kid? Your parents may have told you that you could be anything when you grew up: president, CEO, firefighter, Pittsburgh Steeler.

Well, back before you were even a kid—when you were a teeny blastocyst—you were a mass of embryonic stem cells, which truly could become anything: lung tissue, heart tissue, bone, brain, or other. Even as a grown-up, other cells known as adult stem cells allow your body to replenish blood, skin, hair, muscle, gut …

Nice tricks. But not so nice when it comes to cancer. Pitt researcher Eric Lagasse seeks to understand the evil stem cells scientists believe lead to cancer. These are genetically unstable mutants that may be responsible for the spread and recurrence of cancer.

Lagasse, a PhD professor of pathology, notes that chemotherapy is often successful in shrinking tumors. Yet, cancer frequently returns. Chemotherapeutic agents target actively proliferating cells, but cancer stem cells evade the chemical onslaught. They only divide and proliferate when necessary and, therefore, seem immune to the usual run of cancer therapies.

Let's say a patient is treated for colon cancer. Surgery and chemo render that person free of any detectable cancer. Lagasse likens what happens next to when a person suffering from a bacterial infection quits her course of antibiotics as soon as she's feeling better.

"The problem (with cancer) is the short exposure to chemotherapy," Lagasse says. He explains that if you go any longer than three weeks, normal dividing cells and, eventually, the patient die. "But after several rounds of chemotherapy, you have a cancer that is incurable. You're left with a very strong, selected population of cancer stem cells that are very resistant and will kill the patient."

Vera Donnenberg, PhD assistant professor of surgery, says one of the major problems associated with killing cancer stem cells is they have taken on the guise of normal adult stem cells and can protect themselves by the same mechanisms healthy cells use. So, if you kill cancer stem cells, you kill normal cells.

"Vital organ functions cannot be disrupted for long without lethal consequences," she says. "It is not the death of normal tissue stem cells that kills the patient. It is the race between normal tissue repair and killing or injuring the tumor stem cells."

And these dodgy cancer stem cells live on to create new tumors and go to new places, colonizing other tissue.

Lagasse says much work must be done before a drug can be developed to target these cancer seeds while sparing adult stem cells and normal tissue.

"Drugs come at them. But because of their genetic instability, they can mutate so fast that they can survive," he says.

CON MAN

Cells that form tissue are kind of like the three musketeers. They're one for all and all for one as they stick together to be skin, or a heart, or a liver. Among the glues that hold cells in formation is a surface molecule called E-cadherin.

It makes sense to scientists that spreading cancer cells turn off the production of E-cadherin; otherwise, the cells wouldn't be able to grow unchecked or make their way out of their orderly home in healthy tissue.

Pitt's Alan Wells (an MD/DMSc, the Thomas J. Gill III Professor of Pathology, and vice chair of the Department of Pathology) and his former student Christopher Shepard (PhD '07) recently discovered that cancer cells don't cancel E-cadherin production permanently, as had been thought. After a cancer cell travels from its original home, it can insinuate itself into healthy tissue, where it resumes E-cadherin production. This allows the cancer cell to appear to be normal when it joins healthy tissue.

Imagine a cancer cell migrating from a prostate tumor to the liver. Once it resumes E-cadherin production and blends in with its neighbors, it relies upon survival signals from surrounding liver cells and is able to evade chemotherapy, which does not kill normal, nondividing cells.

Wells' lab is continuing its investigation into the signaling process that permits the resumption of E-cadherin production. He also hopes to discover the catalyst that causes cancer cells that have weaseled their way into healthy tissue to begin to reproduce unchecked and create a new tumor.

Therapeutically, says Shepard, now a visiting scientist at the Massachusetts Institute of Technology, this cellular trickery presents a problem. Because E-cadherin is vital to normal cellular function, slowing down or stopping its production could disrupt all manner of physiological processes in normal cells.

"The targeting mechanism would have to be very intricate," Shepard says.

CAN IT EVER BE FIXED UP?

When it comes to cancer, the answer is ... maybe.

DNA damage occurs constantly, whether from ultraviolet light or the byproducts of metabolizing your lunch. It doesn't usually lead to cancer, because your beleaguered cells are capable of doing all kinds of things when the genome goes bad. Hundreds of genes are devoted to DNA damage repair. Each is responsible for a different aspect of repairing the long, twisting ladders of microscopic DNA inside each cell. Some proteins "climb" the ladder and flag the errors. Some nucleases excise faulty base pairs, and others break the interstrand crosslinks that kink the ladder.

Laura Niedernhofer, an MD/PhD and Pitt assistant professor of microbiology and molecular genetics, theorizes that some deficiencies in DNA repair can lead to cancer. In her lab, mice that are disabled in DNA repair succumb to rapid aging and death, but not cancer, if they suffer damage to both strands of the DNA ladder.

Mice with damage to a single strand live longer but get cancer.

"The cells won't die," she says, "but you're at a huge risk, then, of mutations being fixed into the genome, and that's what contributes to genomic instability and cancer."

In the lab, basic scientists have developed drugs to inhibit certain aspects of the DNA repair process. This allows them to tease apart the pathways and better understand what's happening, but these approaches are not yet used clinically. The NCI is encouraging investigators to get to the next step. This fall, Niedernhofer will take part in a special NCI workshop devoted to DNA repair as an "emerging translational field."

Theoretically, a doctor might increase DNA repair to protect cells from becoming genetically unstable, or she might down-regulate DNA repair in tumor cells so they are unable to survive the onslaught of chemotherapy. In other words, a tumor might get fixed up or fixed down.

A LITTLE CHEMISTRY

After biopsy, some tumors reveal a molecular signature that tells clinicians which chemotherapy treatments are most likely to work. Like insects that can read the molecular signatures of one another in the dark to determine so much—species, gender, health, availability for mating, status in the colony—scientists are rapidly learning to identify the endless organic molecules in existence, including those that are associated with specific cancers and stages of cancer.

A slew of researchers at UPCI are finding ways to use such biomarkers for early detection. For example, Anna Lokshin, a Pitt assistant professor of medicine in the hematology/oncology division, has developed a simple blood test that can reliably diagnose early-stage ovarian cancer in more than 97 percent of women with cancer who undergo it.

ENABLERS

A tumor doesn't exist in a vacuum. It needs help.

"The tumor is not there by itself," says Theresa Whiteside, a PhD professor of pathology, otolaryngology, and immunology at Pitt. Tumors have hosts—namely our bodies—and those hosts can be gracious to a fault.

It was once assumed that immune cells found on the tumor were there to fight the tumor. But evidence shows that some immune cells are actually recruited by the tumor and help it grow. Other cells in the immediate environment of the tumor are clearly not cancerous, but they help create new blood vessels to feed the tumor.

"We have already learned a great deal about the tumor microenvironment and how to explore it to benefit the host, not the tumor," says Whiteside.

With Pitt's Soldano Ferrone, she has developed a vaccine able to target a unique molecule that appears on head and neck tumor cells as well as on the normal cells building blood vessels to sustain it.

MARKED AND ESCORTED OUT

In the old days, the only vaccines around were those that turned the immune system against foreign invaders such as smallpox or polio viruses. A vaccine essentially showed the immune system a sample of the virus in killed or incapacitated form so that it would recognize the real deal if it ever showed up.

But cancer isn't a foreign invader. It's your own cells gone bad. To teach the immune system to target cancer, scientists must first identify molecules that distinguish cancer cells from normal cells. Even then, the markers might appear in some form on normal cells. The first clinical trial in the world of a synthetic peptide cancer vaccine—at Pitt in 1993—enrolled patients with very advanced cancer and poor prognoses. Regulators deemed the risk of a vaccine precipitating an immune attack against healthy tissue too great to include patients with better odds.

"The first patient was a stage-four breast cancer patient who had two pumps: one emptying liquid from her lungs and one emptying liquid from her abdomen," says Olivera Finn, professor and chair of the Department of Immunology at Pitt. "She had chest disease like you wouldn't believe. She was an absolutely end-stage cancer patient, and she died within a month of us starting the trial."

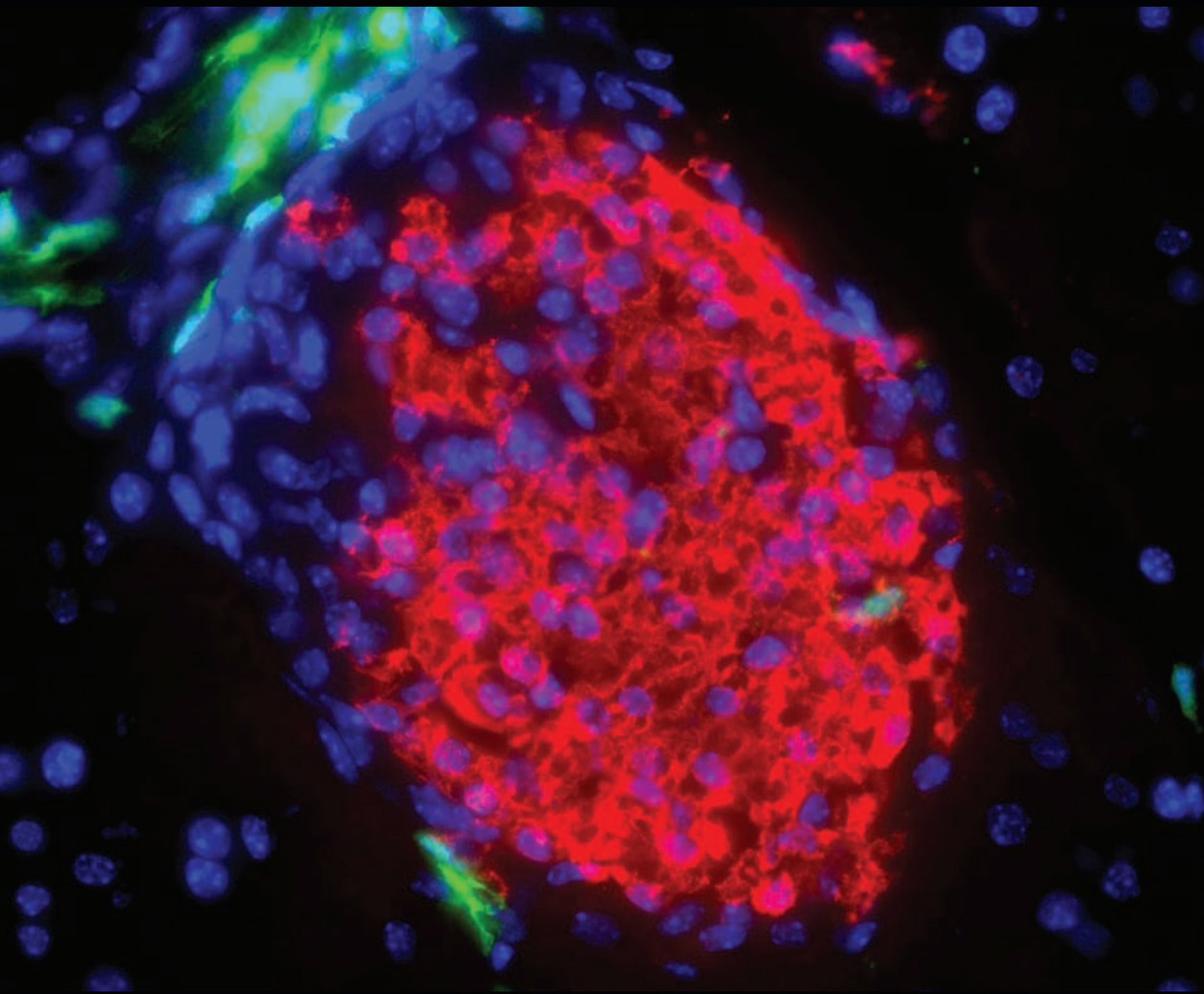
A lot has happened since then, and cancer immunotherapy is now more realistically expected to prevent cancer, prevent recurrence, or cure it in its early stages. For example, Pitt's John Kirkwood, professor and vice chair for clinical research in the Department of Medicine, developed the first adjuvant therapy for patients recovering from melanoma, a disease likely to recur. The interferon therapy stimulates the immune system's natural killer cells (see below) against melanoma. And Finn will initiate a vaccine trial this year against colon cancer.

