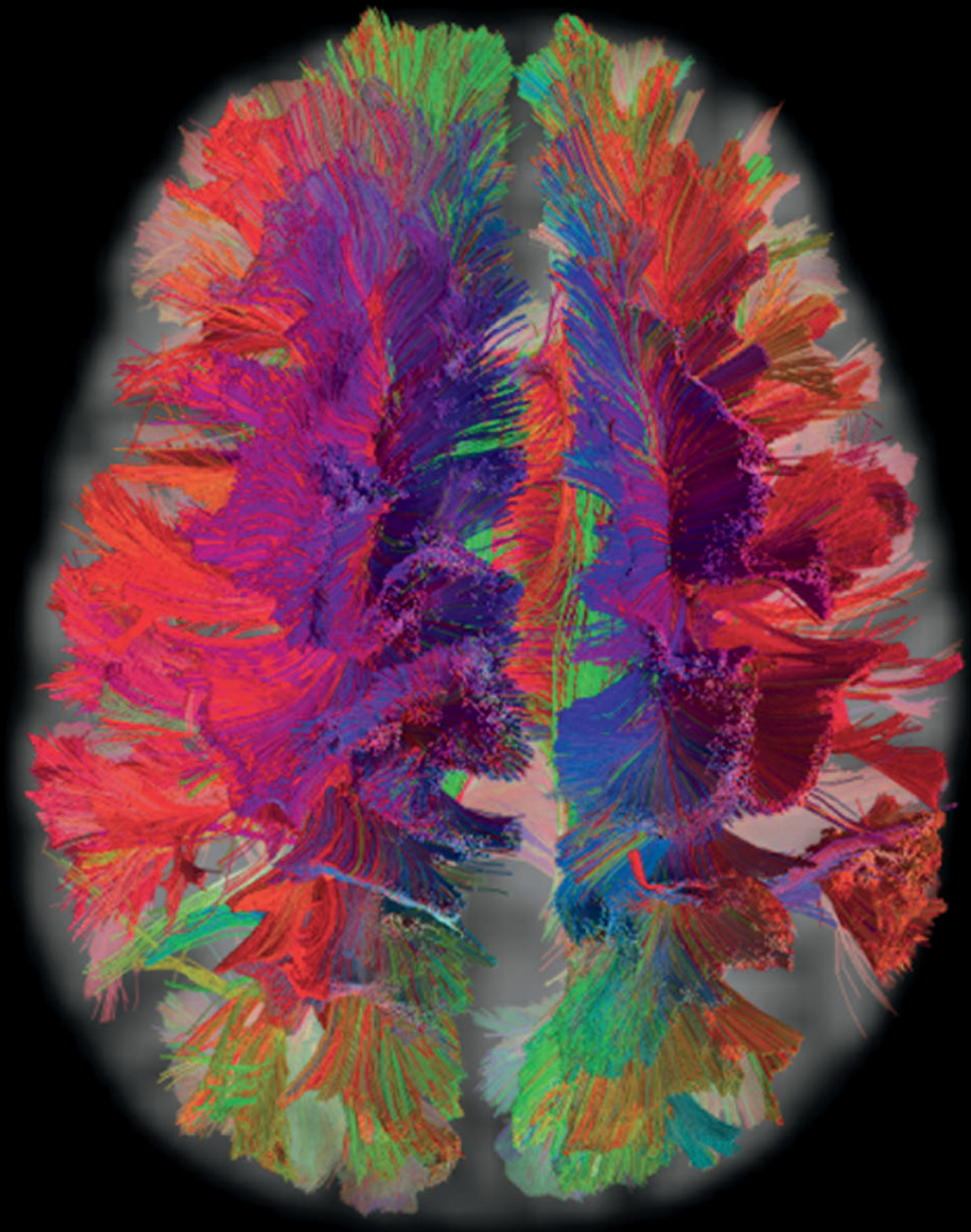
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2012

PITTMED



MISSING LINKS

PITT DOCS CAN NOW SEE WHERE BRAIN NETWORKS ARE CUT OFF

A FAIR GRADE

Congratulations to my grandniece, Jenelle Pifer, for her wonderful remembrance of Dr. Hooker ["The Great Equalizer," Summer 2012]. In those days we had tests known as "rat races" in which we were to identify tagged parts of the human body laid out on a table. I failed one. Dr. Hooker later called me into his office and said, "I realized you were sick that day, and I should have told you to go home and rest. Your grades in anatomy have always been high, and I'm not going to allow one bad grade to destroy your record. Therefore, I'm throwing it out!" I was very touched by his awareness and caring.