DON'T YOU MESS AROUND WITH MY LITTLE SISTER

They prowl your body like paranoid and protective big brothers. And, by design, they don't like intruders. Dubbed natural killer (NK) cells, they were discovered in Ronald Herberman's laboratory at the National Cancer Institute in the early 1970s, before he established UPCI. For cancer researchers, NK cells were an exciting revelation.

To fight a virus, most immune cells need to ramp up the system first. But a tiny percentage of immune cells—the natural killers—are rapid responders, born ready to identify and destroy aberrant cells, including cancer cells.

Researchers are slowly learning about the complex chemical signals that activate NK cells. A successful treatment for bladder cancer, for example, has been found to owe some of its success to NK cells. Stem cells have been coaxed into becoming NK cells in the lab, and such customized cells may be introduced into cancer patients one day. ■



In type 1 diabetes, the body's immune cells mercilessly attack insulin-producing cells like the red cells shown in this image that are clumped together to form a pancreatic islet. University of Pittsburgh scientists have figured out how to disarm the attackers and could soon be the fathers of a cure.

A PROMISING TREATMENT FOR TYPE 1 DIABETES, IN THE LAST PLACE ANYONE WOULD EXPECT TO FIND IT | BY MELINDA WENNER

DIABETES TRIALS

It looks a lot like any other hospital room. There's a bed, sink, bench, and a closet overflowing with gloves and syringes. On the wall hangs a poster about diabetes and an advertisement for the University of Pittsburgh Medical Center, which, the poster reminds its readers, is the number one hospital system in the region. But in this room on the sixth floor of UPMC Montefiore, 14 people are changing history.

They're volunteers in a phase I clinical trial that, at first glance, looks like the worst idea ever: In an attempt to calm the overactive immune response that causes type 1 diabetes, doctors are injecting the volunteers with cells notorious for doing the exact opposite. In other words, the patients are being pumped full of something that would normally make them much, much sicker. But no one—not the volunteers, not their families, not the doctors—seems worried. In fact, everyone seems excited: They might just be testing the first diabetes cure.

TRUCCO M. "REGENERATION OF THE PANCREATIC BETA CELL." JOURNAL OF CLINICAL INVESTIGATION VOL. 115 NO. 1 © 2005. THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION.

A disease that plagues more than a million Americans, type 1 diabetes is no picnic. Sufferers must inject themselves with insulin daily just to stay alive, which means that 36-year-old Chad Shumaker, one of the volunteers in the Pitt trial, has given himself nearly 14,000 injections since he was first diagnosed 19 years ago.

"Giving yourself shots twice a day loses its appeal after the first few," he says.

What's more, later in life, Shumaker and others with diabetes are at a heightened risk of developing blindness, nerve damage, and heart disease. At its core, the illness (not to be confused with its more common cousin, type 2 diabetes) is a disease of the immune system, which, thanks to a combination of genetic and environmental triggers, mistakenly attacks and kills the cells in the pancreas responsible for producing the hormone insulin. Without insulin, the body cannot store sugar and fat for energy and will eventually fall into a coma.

Shumaker, who owns a garage-door company and has just built a new home in Monroeville, Pa., doesn't yet know whether he's being treated with the "real deal" experimental treatment or a placebo in this study that will determine the safety, but not the effectiveness, of the new approach. He's probably too old to get much benefit out of such a treatment anyway. It's likely that the illness has already killed off too many of his insulin-producing cells to make a full recovery possible. But he's not participating in the trial for himself, so he doesn't really mind.

"I've got two kids," he says—Merrick, 1, and Declan, 5. "If the disease passes on, I'd like to see them have a cure."

Although a cure might seem simple—stop the immune response already!—it has been anything but. Suppress general immunity, and patients suffer deadly infections. Replenish dead pancreatic cells with healthy ones, and the body mercilessly attacks them, too. To solve the problem, scientists must intervene in the attack without affecting other crucial immune functions, a feat many thought impossible. But with a plan to outsmart the very cells that do diabetes' dirty work, two Pitt doctors may soon prevail. Their approach has already cured mice of the disease. Soon, thanks to Shumaker and other volunteers, they'll know whether it can cure people, too.

Massimo Trucco and Nick Giannoukakis could not be more different. Trucco is the Hillman Professor of Pediatric Immunology and an MD professor of pediatrics, pathology, human genetics, and epidemiology at the University of Pittsburgh who heads the Division of Immunogenetics at Children's Hospital of Pittsburgh of UPMC. He is easily excited, has a guttural laugh that slips out frequently, and speaks with a strong Italian accent occasionally peppered with a "bravissimo!" Giannoukakis, who has a PhD in endocrine genetics and is an associate professor of pathology and immunology at Pitt, was raised in Montreal, speaks crisply and carefully, and emphasizes that science is less about achievements than about making careful choices.

The two do, however, have something important in common: Both like to tackle only the most difficult problems.

"When someone says, 'Oh, that doesn't work,' or, 'Oh, that's impossible,' I say, 'Okay, we have to do that,'" Trucco explains. Although scientists have been working on a cure for type 1 diabetes for decades, efforts have so far yielded little.

"It's easy to activate the immune system," Giannoukakis says. "You put yourself inside a cold or a hot room, and—guess what?—you activate your immune system." It's much, much harder to calm it. So the two doctors knew they had to give it a shot.

Type 1 diabetes is not a simple disease. First, an environmental trigger such as a viral infection causes insulin-producing beta cells in the pancreas to become inflamed. It doesn't take much—the cells are already "overworked factories," Giannoukakis says, chugging out insulin every time we swallow even a handful of M&Ms. When the beta cells become inflamed, they catch the eye of specialized immune cells called dendritic cells, whose job it is to patrol the body to look for problems, much like a police officer who patrols a neighborhood.

When the dendritic cells notice that all is not right in the pancreas, they assume the beta cells are the culprit—perhaps they are dangerous intruders. The dendritic cells then travel to the lymph nodes to summon backup from other immune cells, including T cells. As Giannoukakis puts it, the dendritic cells say, "Hey, you know what? You better go back to where I'm coming from because there's trouble over there."

That's when the genetic predisposition to type 1 diabetes comes into play. Normally, after the dendritic police instruct the T cells to attack (these are rough cops), the body performs a quick check to ensure that its T cells have not just been told to pummel something made by the body itself. People born with a genetic predisposition to diabetes, however, have slightly misshapen T cells, so they don't get the body's message that the beta cells are innocent, well-meaning guys. Soon enough, the T cells are sent off to work over the beta cells, which surrender and stop producing insulin. The person has developed type 1 diabetes, and the cycle continues indefinitely.

Trucco and Giannoukakis figured there had to be a way to intervene. Perhaps they could manipulate the body's police in a way that would prevent them from communicating with T cells. T cells become activated in two steps, both involving contact with proteins on the surface of dendritic cells. Without the second interaction, there will be no T-cell response. In fact, the T cells will self-destruct or become quiescent.

"I've got two kids. If the disease passes on, I'd like to see them have a cure."

Trucco and Giannoukakis took advantage of this loophole that nature provides, treating a patient's dendritic cells in the lab with short DNA sequences called antisense oligonucleotides, designed to down-regulate the levels of the proteins involved in that second interaction with T cells.

The two scientists went to work to devise their concoction. (Trucco thinks research isn't all that different from cooking: "The difference is, when you're cooking, you eat the result, while in the other case, you publish it.")

Here's what they came up with: Draw blood from one arm of the patient, pass it through a machine that separates out and retains all the progenitors of dendritic cells, and return the rest of the blood via the other arm. Then take the dendritic cell progenitors to a therapeutic lab at the University of Pittsburgh Cancer Institute, where collaborator Theresa Whiteside, Pitt professor of pathology, grows the dendritic cells in the presence of antisense oligonucleotides according to the Trucco/Giannoukakis recipe. Inject these cells back into the patient's abdomen, near the pancreas, where they replace or

take over the functions of their naturally occurring counterparts inside the pancreas.

The altered dendritic cells start redirecting immune cell traffic—including the T cells—which either leave the pancreas, become inactive, or die.

And because the dendritic cells are injected under the skin in an area that serves as a fast-track highway to the pancreatic precinct's police station, and do not stray far from there, the treatment doesn't affect the policing cells in the rest of the body, which are crucial for fighting infections.