Charles Pifer (MD '56)
Carmel, Calif.



RECENT MAGAZINE HONORS

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

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

2011 CASE, District II Silver, Staff Writing

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

2011 IABC Golden Triangle Award of Honor, Magazines

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

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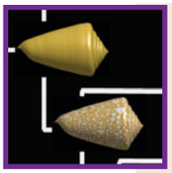
STEP RIGHT UP

Okay, maybe your life feels like a three-ring circus. But you can spare a minute to catch us up on your doings, right? Tell us about your career advancements, honors you've received, appointments, volunteer work, publications, and other death-defying acts. And we love to hear old Pitt memories. For instance, what's the story with this uni-doc we found in Pitt's 1970 *Hippocratean*? Quit clowning around and drop us a line at the contact info listed to the right, or friend us on Facebook at www.pittmedfb.pitt.edu/.

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UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2012 (SEPT/OCT/NOV)

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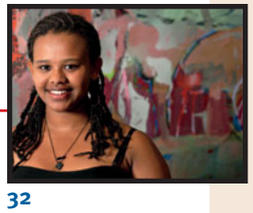
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Neurosurgeon and basic scientist Robert Friedlander, who makes astonishingly good use of his time, says Pitt has everything he was looking for in a chair opportunity.

BY DAVID R. ELTZ

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New technology, developed at Pitt, tracks the physical connections that allow the brain to work. It's already helping patients and neurosurgeons.

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Mitochondria's Many Missions 22

Addicts, Parkinson's, ischemia/reperfusion injury, and very sick flies. Mitochondria tie them together.

BY JOE MIKSCH

Survival of the Funded 27

Nationally, the ecosystems that support getting scientific discoveries into the clinic have been pretty fragile. A few years ago, the NIH stepped in to help. Pitt's Clinical and Translational Science Institute has helped create a healthy environment here.

BY ELAINE VITONE

CONTRIBUTORS

SUDHIR PATHAK and KEVIN JARBO [cover, "Missing Links"] are two of the figures behind why the new enhanced MRI technique called high-definition fiber tracking (HDFT) works, and why it looks so cool. Pathak studied mathematics and scientific computing in India and later received a master's in biomedical engineering from Carnegie Mellon University. As a programmer in the Schneider Lab at Pitt, he developed HDFT's complex algorithms and now enjoys exploring how information and art intersect. HDFT is "art constrained by information," he says. Pathak finds the scans so visually compelling he's been using his free time to adapt them into original artwork; his pieces are featured in the online gallery of the Organization for Human Brain Mapping. Jarbo is more interested in the scans' clinical applications. He received his bachelor's in biology at Pitt in 2006. Now, as assistant researcher in the lab, he helps doctors read the scans properly. HDFT finally does the organ justice. "The reason why it ends up looking so cool," he says, "is because the brain actually looks that cool."

COVER

The brain, in all its connective glory, revealed. (Cover: Schneider Lab © 2012.)

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JOSHUA FRANZOS

Pitt med alumnus Gordon Sun (MD '06), a Robert Wood Johnson Clinical Scholar at the University of Michigan, details in an August *New England Journal of Medicine* paper how emerging Asian powers are ramping up national funding for medical research and development; they are poised to fill the void being created by contracting federal U.S. funding. The NIH's proposed FY 2013 budget continues the 10-year failure to match the increasing cost and opportunities of medical research. Unless Congress changes its course, the debt reduction "sequestration" would lead to the closure of many good labs and the end of many careers, especially those of young investigators.