Type 1 diabetes could, therefore, have a cure, if all goes well with the ongoing phase I safety trial in which Shumaker is participating—it began in July 2007—and subsequent trials. What's most ingenious (and, some might add, risky) about the Pitt approach is that it engineers dendritic cells to perform a task they've never been asked to do. Past dendritic cell treatments have always activated, rather than suppressed, the immune system to treat diseases like cancer. Obviously, an activating treatment in type 1 diabetics would be bad news—it would worsen the immune attack rather than alleviate it. But both doctors have faith that their cells will do the right thing.

At the moment, Trucco and Giannoukakis' approach is not ideal. The first step—when the blood is collected for the eventual generation of dendritic cells—requires patients to lie still for almost three hours. They'd like to offer patients something more convenient.

In 2002, Giannoukakis flew to Boston for the annual conference of the American Society of Gene Therapy. One of the talks caught his eye because it had to do with dendritic cells and microspheres—tiny balls, each about the size of a bacterium, that can be used to deliver drugs or engineered genes. The talk focused on using microspheres in cancer treatments, which wasn't exactly pertinent to his work. Still, Giannoukakis popped in.

The first two talks were irrelevant to Giannoukakis' interests. Yawn. But then the third speaker walked up to the podium. The scientist began his talk by comparing different formulations of these microspheres and remarked that one of them was neutral with regard to the immune system. Giannoukakis immediately perked up. Neutral microspheres? So the exterior of the microspheres did not contain chemicals that would startle the dendritic cells into activating. Maybe the little balls could deliver the antisense oligonucleotides directly into the pancreas; then, the patrolling dendritic cells could ingest the oligonucleotides inside the patient and achieve the same result as the treatment requiring patients to stay put for three hours. Giannoukakis ran back to his hotel room to e-mail the company that made the neutral microspheres, Epic Therapeutics, now a subsidiary of Baxter Healthcare Corporation. Less than 48 hours later, he met the company's chief technology officer, Larry Brown.

Brown, who happens to have type 1 diabetes, was eager to help. Brown and Giannoukakis discussed how to marry Pitt's oligonucleotides with Epic's technology. Then Brown went back to his lab and built what are known as PROMAXX technology microspheres that would deliver the payload Giannoukakis needed. When Giannoukakis added the microspheres to dendritic cells in a petri dish, the cells ate them and digested the payload, rendering them unable to stimulate T cells. Perfect. Then they tried the microspheres (which Trucco affectionately refers to as onions, one of his favorite vegetables) in diabetic mice, performing the experiment five times in a row. Worked every time.

Giannoukakis and Trucco wrote a proposal to have the new vaccine tested by TrialNet, a network of 18 clinical centers around the world that screen only the most promising new treatments for type 1 diabetes.

They reasoned that if the safety trial using the patient's dendritic cells were a success, TrialNet would be more enthusiastic about testing the microspheres head-to-head against the injected dendritic cells.

TrialNet agreed: Assuming the microspheres are shown to be safe and Trucco and Giannoukakis successfully complete one last experiment, TrialNet will sponsor a phase II clinical trial comparing the two vaccine approaches. The scientists are eager to realize this as soon as possible.

Even if these approaches work, potential limitations loom. First, how long will the treatments last? No one knows how long dendritic cells or regulatory T cells live in the human body, but they eventually die. New, immune-attacking populations could then take over again. Patients might have to return to the hospital for boosters once or twice a year. The phase II TrialNet studies will help answer that question.

The treatments also won't be for everyone. They'll only work in patients who still have some remaining healthy beta cells—in other words, patients who've recently been diagnosed. It's not going to do much good to stop the immune response against beta cells if no beta cells are left to make more insulin. That said, these treatments might be paired with beta cell transplantations or stem cell treatments, which would help restore insulin production.

Trucco and Giannoukakis hope that the treatments will not only cure diabetic patients, but one day will also prevent the disease in those destined to develop diabetes. Children who are born with the genetic disposition and suffer one of the many potential environmental insults that cause the beta cells to become inflamed are sure to end up with the disease. Because there's a way to test for both the genes and the inflammation, Giannoukakis and Trucco envision screening children whose parents or siblings have type 1 diabetes and treating those at risk to prevent the disease from ever developing.

With a potential cure for such a devastating illness in hand, you'd think Trucco and Giannoukakis would be jumping for joy. Well, Trucco is always high energy—he hardly ever sleeps, preferring instead to wander around his house thinking and occasionally indulging in pots of spaghetti at 3 a.m. (He wakes up his wife each time. "Eating spaghetti alone is bad," he says.) Giannoukakis says that he most enjoys the beginning of an experiment, when the glint of a potential solution flashes in front of him as it did in Boston that day in 2002. And he argues that he and Trucco aren't the people to thank should the treatments prove successful.

"We can sit and we can theorize and we can intellectualize and we can treat a thousand mice, but at the end of the day, the real hero is the human volunteer," he says. "If anything does work out, they are the people who should be thanked first."

Shumaker doesn't think of himself as a hero. "I figured, *What the hell? Somebody needs to do it*," he says of his decision to volunteer, which requires a total of 24 visits to the hospital. But he's well aware of how momentous the Pitt trial is.

"It's the first good opportunity they've had at a cure for diabetes, so it's something exciting to be involved in," he says, noting that he hasn't experienced any side effects.

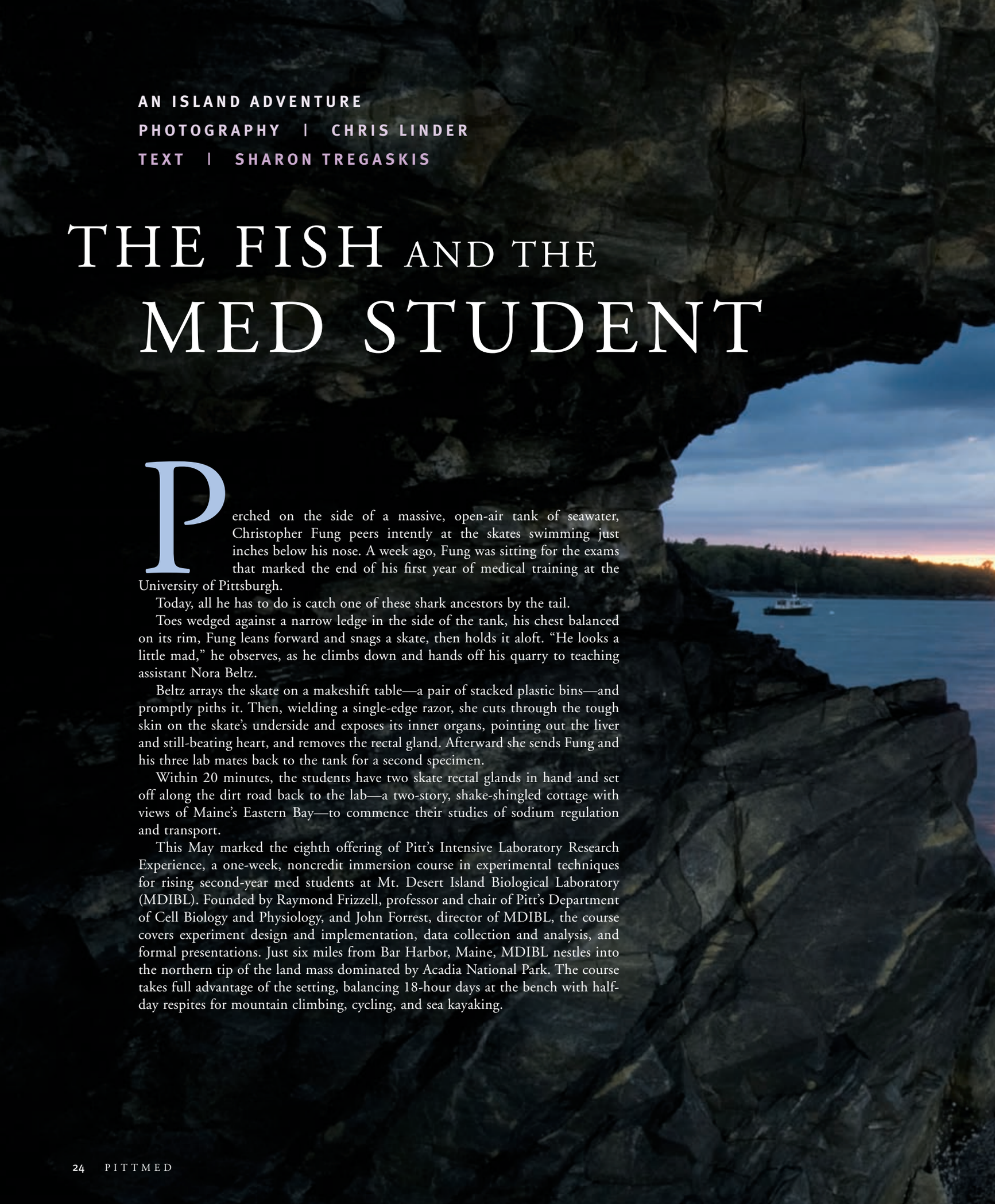
"No extra heads or arms or anything growing out of me," he says with a chuckle, "so it's a success all the way around." ■

AN ISLAND ADVENTURE

PHOTOGRAPHY | CHRIS LINDER

TEXT | SHARON TREGASKIS

THE FISH AND THE MED STUDENT



Perched on the side of a massive, open-air tank of seawater, Christopher Fung peers intently at the skates swimming just inches below his nose. A week ago, Fung was sitting for the exams that marked the end of his first year of medical training at the University of Pittsburgh.

Today, all he has to do is catch one of these shark ancestors by the tail.

Toes wedged against a narrow ledge in the side of the tank, his chest balanced on its rim, Fung leans forward and snags a skate, then holds it aloft. "He looks a little mad," he observes, as he climbs down and hands off his quarry to teaching assistant Nora Beltz.

Beltz arrays the skate on a makeshift table—a pair of stacked plastic bins—and promptly piths it. Then, wielding a single-edge razor, she cuts through the tough skin on the skate's underside and exposes its inner organs, pointing out the liver and still-beating heart, and removes the rectal gland. Afterward she sends Fung and his three lab mates back to the tank for a second specimen.

Within 20 minutes, the students have two skate rectal glands in hand and set off along the dirt road back to the lab—a two-story, shake-shingled cottage with views of Maine's Eastern Bay—to commence their studies of sodium regulation and transport.

This May marked the eighth offering of Pitt's Intensive Laboratory Research Experience, a one-week, noncredit immersion course in experimental techniques for rising second-year med students at Mt. Desert Island Biological Laboratory (MDIBL). Founded by Raymond Frizzell, professor and chair of Pitt's Department of Cell Biology and Physiology, and John Forrest, director of MDIBL, the course covers experiment design and implementation, data collection and analysis, and formal presentations. Just six miles from Bar Harbor, Maine, MDIBL nestles into the northern tip of the land mass dominated by Acadia National Park. The course takes full advantage of the setting, balancing 18-hour days at the bench with half-day respites for mountain climbing, cycling, and sea kayaking.



For 15 students in the Class of 2011, summer started with an *ahh*. Within a day of finishing their first-year exams, the group boarded an airplane bound for coastal Maine and a six-day research immersion program at Mt. Desert Island Biological Laboratory, where the mountains of Acadia National Park serve as a backdrop. RIGHT: One morning, students rose before dawn and drove to the summit of Cadillac Mountain to watch the sun rise. Shared body heat and blankets helped them stave off stiff winds.













The 15 students in this year's program were assigned three rotations, each investigating the structure and function of polarized epithelial cells from a different angle. While the rotation with Forrest examines the workings of the intact skate rectal gland—an organ roughly the size of a pinkie—Frizzell and Tom Kleyman's students explore protein expression in frog eggs. (Kleyman is chief of Pitt's Renal-Electrolyte Division and an MD professor of medicine, cell biology and physiology, and pharmacology and chemical biology.)

In the basement of MDIBL's brand-new research building, students participate in a tutorial on live-cell imaging using MDIBL's pair of half-million-dollar confocal microscopes. Upstairs, in a lab fully equipped for gene analysis, they learn methods for investigating gene transcription and expression.

"The idea is not to turn everybody into researchers," says Frizzell, "but to try to instill an inquisitiveness and a kind of jaundiced or skeptical eye ... so that they don't accept everything at face value but rather think about what went into [research claims]."

Back in Forrest's lab, the students have begun monitoring the effects of various drugs on the flow of sodium, chloride, and other ions through the gland. At a rustic wooden bench on the lawn nearby, Frizzell and Kleyman wrap up their introductory session on protein expression. Their students will investigate two of the epithelial ion channels implicated in cystic fibrosis, the subject of Frizzell's research.

"When you're sitting in class and hearing about the techniques, they almost seem magical, fantastical," says student Aaron Hougham. "Actually getting a chance to do it and see it ... is kind of cool."

Earlier this week, in his gene analysis rotation with Pitt associate professor of cell biology and physiology William Walker, Hougham initiated a study of his own. While setting up a protein detection protocol, the 26-year-old got talking to his lab mates. "I said it would be fun to do something different, even if it

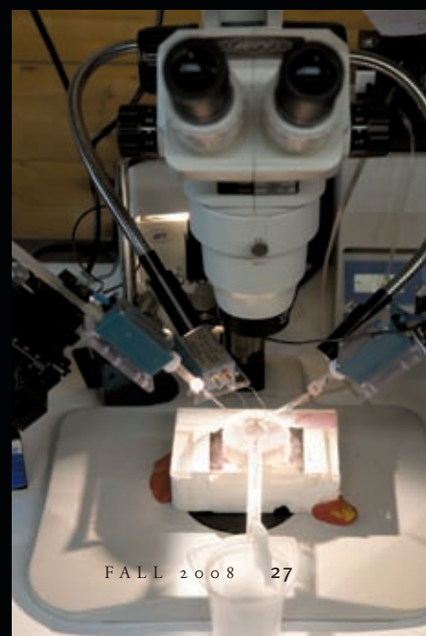
LEFT: Pitt med students work with skates for a study of ion transport. (MDIBL is leading the effort to sequence the genome of the little skate, *Leucoraja erinacea*.)

ABOVE (FROM LEFT): Atop makeshift stepladders, students catch skates for examination. • Renee Dallasen hands off a catch. • Students work in a rustic lab with ocean views.

BELOW: The MDIBL week makes science more real. Faculty mentors, research techs, and graduate teaching assistants offer context and coaching throughout each rotation. (FROM LEFT): MDIBL director John Forrest stresses a point in his lab. • Jessica Lee and Laura Viccaro prepare gene samples for analysis. • To study protein function in the oocyte rotation, students pass an electrical current through eggs of the South African claw-toed frog.









ABOVE: This summer's course participants (all from Pitt's Class of 2011): Daniel Doan, Rebecca Meyer, Michael Cosimini, Laura Viccaro, Gail Joseph, Michael Cho, Veronica Jarido, Hannah Lee, Renee Dallasen, Joshua Levenson, Sarah Luthy, Christopher Fung, Cary Boyd, Jessica Lee, Aaron Hougham

BELOW (FROM LEFT): In the imaging lab, Rebecca Meyer, Sarah Luthy, and Renee Dallasen examine living cells. • Specimens for imaging from a nearby woodlot. • A kayaking break. • At Mt. Desert, even a stroll across campus is a minirespite.

were kind of an elementary school experiment," he says. "I asked if we could use some media and a stick or something. Just see what we could grow."

Eager to foster the students' creativity, Walker handed over the media. Within a few days, Hougham's project has gained momentum, and mealtime chatter includes energetic speculation about what might reveal itself in imaging. (There's plenty of ribbing about the specimen itself, which includes a stick, leaf litter, dirt, and some of Hougham's saliva.)

After lunch, students in the imaging rotation dye Hougham's sample and mount it on the confocal microscope. Then Simon Watkins, head of Pitt's Center for Biologic Imaging, coaches them through the computerized controls to bring the images into focus. They zoom through the image in three dimensions, zeroing in on a region where bacteria wriggle past a spot of yeast. "Oh, wow," says student Renee Dallasen as a microbe swims across the screen. Watkins isn't charmed.

"Ew, this is gross," he says, searching for a particularly active zone. "There's all manner of good stuff in here." Then Watkins invites Dallasen to take the controls, and she sits at the screen, bringing images into and out of focus.

"I don't mind what they're looking at, as long as they learn something about the scientific method, enjoy the process, and it makes them think," says Watkins, who admits that he ensured the wild specimen was triple wrapped before it went in the incubator, to guard against contamination of nearby specimens.









After a full day in the lab and a few hours early the next morning to polish its thoughts, each group gives a presentation introducing classmates to the concepts covered in the rotation. The skate group, calling itself Skateorade, includes a logo modified from the sport drink of a similar name among its slides. When the imaging group takes the floor, the students discuss Hougham's sample and detail the techniques they used.

"Knowing I was going to have to describe my group's results in front of others who had far greater understanding than I do forced me to ... ensure that I really understood exactly what was happening," says group member Rebecca Meyer.

The night before the students depart, Watkins—clad in khaki shorts, an MDIBL sweatshirt, and battered oven mitts—bustles among three fire pits, poking at embers and tugging at grates. Already he's demonstrated how to pacify a lobster by stroking its belly. He even stood one on its head. Now he's intent on preparing dinner. Small groups warm themselves near the fires while a dozen students gather at the base of a soaring evergreen, strategizing about how to free the Wiffle ball lodged in its branches that only moments earlier was the centerpiece of a spirited game.

"This has been a bonding experience," says class president Cary Boyd, as another student scales the tree trunk. "A lot of the barriers between faculty and students have been broken down."









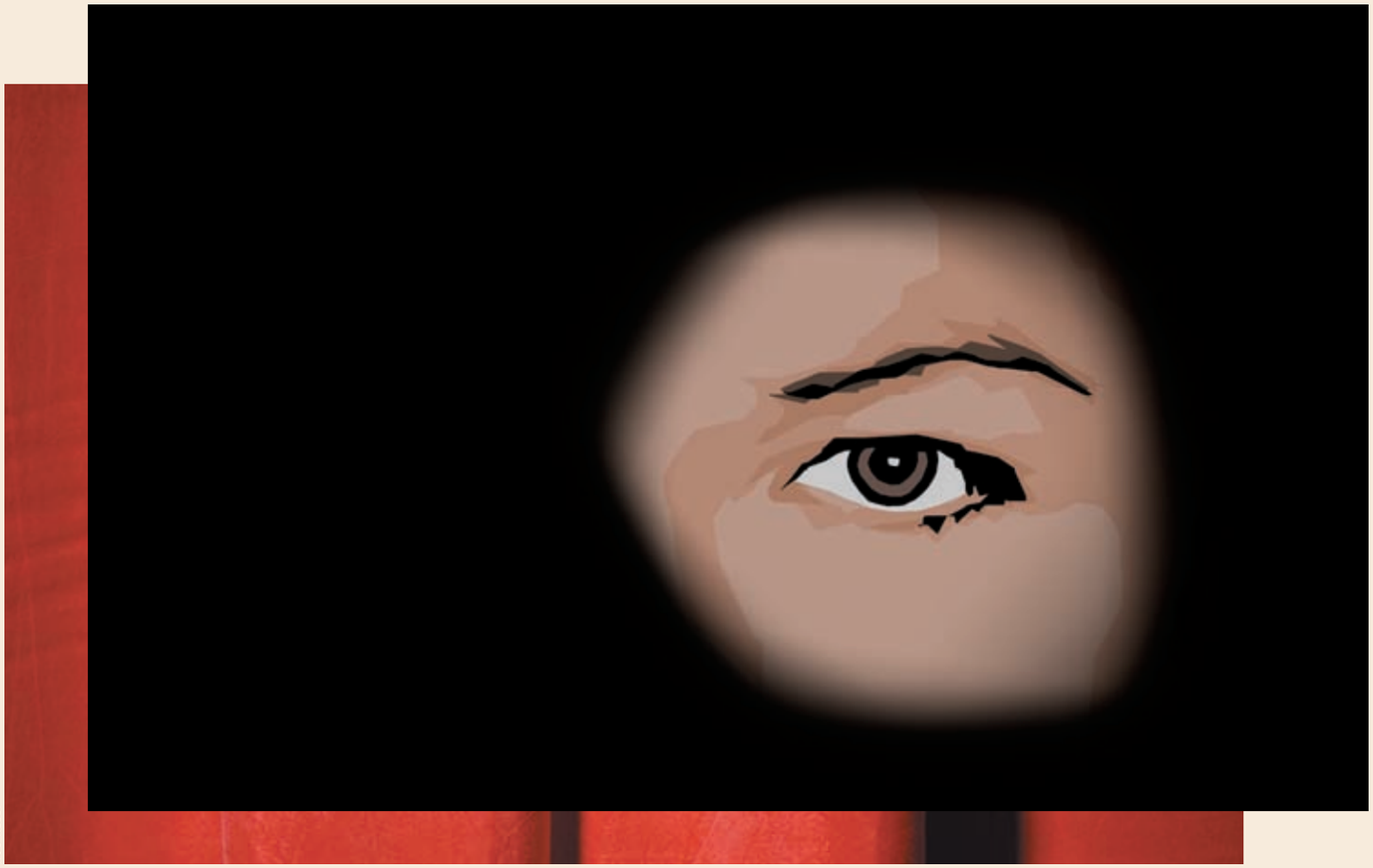






After a week of coaching students through the finer points of confocal microscopy, Simon Watkins doles out a lobster dinner. But he's always teaching. During the feast, he wanders among students offering tips for extracting optimal enjoyment from the regional delicacy.