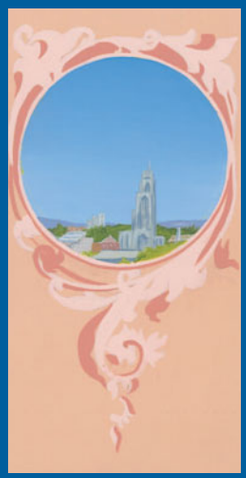
Of course, China, India, South Korea, et al. have some catching up to do. The United States has held a premier position in medical research for more than half a century; it certainly won't be outpaced overnight. But perhaps the words "catching up" and "outpace" evoke the wrong images. Science is not a horse race—it's a global collaboration. As others invest in acquiring knowledge, we all benefit. Yet I admit that I'd prefer that our country also continue to value medical research as an engine for innovative care and economic growth. Our federal investment in medical research is less than 1 percent of our GDP; the Asian powers invest 2 to 5 percent, with as much as a 67 percent increase, year to year. Already this is leading to the transfer of talent and resources from our shores. Our nation is likely to suffer a loss of jobs, access to experimental treatments, and other, more difficult to measure, windfalls that accompany a commitment to inquiry and innovation.

Still, this is an exciting time here at home. Our medical school's extraordinary rise in prominence continues. Yet another stellar class has joined us this August; we also welcomed some of China's best and brightest to our campus—and we are pleased to have taken this step in global collaboration. These young people will be working with our faculty as the first group to pursue a new, required, two-year biomedical research component of the medical school curriculum of Tsinghua University ("the MIT of China"). Yigong Shi, dean at Tsinghua (and a renowned structural biologist lured back to China from Princeton), has partnered with us so that Tsinghua students will be immersed in Western research culture and the critical thinking it promotes—as he was during his own U.S. graduate training. While Chinese students often gain a deep and impressive understanding of their subjects, their academic tradition does not encourage them to challenge scientific dogma.

When considering such cultural and philosophic nuances, I was introduced to this passage penned by an 8th-century Taoist poet: *Wild geese fly across the long sky above./Their image is reflected upon the chilly water below./The geese do not mean to cast their image on the water;/Nor does the water mean to hold the image of the geese.* Although I confess to a limited knowledge of classical Chinese poetic form, I think that the reflection of geese can be understood as a metaphor for the often serendipitous nature of scientific observation and the creativity inherent in how we capture the accidental observation.

I look forward to the serendipity and creativity ahead. And to watching our students soar—whether they started their journeys by flying across the long sky from Beijing or busing it on the 61B from Braddock.

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



Devoted to noteworthy happenings

at the medical school

TAKING MEDICINE PERSONALLY

The numbers are big: $300 million, 350,000 square feet, 375 jobs. So is the focus: to delve into the inherited and environmental factors that account for individual susceptibility to illness. Planning is under way for the UPMC Center for Innovative Science. Officials are evaluating what was the Ford Motor Co. building—which sits on Baum Boulevard near the Hillman Cancer Center and UPMC Shadyside—as a potential site. The new center will give University of Pittsburgh School of Medicine faculty members a base for work they hope will lead to tailor-made treatments. *—Joe Miksch*



ZGF ARCHITECTS

A rendering of the UPMC Center for Innovative Science, at a proposed site in Shadyside.

FOOTNOTE

World Wrestling Entertainment star The Great Khali expects to return to the ring following a successful operation this summer at UPMC Presbyterian to remove a tumor from his pituitary gland. The tumor caused surplus production of growth hormone, leading to a condition known as acromegaly, characterized by excessive growth in muscles and organs. The Great Khali, whose real name is Dalip Singh, finds such symptoms of use in his wrestling career—as did the late André the Giant. Khali stands 7-foot-1 and weighs 347 pounds.

Critical Success

Despite being only a decade old, the University of Pittsburgh's Department of Critical Care Medicine—believed to be the nation's first—recently received a significant acknowledgment of its influence. Of 20 intensive-care specialists granted the new title of Master in Critical Care Medicine Fellow, the Society of Critical Care Medicine's highest honorific, seven were former or current faculty of Pitt's ahead-of-its-time department.

Three of the new fellows represent the legacy of intensive-care research at Pitt: Mitchell Fink, an MD and founding chair of the department; emeritus professor Ake Grenvik, an MD/PhD; and legendary intensive-care physician and researcher Peter Safar, who died in 2003 and was bestowed the title posthumously.