ROB KELLY

WHEN I WOKE

HOW TO RECLAIM A LIFE

BY EMILY STORCH (MD '08)

There was no discrete moment when I realized I had been in an accident. I had been unconscious in the ICU for four weeks, during which time my family was talking to me and explaining what had happened. When I came to, it was as if this knowledge had just slowly trickled in. My life prior to the accident came back in bits and pieces: "Hmmm, I was in medical school. I must be missing classes about now." "I have a cat. I hope someone is taking care of her." Gradually, I started to piece together what had happened and what the implications would be.

On Jan. 22, 2007, I was in Virginia, where I had an interview for a residency. As I left, I may have felt relieved that I'd finished up the last of my interviews. On my drive back to Pittsburgh, I was probably trying to organize my thoughts about residency and the upcoming year. The next thing I remember is waking up in UPMC Presbyterian next to one of my aunts from St. Louis.

My accident occurred on the Pennsylvania Turnpike about 45 minutes outside of Pittsburgh. I have no memory of it or of the day leading up to it. I have been told that it was dark and icy, and that I lost control of my Jeep Cherokee, hitting the median, at which point an 18-wheeler rammed into my car. The driver didn't even know he'd hit me. I may have been catapulted out of my car and smashed between it and the median. Possibly I was already out of the car when I was hit. (Some people have theorized that after I hit the median, I got out of the Jeep, and then the truck came and pinned me.)

I suffered bilateral open femoral fractures and bilateral crushed tibias. My bladder was ruptured, and I had a pulmonary contusion, broken ribs, and a fractured pelvis. The trauma tore veins in my brain and resulted in bleeding that can often be fatal (both subarachnoid and subdural hemorrhages).

Fortuitously, an MD and a paramedic happened to be driving by with equipment in their car. They stopped and started an IV on the scene. I was then life-flighted to Pittsburgh, where I was met in the trauma bay by the physicians I had seen in action many times before. I had multiple laparotomies (incisions into the abdominal wall).

When I woke, my belly was gaping open, left that way because of increased intracranial pressure. I later had to have a wound vac attached—imagine a machine with a tube taped to the wound to suction out extra fluid and encourage growth of connective tissue. A very strange and uncomfortable experience. I never got used to having the bulky machine attached. I would frequently forget about it and start moving in my wheelchair, only to feel something pulling me back. It is very odd to be plugged into the wall. I vehemently opposed the vacuum, but came up against an aggressive wound nurse who would not be deterred. In the end, I appreciated her insistence. My wound healed well, without any need for a skin graft.

I spent about four weeks in the ICU, where my care was excellent. I remember none of it.

After those four weeks, I moved to the general floors. In my former life as a medical student, I'd felt very involved in patient care. In addition to visiting a patient, my team members and I would discuss that patient all day long, monitor results, "run the list." But the patient sees little of this. The experience becomes dominated by nurses, nurse assistants, and techs. As a patient, I felt disconnected from the doctors. I often saw them only once a day and not always the same ones. Typically, I was tired or confused when they stopped by.

My first night out of the ICU, I experienced delirium, probably because of a combination of bacteremia and pain meds. That night, I decided I could make it to the bathroom by myself. I scooted across the room to the toilet, then realized I was stuck. This is where I stayed, huddled in the bathroom in front of the toilet, until the orthopaedics team found me. From then on, my family decided that either a relative or a sitter would be with me at all times. This was difficult to swallow. I even needed someone to lift me to the commode. In general, I could accept the assistance with fairly little resistance. But one day, two nurse assistants were sent in to brush a large knot out of my hair. I couldn't take it. I sent them away. It was too symbolic of my total loss of autonomy.

Two nurse assistants were sent in to brush a knot out of my hair. I couldn't take it. It was too symbolic of my loss of total autonomy.

From Presbyterian, I was taken on a stretcher in an ambulance to a small plane, then flown to St. Louis. An entourage that included two reassuring nurses and a claustrophobic aunt took me to a rehabilitation hospital.

Before the accident, I didn't really know such hospitals existed. I was in the brain injury unit, which was a sobering experience. Many of the patients were stroke victims who needed help with eating and other basic functions. I had speech, occupational, and physical therapy. In physical therapy, I concentrated on bending my legs, rather than leaving them stretched straight out like sticks. The speech and occupational therapy weren't geared to individual levels, and many days I found myself playing simple number games or connect the dots. Even in my fuzzy state of mind these activities were frustratingly simple.

I didn't sleep well in the rehab hospital. One night I fell asleep late, only to be awakened at 1 a.m. by a man emptying my trash. The nursing staff came in at 5 a.m. to take my vitals and give me shots.

My next-door neighbor in the unit was Sophia, all of 4'9" with a wild mop of white hair. She would frequently visit me in my room, despite the fierce efforts of the staff to confine her.

Deemed an "escape risk," Sophia was supposed to sleep in a hammock-like restricting contraption, but she Houdinied her way out of it. Her visits would invariably be followed by frantic nurses rushing in to find her. Unperturbed, Sophia would continue her tirade of the moment, most of which I usually couldn't follow. (I'm not sure if that was because of the state of my mind, hers, or both.)

After two weeks in the rehab hospital, I was discharged. I then stayed with a cousin who lives in a ranch home, because I couldn't make it up the two stairs to my dad's place in my wheelchair. In fact, I could manage little myself. I couldn't get myself breakfast. My cousin would bring me a cup of coffee in the morning. She fixed up the bathroom with a shower bench and strategically placed towels so I could take a shower, which I did infrequently because it was such a hassle.

I was tired. Despite sleeping long nights, I usually napped in the afternoons. In the mornings, I went to physical therapy. I was unprepared for how difficult and unsettling this would be. I had been told that I would have to learn to walk again, but I didn't realize

that I wouldn't even be able to stand upright or balance without a lot of practice. My physical therapist told me to practice standing in front of a mirror in the bathroom; but at first I was too frightened. What if I were to fall?

At one point, I got what we thought was a stomach virus. I had a low-grade fever, stomach cramps, and diarrhea. My dad, an infectious diseases specialist, speculated that I got the virus from another patient. He knew that we shared therapy mats. That made me remember the day before, when an occupational therapist was helping "Doris" out of her wheelchair and whispered loudly in alarm to her: "Doris, you're wet!" But it was either share the mats or forgo rehab.

That stomach ailment, later rediagnosed as a *Clostridium difficile* infection, lingered for months. I don't know where my colon would be today without insurance. Certainly my family would have been bankrupt many times over.

When I was still hobbling around with a cane, and nowhere near independent, my otherwise lifesaving insurance plan stopped covering my physical therapy. I had to write a letter requesting more sessions. It took nearly two months to get approval. In the meantime, I started working with a clinical exercise specialist. On my first visit, she told me to throw my cane away. Walking without the cane forced me to rely more on my own strength and balance. By the time the insurance approved my return to the rehab hospital, I was reluctant to be once again grouped with the other patients, many in wheelchairs, many at a very low level of functioning. I had moved on from that place and didn't want to go back.

In the accident, I'd also injured the superficial peroneal nerve in my left foot, causing foot drop. A surgeon from Washington University in St. Louis, who specializes in nerve repair, determined the nerve was compressed and performed a procedure to release it.

Since then, I've seen slow but steady improvement: first a twitch in the toe, now significant movement.

In a lot of ways, that regaining of function has been a metaphor for my entire recovery process—almost imperceptible at first, but with time, patience, and good support and care, heading steadily toward the ultimate goal of no noticeable deficit. I realize that I am fortunate to have come as far as I have, and that has only been possible through a wide and tight support network. Family and friends made infinite sacrifices and contributions. Two Pitt med physicians who live down the street from the University housed one member of my family after another for months.

I was in the ICU for the first month, then on the general Presbyterian floors for a few weeks, the rehab hospital for another two weeks. By the end of March 2007, I was home. Mid-April, I began weight-bearing. In June, I resumed my classes. In September 2007, I reapplied for the residency match. Only now am I reclaiming my independence, and my recovery is moving to the background.

But I'll never forget what it's like to be a patient. ■

Editor's note: Emily Storch is starting her residency in internal medicine at Yale–New Haven Hospital. She plans to also train in critical care—a field that interested her before her accident. Now she's motivated to bridge the divide between rehabilitation and critical care.

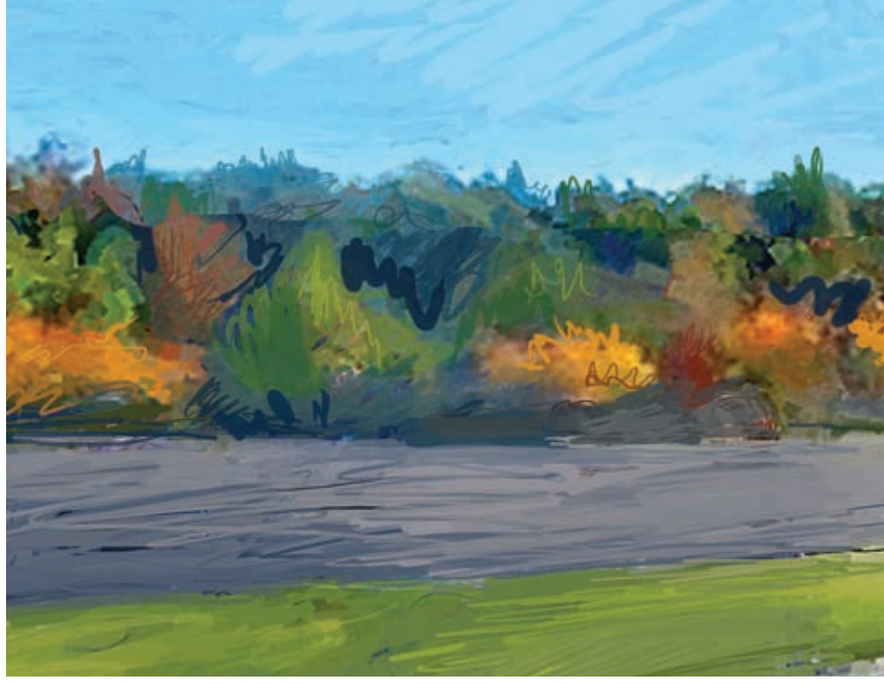


ROB KELLY

Emily Storch (seated) at graduation ceremonies in May 2007 with classmates Gina Howell, Vladimir Manuel, and Brian Sullivan. (She officially graduated this year.) Storch no longer needs a wheelchair or crutches—thanks to the "outstanding orthopaedics work" of Pitt's Hans-Christoph Pape, she says.

People and programs that keep the school healthy and vibrant





THIS CHECK CAME WITH A KISS

ORPHANED BUT NOT FORGOTTEN

BY CHUCK STARESINIC

Being diagnosed with an orphan cancer (one that affects fewer than 200,000 people in this country) can leave a patient feeling, well, orphaned.

Tania Stutman knows what it's like. In 1998, surgeons removed a tumor from her small intestine. In less than a year, it was back; cancer had spread to her liver, too. An oncologist advised her to go home and get her affairs in order because she was not likely to live more than a year. She was a victim of a rare, deadly cancer called gastrointestinal stromal tumor, or GIST. There was no cure and little or no research.

Ten years later, she says the worst part of that experience was that she felt robbed of hope. Yet three years after diagnosis, she was accepted into one of the first clinical trials of a drug therapy for GIST. Of roughly 140 patients in that trial, she believes that fewer than half are alive today. Her experience of finding hope when she thought none existed led her to try to build a reason for others to hope. She and her husband, Robert Stutman, decided to raise money to fund GIST research. They created the GIST Cancer Research Fund (GCRF) in 2001. They knocked on doors all around New City, N.Y., where they live. They made flyers and signs by hand and hosted a walk for a cure. They raised $26,000 and put every penny into the hands of GIST researchers.

Gastrointestinal tumors are not rare, but most arise from the epithelial cells that line the GI tract. GISTs are different in that they arise from the interior cells of the bowel and stomach walls. (The term "stromal" in GIST refers to the structure of the organs.) These cells are important for coordinating contractions of the bowel and produce a great deal of a protein kinase called KIT. Sometime in the late 1990s, scientists found that the gene for this protein was mutated in many GIST patients.

As volunteers held fundraising events, GCRF grew. The fund supported, in particular, researchers who found that the leukemia drug Gleevec could stop GIST in its tracks. It was not a complete cure, but it seemed to kill tumor cells and extend the life of patients, including Stutman. In 2006, Mark Landesman—a GIST patient himself and a member of the fund's board—attended a small GIST conference where Anette Duensing, a University of Pittsburgh research assistant professor of pathology, presented a paper revealing that a cellular protein called histone H2AX was required for the death of tumor cells after treatment with Gleevec.

At a recent gathering of GIST patients and supporters at the Duensing lab in Pittsburgh, Landesman recalled that conference, saying, "When Anette presented her paper on histone H2AX, you could sense the excitement in the room. Another scientist compared it to the actual discovery of KIT. I was just so overwhelmed that when we got together for the next board meeting, I said, 'We have to find a way to fund the research here.'"

In 2006, most of GCRF's funds had already been spoken for, but Landesman convinced the board it needed to support the researcher he'd just heard speak. Five thousand dollars would go toward supporting the Duensing lab. Anette Duensing was so appreciative, says Landesman, that he and others were almost embarrassed by the amount. In 2007, GCRF gave $26,000 to the lab, and in April of this year, members of the board and GIST patients and families came to Pittsburgh to present a check for $135,000. It was Duensing's turn to be overwhelmed.

With the gift, her lab will run a series of experiments screening all 700-plus known protein kinases in the human genome. They hope to identify kinases in addition to KIT that are critical for the survival of GIST cells. Kinases are easily targeted by a new class of drugs called small-molecule inhibitors.

"We feel like an extended family to them," Duensing said of the patients and families from GCRF after they toured her lab and showed their appreciation for all those who work there. She has traveled to GCRF fundraising events multiple times.

"It's not someone just dropping off a check here," Duensing said to the group as she stood with one arm around Stutman. That point was clearly driven home when, shortly after presenting the check, Stutman planted a kiss squarely on Duensing's right cheek.

FOR MORE INFORMATION: **www.gistinfo.org**



The GIST Cancer Research Fund raises money through walkathons and other events. Fund organizers are ardent supporters of Anette Duensing's work on rare and deadly gastrointestinal tumors.

ILLUSTRATIONS FRANK HARRIS. WALKATHON PHOTO COURTESY GCRF/ O'MALLEYS' PHOTO COURTESY B. O'MALLEY.

REWARDING SCHOLARS

THE O'MALLEY AWARDS

BY JOE MIKSCH

Bert O'Malley lives and works in Houston, but his time at the University of Pittsburgh, where he earned his Bachelor's of Science in 1959 and his MD in 1963, is never far from his mind.

Today he is one of the leading authorities on how hormones turn genes on and off. His particular interest lies in how these mechanisms work with breast cancer. He's a member of the National Academy of Sciences and Ireland's Royal Academy of Medicine. He invented the GeneSwitch, a technology that regulates protein therapy. In 1981, he received the Philip S. Hench Award, the highest honor given by Pitt's Medical Alumni Association.



Bert and Sally O'Malley

At Pitt, a divergence from the usual med student path—made possible thanks to mentors in the laboratory—gave O'Malley the inspiration and tools to embrace a career in research. He is currently chair of the Department of Molecular and Cellular Biology and director of the Center for Reproductive Biology Research at Baylor College of Medicine.

O'Malley's interest in the bench was piqued after he spent time in the labs of Pitt's Jim Field and Klaus Hofmann.

With appreciation for those mentors, O'Malley and his wife, Sally, recently made a gift to the School of Medicine that may encourage others to become physician-scientists. (Sally O'Malley also earned a bachelor's from Pitt in '59. She was president of the women's student body and homecoming queen.)

On April 30, members of the School of Medicine's Class of 2008 were feted during Scholars Day. Theirs was the first class to complete the school's new scholarly project requirement, which is intended to help create physician-scientists and questioning physicians by giving students a taste of research during their formative years, as O'Malley had. On that date, the school recognized the first recipients of the Bert and Sally O'Malley Awards for Outstanding Medical Student Research: Andrew Fisher and Rob Klune (both now MD '08).

Fisher's project explored health care quality in geriatric nursing homes. Klune identified a signaling pathway related to tissue damage.

O'Malley says he's proud of the school for instituting the scholarly project requirement.

The O'Malleys' initial gift of $10,000 represents seed money. The couple intends to make an additional donation to endow the award permanently.

"I wanted to add a little luster and backing to a program I think a lot of," O'Malley says. "When you allow students to take some time in medical school to do research, you're not only preparing physicians to treat people, you're growing new academic researchers." ■

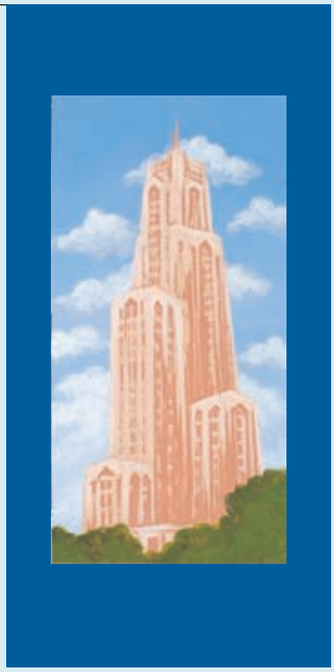
FOR MORE INFORMATION ON GIVING TO THE SCHOOL:
Deb Desjardins, 412-647-3792 or ddeb@pmhsf.org.

BOOSTER SHOTS

There was always something cooking in the late **Jane Citron's** kitchen. Now, her family hopes to raise enough money to make sure the University of Pittsburgh's cancer research laboratories see the same kind of action. This spring marked the second annual Cooking Up a Cure event inspired by Citron, a victim of colon cancer and a gifted cook and food writer who died in 2006. The silent auction, with items reflecting Citron's love of food and travel, raised $250,000 toward the $2 million needed to endow the Jane and Carl Citron Chair in Colon Cancer at the University of Pittsburgh Cancer Institute. A cookbook of Citron's recipes is in the works. Proceeds will go toward the endowment fund.

— Hayley Grgurich

David Levidow served as the primary caregiver for his mother, Lulu, in the last three years of her life. Alzheimer's disease took hold of her rapidly and tenaciously, but little was known about why or how it developed. One morning last December, Levidow opened *The New York Times* in his Manhattan apartment to see a series of articles about Alzheimer's research. He noticed how often Pitt researchers were named. When he finished reading, he was sufficiently impressed and called the school to make a $500,000 donation. "What interests me really is that this research will eventually lead to a cure or, at least, palliative measures," Levidow says. He admits that half a million dollars to a program he's never seen is no small show of faith, but he says, "It's all about faith when you get involved in research." The David and Lulu Levidow Endowed Fund will support Alzheimer's disease research in Pitt's Department of Neurology. *—HG*



CLASS NOTES

'70s

George Magovern Jr. (MD '78) performed Allegheny General Hospital's first heart transplant in December 1987. "The patient had a lovely family, and he knew that he wasn't going to live otherwise, so it was a nice Christmas present," Magovern says.

Magovern is currently the surgical director of cardiac transplantation at Allegheny General Hospital, chair of the department of thoracic and cardiovascular surgery for the West Penn Allegheny Health System, and a Drexel University professor of surgery.

As a Pitt sophomore, **Mary Mancini** (MD '78) went behind her parents' backs and took the MCATs. "I was bored," she says. "I come from a very traditional Italian family where the women get married, have kids, and don't have a career, so it was an uphill battle."

Mancini interviewed with Pitt's former associate dean of student affairs, the late Rebecca Frances Drew Taylor, known to her colleagues as Penna Drew.