Four current faculty members also were named fellows: department chair and professor Derek Angus, who is an MD/MPH, and MDs Patrick Kochanek (professor and vice chair, as well as director of Pitt's Safar Center for Resuscitation Research) and professors Michael Pinsky and Ann Thompson. *—Justin Hopper*



CAMI MESA

Edward Chu

On Herbal Relief from Chemotherapy

In an open-air market in China, locals might be stocking their kitchens or grabbing a snack; they might also be visiting a doctor, often a practitioner of both Western and traditional Chinese medicine. After an on-the-spot exam, if the complaint is of belly aches, nausea, or diarrhea, the physician might prescribe an herbal formulation called Huang Qin Tang, serving it as a tea or a smoothie.

University of Pittsburgh professor Edward Chu (shown above), an MD who is deputy director of the University of Pittsburgh Cancer Institute, chief of Pitt's Division of Hematology/Oncology, and an associate director of Pitt's Drug Discovery Institute, and his colleague, Yung-chi (Tommy) Cheng, a PhD pharmacologist at Yale University, have tested the herbal compound in animal and blind clinical pilot studies. The preliminary studies showed it offers profound relief from gastrointestinal ailments for patients undergoing various chemotherapies. Huang Qin Tang has been used to treat such ailments for nearly 2,000 years.

It may even help fight certain cancers. Chu and Cheng's work is supported by the National Cancer Institute's Office of Cancer Complementary and Alternative Medicine.

Why they took on the studies

We've seen friends, relatives, and colleagues who've had a variety of cancers experience significant side effects of traditional Western medicines; and unfortunately, their disease continues to progress. Then they'll be treated with these herbal Chinese medicines and have some pretty dramatic responses—either alone or when used with chemotherapy. Their quality of life seemed to be better, and their toxicity was diminished. And since both of us are of Chinese origin, we said, "Maybe we need to study this in a scientifically rigorous fashion."

What he might not have guessed when he started

We found when we combined the herb with chemotherapy, the anti-tumor activity was maintained. In fact, [it seemed to be] enhanced. So in a new study [in patients undergoing chemotherapy for metastatic colon cancer], we're going to be looking at not only the effect on toxicity but also response rates, progression-free survival, overall survival, and quality-of-life issues.

We are trained, as Western physicians, to look for the active ingredient that can target a particular key pathway involved in tumor growth and proliferation. In traditional Chinese medicine and Eastern medicine, the idea is to use a formulation that's made up of multiple components [like HIV drug cocktails]. In animal studies, what we found is you needed all four herbs to be able to maximize the anticancer therapy and to maximize the so-called cytoprotective activity.

—Interview by Erica Lloyd

Faculty Snapshots

This year, Brian Zuckerbraun and Nuria M. Pastor-Soler were invited to join the American Society for Clinical Investigation (ASCI). The society, established in 1908, is one of the nation's oldest and most respected medical honor societies. According to its Web site, it "represents active physician-scientists who are at the bedside, at the research bench, and at the blackboard."

Pastor-Soler, an assistant professor of medicine and of cell biology, is investigating the regulation of a protein complex that pumps protons across membranes, helping to guide the normal function of kidney tubules and the male reproductive tract. Pastor-Soler's work has led to significant findings regarding the behavior of kidneys when acid levels in bodily fluid are abnormally high (acidotic states) as well as sperm maturation and male fertility. She believes that her lab's work will also help elucidate how kidney cancer cells metastasize.



Pastor-Soler



Zuckerbraun

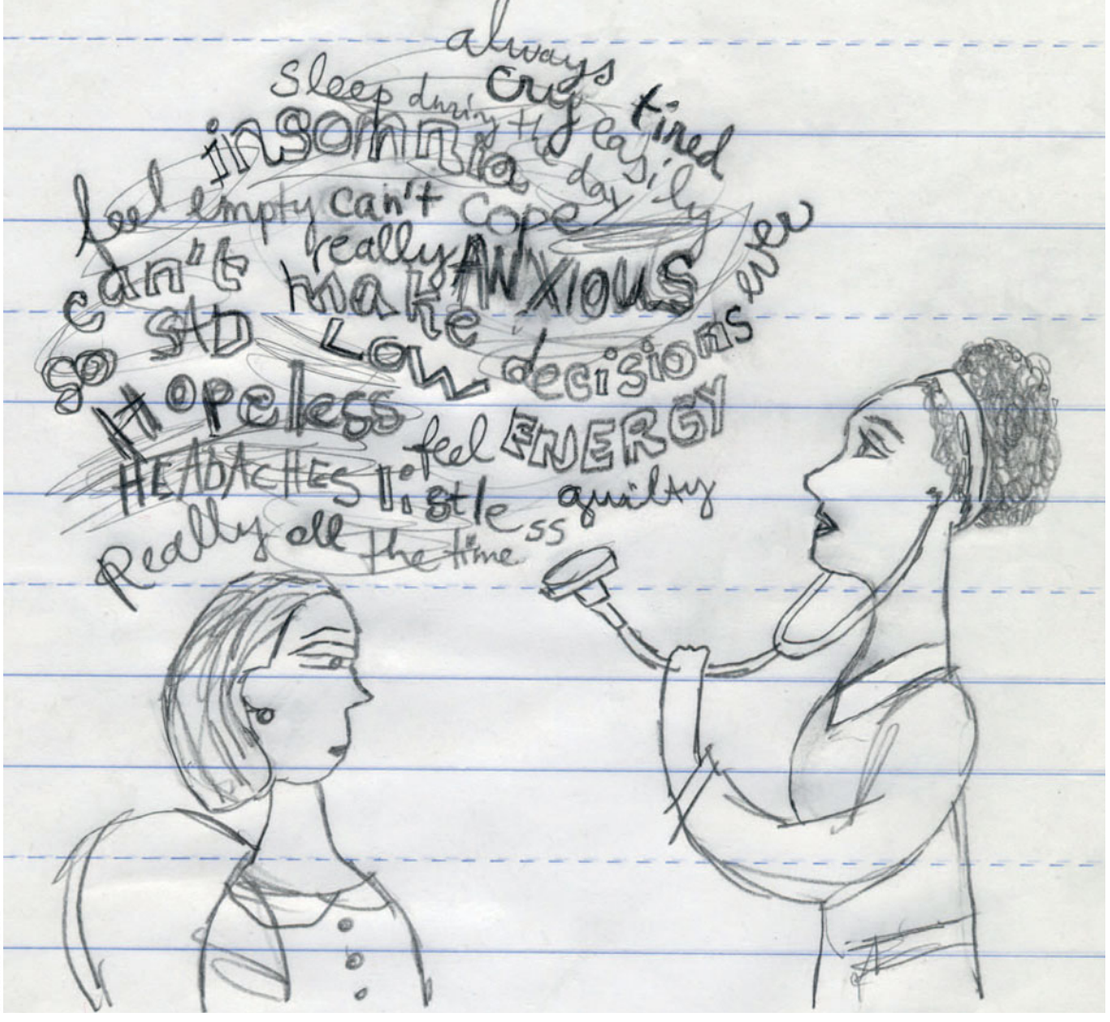
Zuckerbraun's laboratory has focused primarily on the use of gaseous signaling molecules and their protective effects. He has investigated the use of carbon monoxide and nitric oxide as shielding agents against organ and vascular injury in a number of disease states. He says he is "very interested in developing therapeutics that harness the effects of these gaseous molecules and signaling pathways to protect against tissue injury and death."

Up to 80 individuals can be inducted each year—ASCI's active members must first approve the group—and only those who are under 45 years of age are considered. Pitt med claims 22 ASCI members.

In addition, two School of Medicine faculty members were elected to the Association of American Physicians (AAP) this year. Neurological surgery chair Robert Friedlander, an MD and UPMC Endowed Professor of Neurological Surgery, and Ian Pollack—MD, codirector of the Brain Tumor Program at the University of Pittsburgh Cancer Institute, chief of pediatric neurosurgery at Children's Hospital of Pittsburgh of UPMC, and Pitt's Walter Dandy Professor of Neurosurgery—were among the 61 named to join the elite, 127-year-old organization. *—Hayavadhan Thuppal*

All in the Family

This summer, Pitt's Department of Family Medicine, with UPMC and Western Psychiatric Institute and Clinic (WPIC), graduated its second trainee from the joint family medicine and psychiatry residency program, which was established in 2007 and is one of only a handful in the country. James Dewar, an MD, associate professor of family medicine, and the department's vice chair for education, says the program addresses an underserved need in family medicine. About 30 to 40 percent of patients seen by family physicians show symptoms of mental disorders, he says. The joint program, says Michael Travis, MD and director of Psychiatry Residency Training at WPIC, teaches its graduates to excel as family physicians and psychiatrists. *—JM*



CATHERINE LAZURE

FLASHBACK

Today, the Falk Medical Building is known as a hub of clinical care and is home to the General Infectious Diseases Clinic and HIV/AIDS Care Center. But another kind of home occupied the space opposite Meyran Avenue at Fifth Avenue until construction of the Falk Clinic, funded by brothers Maurice and Leon Falk, began in the late 1920s. Instead of demolishing the private residence standing on the site, workers put it up on rails and moved it down the street to make room for the new outpatient dispensary.



UNIVERSITY OF PITTSBURGH HISTORIC PHOTOGRAPHS

EVOLUTION OF A DEPARTMENT

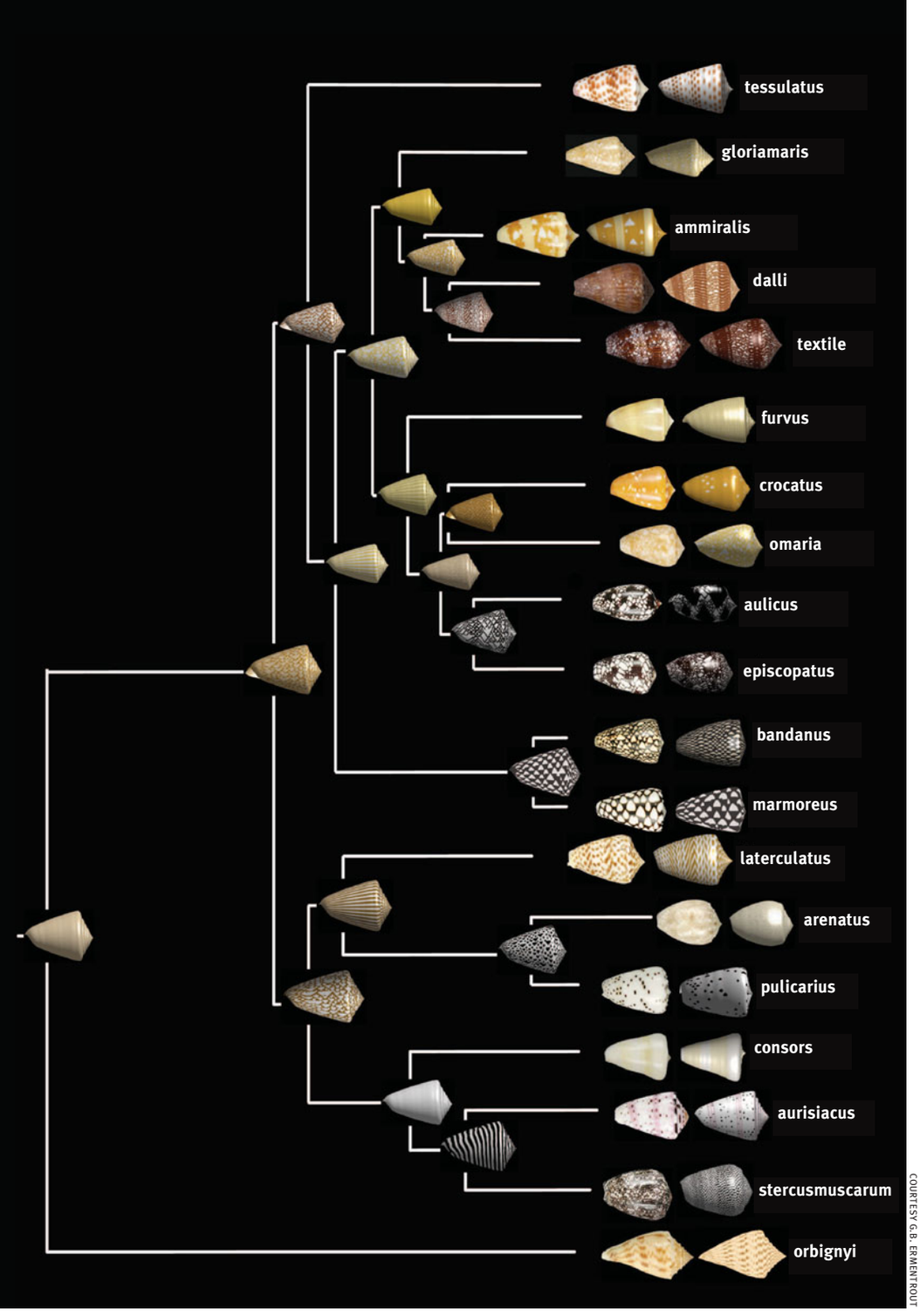
Plastic surgery has long been one of the School of Medicine's strengths. On July 1, this strong division of the Department of Surgery became a department in and of itself.

Founding chair of the Department of Plastic Surgery, J. Peter Rubin, an MD, says that coming out from under the umbrella of the larger department is a logical step. "We've seen this [similar evolution] with orthopaedics, otolaryngology, and neurosurgery," he says. "We have developed our own educational pathway, separate board certification; we've had our own journal since the 1940s. Taken all together, plastic surgery is truly an independent specialty."



Rubin

The division's ascension to department status was celebrated in a ceremony in the Commons Room of the Cathedral of Learning on June 29 with a crowd of 275, including plastic surgery specialists from around the nation, 50 of them residency alumni. The new department has 19 clinical and five research faculty with the rank of associate professor or higher. *—JM*



COURTESY G.B. ERMENTROUT

A SNAIL'S TRACE

Sea snails in the *Conus* genus are known for their beautiful shell patterns that vary from species to species. These intricate patterns are created by the snail's neural responses. The patterns amount to a visible record of the nervous system—an organ that can't be preserved in the fossil record. Earlier this year, researchers, including Pitt's Distinguished University Professor of Computational Biology G. Bard Ermentrout, announced they'd created a computer model capable of illustrating evolutionary changes in *Conus* pigmentation and used it to model living as well as ancestral species. The snails (and some heady computing) have given scientists a window to neural evolution. (In the above graphic, brackets to the far left show modeled, ancestral shells. On the far right are actual, present-day shells paired with their models.) —*JH*

Name Dropping

The University's annual science festival reliably brings a number of fascinating folks to campus.

This year's festival, Science2012—Translation, which kicks off October 3 this year, features a lecture by Brian Druker, winner of Pitt's Dickson Prize in Medicine. Druker, an oncologist most known for his central role in the development of imatinib (Gleevec), a drug that targets the molecular defect in chronic myeloid leukemia, also spearheaded the clinical trials of the drug. (It's an approved treatment for seven cancers.) He directs the Knight Cancer Institute at Oregon Health & Science University, where he is also associate dean for oncology, JELD-WEN Chair of Leukemia Research, and a Howard Hughes Medical Institute (HHMI) Investigator. Among Druker's litany of awards are the American Cancer Society Medal of Honor, the Charles F. Kettering Prize from General Motors Cancer Research Foundation, the Lasker-DeBakey Clinical Medical Research Award, and the Japan Prize in Healthcare and Medical Technology. He is a member of the National Academy of Sciences and the American Academy of Arts and Sciences.

Ronald R. Breaker, HHMI Investigator and Henry Ford II Professor and chair of the Department of Molecular, Cellular, and Developmental Biology at Yale University, will deliver the 2012 Mellon Lecture. His work led to the discovery and characterization of many new RNAs, including riboswitches—a mode of gene regulation in which metabolites regulate the activity of certain pathways by directly binding to messenger RNA without the direct involvement of proteins. Breaker's work has been honored with the National Academy of Sciences' Award in Molecular Biology.

Hofmann Lecturer Karl Deisseroth, an MD/PhD, led the way in the development and application of optogenetics, a technology that "uses light to control millisecond-precision activity patterns in genetically defined cell types within the brains of freely moving mammals," says Deisseroth. This method allows for the real-time study of the relationship between neural circuits and behavior. Deisseroth, associate professor of bioengineering and of psychiatry and behavioral sciences at Stanford University and an HHMI Early Career Scientist, received the 2010 Koetser Prize and the 2011 W. Alden Spencer Award for his work. —*JM*



BACK TO YOU, SUSAN

As a woman lay in front of her on Pittsburgh's South Negley Avenue, fourth-year medical student Vanessa Franco was faced with a premature and unexpected test of her training.

"Her face was pretty blue," says Franco. "When I checked her pulse, I realized she didn't have one." A fellow fourth-year, Ranmal Samarasinghe, monitored the woman's vital signs as Franco performed CPR chest compressions. (Med students at Pitt are required to be certified in CPR, though neither Franco nor