"I walked into her office for the interview, and she's sitting there, smoking a pipe," Mancini says. Drew asked her to interpret a journal article. Instead of panicking, she tried to make sense of it on the spot, earning Drew's respect, as well as an acceptance letter.

Mancini is a professor of surgery and chief of cardiothoracic surgery at Louisiana State University Health Sciences Center in Shreveport. She also makes use of her studies at the Conservatorio di Musica Benedetto Marcello di Venezia by singing with the Shreveport Opera.



Mancini in *Madame Butterfly*

'80s

Last year, **Susan Dunmire** (MD '85, Emergency Medicine Resident '88) made more than 60 attempts on the patient simulator SimMan's life. She shot him, stabbed him, and ran over his foot with a lawn mower; for this she received the 2008 Chancellor's Distinguished Teaching Award. Dunmire, an associate professor of emergency medicine at Pitt, is continually praised by students for the creativity and enthusiasm she brings to teaching—and the breakfast she serves on exam days. "I think students like me because I bake for them," Dunmire says, wryly. "They're easily bought." But accolades from Pitt's Chancellor Mark A. Nordenberg and her appointment to the School of Medicine's Academy of Master Educators suggest Dunmire has more going for her than baked goods. "Get Ready for Residency"—her crash course in worst-case scenarios that mixes lectures with patient simulations, urgent phone calls, and confounding interruptions—prepares students for the chaos of life as an intern. With days like this, it's a good thing they're eating breakfast.

Andreas Tzakis (Transplant Surgery Fellow '85) recently performed an unusual series of organ transplants—removing six of a patient's organs in order to burn away a tumor tangled between them, then returning the organs to their proper places.

A professor of surgery and director of the Transplant Institute at the University of Miami/Jackson Memorial Medical Center, Tzakis is focused on promoting organ tolerance in transplant patients. His ambitions in transplant surgery include taking surrogate motherhood a step further by transplanting



Dunmire

RANDY BRUNO

TICKLING WHISKERS

On a typical day at the Max Planck Institute for Medical Research in Heidelberg, Germany, Randy Bruno (Neurobiology PhD '02) would squeeze into a workspace packed with monitors and affix electronic sensors to a sedated rat. One component of the equipment tickled the rodent's whiskers and another translated neuron activity into sound. Over the loudspeaker, Bruno could hear when a selected neuron fired, triggering the release of a neurotransmitter.

Bruno's Nobel Prize–winning mentor, Bert Sakmann, always reacted to the sound of data played aloud. "He would come running from his office whenever he heard it, because he knew there was an experiment going on," Bruno says. "He had almost a childlike enthusiasm."

Now an assistant professor of neuroscience at Columbia University, Bruno teases apart the workings of sensory perception. Bruno started this work with Daniel Simons, PhD professor of neurobiology, at the University of Pittsburgh School of Medicine. He then did his postdoc under Sakmann at the Planck Institute. "I'm trying to take a little bit of both of them," Bruno says of mentors Sakmann and Simons. He credits the former with embracing new methods in the lab and the latter with innovative tweaks in the experimental structure.

At the Planck Institute, Bruno and Sakmann developed a way to measure the strength of a connection between a cell from the thalamus—which relays input from a sensory organ (be it a whisker or an eardrum)—and one from the cortex in a living animal.

COURTESY BRUNO

a human uterus. "We are trying to make the procedure as simple as possible for a human. Whether or not we do it here first, I just want it to be safe," he says.

As a self-proclaimed "matchmaker for scientists," **Renee Carder** (Neurobiology PhD '89) doesn't link researchers romantically. Instead, the deputy to the lab director at Argonne National Laboratory in Illinois integrates their scientific pursuits, particularly by fostering collaboration between Argonne and the University of Chicago. Carder served as assistant vice president for Strategic Research Initiatives at the University of Chicago before coming to Argonne.

"As science has moved forward, it's become much more collaborative ... so I started helping the University marry the biological and physical sciences," Carder says. Products of this collaboration include a regional biocontainment laboratory, where scientists study infectious diseases and design vaccines and therapeutics, and a joint threat anticipation center, which brings together social and computational scientists to better understand and anticipate terrorism.

'90s

Jean Kim's (MD/PhD '90) overarching research goal is to break the obstruction-inflammation cycle of sinus disease and nasal polyps, a problem affecting nearly 15 percent of adults in America.

"It's a huge problem in the United States," Kim says. "There are treatments, but they're not permanent."



Kim

One fifth of patients with chronic sinusitis will develop nasal polyps. Even when surgically removed, polyps often grow back, blocking the airway, causing facial pain and, in some cases, loss of the sense of smell. Kim studies the epithelial cells that line the nasal airway, focusing on the genetic basis of chronic sinusitis and immune response. She is an assistant professor of otolaryngology and of medicine as well as director of the sinusitis program at John Hopkins Medical Center.

"I jumped [into] the Grand Canyon without a parachute," says **Loretta Dandrea** (Pediatrics Resident '92) of quitting her pediatrics practice to pursue writing full-time. Because she didn't want underage patients thumbing through her adult-themed medical thrillers, Dandrea and the receptionist at her State College practice cooked up the pen name CJ Lyons—a tribute, sigh, to the Nittany Lions. Her debut novel, *Lifelines* (Berkley Books) blends a *CSI*-style crime thriller with *ER* medical drama and an all-female cast of characters that harkens back to *Sex and the City,* according to her publisher. Dandrea took dramatic license with the book, which is set in a fictional Pittsburgh hospital, but tried to keep it true to her own residency experience. "I mean, we never got to have sex in the linen closet," she says.

In his two years as a flight surgeon in the 1990s in Vilseck, Germany, **Charles Egbert** (MD '92) distinguished between pilots who were fit to fly and those who had to be grounded for health reasons. "This is what these guys do for a living, and their identity is wrapped up in it. So theoretically, you can do them no good," Egbert says. He is glad he never had to ground anyone permanently.

During the American deployment to Bosnia, Egbert also served as a U.S. Army commander, administering a clinic in Vilseck. He resigned from the military as a major and now works nights as a hospitalist in Springfield, Vt., a position he appreciates for the family time it affords him. A father of five, Egbert answered *Pitt Med'* s telephone call with a chuckle, saying, "I was just playing dress-up with my daughter."

'00s

During his first year in Pitt's molecular pharmacology PhD program, **Qing Zhang** (Pharmacology PhD '05) grew frustrated with his head and neck cancer research as discovery came slowly. Professor Jennifer Rubin Grandis (MD '87, Otolaryngology Resident '93) helped him change his perspective. "[Grandis] came to me and said, 'If you have an interest in cancer research, you should focus on a broader picture,'" Zhang says. He now looks at research as a means to a greater end—helping the patient population—and doesn't let setbacks deter him. Zhang is now at Harvard University and the Dana-Farber Cancer Institute investigating how tumor suppressors lose function in kidney cancer.

—Meaghan Dorff and Hayley Grgurich

SEE MORE CLASS NOTES ONLINE AT
http://www.medschool.pitt.edu/alumni/index.html



Randy Bruno (at right) finds himself in good company with a pair of Nobelists: his mentor, Bert Sakmann (left), and Columbia University colleague Eric Kandel.

Bruno studies the rodent whisker barrel system. It's a straightforward circuitry model, he says. Each whisker corresponds to a given pocket of tens of thousands of neurons in the brain.

He notes that rodents use whiskers the same way we use our fingertips for doing sensory tasks. "They sweep their whiskers across an object the same way we would sweep our fingers across an object," he says.

"We're coming to understand a lot about the circuitry that allows the brain to work. And a lot of mental disorders—whether it's epilepsy or schizophrenia or autism—are thought to be dysfunctions of the circuit," Bruno says.

He plans to develop a mouse model of autism "without abandoning" the basic science questions of sensory perception. Such questions may tell us more than you might think about how we perceive the world, he notes:

"Lots of different areas of the cortex are very similar in terms of their anatomical structures, their connectivity, and their function. It's almost as if the brain has reiterated the same unit across its whole surface for many different things—for vision, for touch, for thinking." *–Meaghan Dorff*

The 2008 Senior Class Luncheon included the presentation of the Medical Alumni Association's McEllroy Award and Hench Distinguished Alumnus Award. The McEllroy, given to a physician who trained at Pitt, went to Pitt professor of psychiatry Charles Reynolds (Res '77). Reynolds is a senior associate dean at the school and a much-quoted expert in geriatric depression. The Hench went to Randolph Miller (MD '76), professor of medicine at Vanderbilt University, known for his work in biomedical informatics.



Reynolds



Miller

THE WAY WE ARE
CLASS OF '87

Thanks to lifesaving armor, soldiers in Iraq are surviving blasts that routinely killed soldiers in past conflicts. At Walter Reed Army Medical Center, **Colonel Gregory Argyros** (MD '87), the chief of medicine, treats these soldiers for ailments few previously lived to suffer. Argyros is former chief of the blast overpressure division at Walter Reed and a specialist in pulmonary and critical care. He has been learning—and teaching—on the fly about how to treat patients with traumatic brain injuries and unusual wound infections from foreign soil contamination. It's a job he says he's honored to do for those who give so much to their country.


Argyros


Bozik

As the director of the Brain Tumor Center at the University of Pittsburgh Cancer Institute, **Michael Bozik** (MD '87) always felt the work he and his colleagues did to develop cancer vaccines in the laboratory would be invaluable to patients—that is, once they had access to the vaccines. Hoping to bridge the gap between petri dishes and pharmacies, Bozik traded his lab coat for a sport coat to work at Bristol-Myers Squibb and then Bayer. When he left to become president and CEO of the start-up company Knopp Neurosciences, he went from having 30,000 coworkers to 14, all of whom are now attempting to develop a treatment for amyotrophic lateral sclerosis.


Petrakis

Ismene Petrakis (MD '87), associate professor of psychiatry and director of the addiction psychiatry residency program at Yale University, feels that the best way to find treatments that work for patients with schizophrenia and a comorbid addiction like alcoholism is to allow a few variables from the clinic into her studies. Initially she tried to avoid it, stipulating in one study that participants could only take the antipsychotic drug haloperidol. "You know how many people we recruited? Like zero," Petrakis says, laughing. What her studies now forfeit in neatness, they make up for in results. Testing subjects with a whole host of disorders, Petrakis gets practical data by breaking the population down into subgroups to measure how patients with different disorder combinations and variables respond.


Fielding

Julia Fielding (MD '87) jokes that she steps out of her cave to give first-year students a lecture titled "Radiology Urban Legends." She thinks med students may hear shady stories about her specialty, so she reassures them that radiologists aren't antisocial vampires who lurk in darkened exam rooms.

Fielding is an associate professor of radiology and section chief of abdominal imaging in the Department of Radiology at the University of North Carolina at Chapel Hill. Her work involves genitourinary tract disease, CT-based virtual reality imaging of the bladder for cancer screenings, and magnetic-resonance pelvic-floor imaging. She is a consultant to the National Institutes of Health's Pelvic Floor Disorders Network and the institute's chief radiologist for national studies.

Fielding got involved in the nonprofit dance company Boston Youth Moves while she was an assistant professor of radiology at Harvard University. She still dances. "Right now I'm learning hip-hop," she says.

—Hayley Grgurich and Meaghan Dorff

IN MEMORIAM

'40s

JOHN J. ECKBERG
MD '43B
JUNE 7, 2008

'50s

JOSEPH F. FUSIA
MD '54
MAY 8, 2008

'60s

EUGENE C. FELDMAN
MD '61
APRIL 30, 2008

L. ALAN WRIGHT
MD '63
JUNE 22, 2008

'70s

STANLEY BUSHKOFF
RES '72
JUNE 21, 2008

CELESTE J. WELKON
MD '79
JUNE 13, 2008

FACULTY

ANTHONY SUSEN
MARCH 20, 2008

MEDICAL ALUMNI ASSOCIATION OFFICERS

PATRICIA CANFIELD (MD '89)
President

GRAHAM JOHNSTONE (MD '70)
President-elect

MARGARET LARKINS-PETTIGREW (MD '94)
Secretary

PETER FERSON (MD '73)
Treasurer

ROBERT E. LEE (MD '56)
Historian

SUSAN DUNMIRE (MD '85)
Executive Director

ADAM GORDON (MD '95)
JOHN KOKALES (MD '73)
JAN MADISON (MD '85)
DONALD MRVOS (MD '55)
CHARISSA B. PACELLA (MD '98)
BRETT PERRICELLI (MD '02)
VAISHALI DIXIT SCHUCHERT (MD '94)
DAVID STEED (MD '73)
Members at Large

M-200k Scaife Hall
University of Pittsburgh
Pittsburgh, PA 15261
tel 412-648-9090; fax 412-648-9500
medalum@medschool.pitt.edu

THEODORE LIOU

FIRST DO NO HARM

BY REID R. FRAZIER



FRANK HARRIS

Liou sees hope in the daunting numbers facing patients with cystic fibrosis.

Ted Liou (Res '89) spent four years analyzing thousands of records to determine whether lung transplantation was a good idea for children with cystic fibrosis. When Liou and collaborators published their results in *The New England Journal of Medicine* (*NEJM*) on Thanksgiving Day 2007, it took only minutes for all hell to break loose.

The study made the front page in Amsterdam newspapers. (There are a lot of CF patients in the Netherlands.) Reuters called. Through the grapevine, Liou, an associate professor of internal medicine at the University of Utah, learned that some transplant surgeons were upset.

The cause of the trouble? The researchers found that less than 1 percent of pediatric patients showed significant likelihood of increased survival from transplant, yet 60 percent showed significant likelihood that transplant decreased their chances of survival. Liou was raising questions about whether the cure was worse than the illness.

There are about 26,000 patients with cystic fibrosis in the United States; about 60 percent of them are children. The median life expectancy of CF patients is between 25 and 40. (For teenagers or young adults with CF, life expectancy is 25. For those born today with CF, doctors project life expectancy to be 40.)

CF is a genetic condition that inhibits the ability to fight infection in the lungs. After protracted infections, most patients' lungs are so damaged they no longer function. Although only 50 children a year get lung transplants in this country (most of these are for CF), almost every family affected by CF thinks about transplantation, because it is often seen as the best way to extend and improve a sick patient's life. Yet a lung is one of the most difficult donor organs for the body to accept. About half of lung transplant patients die within five years. At UPMC, the nation's busiest lung transplant program, survival is better than average. However, fewer than 10 percent of lung transplants here are for CF patients.

When Liou was looking for a research topic for a statistics class he was taking a few years ago, colleagues at the University of Utah's Intermountain Cystic Fibrosis Center in Salt Lake City, where he was a fellow, suggested he look at survival rates of lung transplant patients with CF.

"Very few people had taken a look at this," says Liou, 47, who now codirects the Intermountain CF Center. "The instinct of people in the field was, they weren't quite sure about this."

Frank Kroboth (Res '80), the George H. Taber Professor of Medicine and director of Pitt's internal medicine residency program, is pleased to see that Liou is demanding evidence for what doctors practice, but he is not surprised. "It was obvious that Ted was very bright and inquisitive the day he stepped into the program," he wrote in an e-mail.

To make sense of the data, Liou asked Sir David Cox, a renowned statistician at the University of Oxford, England, to help shape the analysis. Cox, who has constructed statistical models for epidemiologists, sociologists, hydrologists, and physicists, agreed and became a coauthor.

The resulting study has been applauded by many CF doctors and transplant specialists for bringing statistical rigor to such an important question. Others have criticized it. In a letter to *NEJM* responding to the study, a group of doctors argued that because organs generally go to the sickest patients, you can't compare their outcomes with their healthier counterparts still on a waiting list.

Liou et al. acknowledge these difficulties in comparing the numbers but insist they took these potential biases into account. The best way to address the question, they say, is to conduct a prospective study to monitor patients throughout the next several years.

Liou hopes his study will be the start of a long dialogue on transplants and CF, not the last word. His group has found that for sick adult patients, transplant is a good option.

"I think there's a hidden message of hope there," Liou says. "When you look at CF now, the majority of deaths happen among adults. In Salt Lake City now, you almost never hear of a child dying. If nobody's dying, they don't need to be rescued by lung transplantation." ■



BLOSSOMS

It was an extraordinary spring in Pittsburgh, with blushing azaleas and dogwood blossoms as big as saucers. And in April, a little girl from Virginia was the thousandth patient of University of Pittsburgh neurological and otolaryngological surgeons to undergo an endonasal procedure (an alternative to traditional brain surgery, in which doctors remove cysts and tumors through the nose without making any incisions). But the remarkable nature of the season, and of the surgery, was not so interesting to her. The child preferred to talk about a dance recital or her pink dog, which, she explained with gravitas, "is not real."

The dermoid cyst at the base of her brain was, however, real. So the girl's parents told her that the doctors would remove it. That seemed reasonable. Six weeks after the procedure, as a photographer adjusted his camera, the girl fidgeted happily in a chair. Her mother called her by pet names and made silly faces to elicit a smile. Then the girl caught the flash of a bird in a tree, and, like any wonderfully ordinary child, turned to look.

—Jennifer Lee

PHOTOGRAPHY | JOHN MCCAULLEY

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

WHITE COAT CEREMONY
AUGUST 10
3 p.m.
Scaife Hall, Auditorium 6

LEVY LECTURESHIP
OCTOBER 10
Gary Firestein, MD, Speaker

MUSGRAVE LECTURESHIP
OCTOBER 17
5:30 p.m.
Magee-Womens Hospital Auditorium
Rodney Rohrich, MD, Speaker

BGSA RESEARCH SYMPOSIUM
OCTOBER 22
9 a.m.–6 p.m.
Starzl Biomedical Science Tower
S-100 & Lobby
For information:
www.bgsa.pitt.edu/events.asp

HOMECOMING WEEKEND
OCTOBER 23–26
Welcome Back to Campus Reception
Friday, October 24
6–8:30 p.m.
Pitt v. Rutgers
Saturday, October 25
Heinz Field
For information:
www.alumni.pitt.edu/homecoming

AAMC PITT RECEPTION
NOVEMBER 2
5:30–7 p.m.
AAMC Annual Meeting
Grand Hyatt
San Antonio, Texas
For information:
412-648-9000
vicedeanstaff@medschool.pitt.edu

WINTER ACADEMY
FEBRUARY 21, 2009
Naples, Fla.
For information or to request an invitation:
Pat Carver
412-647-5307
cpat@pitt.edu

MEDICAL ALUMNI WEEKEND 2009
MAY 15–18, 2009
Reunion Classes:

1949	1954
1959	1964
1969	1974
1979	1984
1989	1994
1999	

For information on an event, unless otherwise noted, contact the Medical Alumni Association: 1-877-MED-ALUM, 412-648-9090, or medalum@medschool.pitt.edu. Or visit the Web site: www.medschool.pitt.edu/alumni

TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

WHITE COAT CEREMONY
AUGUST 10
3 p.m.
Scaife Hall, Auditorium 6

LEVY LECTURESHIP
OCTOBER 10
Gary Firestein, MD, Speaker

MUSGRAVE LECTURESHIP
OCTOBER 17
5:30 p.m.
Magee-Womens Hospital Auditorium
Rodney Rohrich, MD, Speaker

BGSA RESEARCH SYMPOSIUM
OCTOBER 22
9 a.m.–6 p.m.
Starzl Biomedical Science Tower
S-100 & Lobby
For information:
www.bgsa.pitt.edu/events.asp

HOMECOMING WEEKEND
OCTOBER 23–26
Welcome Back to Campus Reception
Friday, October 24
6–8:30 p.m.
Pitt v. Rutgers
Saturday, October 25
Heinz Field
For information:
www.alumni.pitt.edu/homecoming

AAMC PITT RECEPTION
NOVEMBER 2
5:30–7 p.m.
AAMC Annual Meeting
Grand Hyatt
San Antonio, Texas
For information:
412-648-9000
vicedeanstaff@medschool.pitt.edu

WINTER ACADEMY
FEBRUARY 21, 2009
Naples, Fla.
For information or to request an invitation:
Pat Carver
412-647-5307
cpat@pitt.edu

MEDICAL ALUMNI WEEKEND 2009
MAY 15–18, 2009
Reunion Classes:

1949	1954
1959	1964
1969	1974
1979	1984
1989	1994
1999	

For information on an event, unless otherwise noted, contact the Medical Alumni Association: 1-877-MED-ALUM, 412-648-9090, or medalum@medschool.pitt.edu. Or visit the Web site: www.medschool.pitt.edu/alumni

TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu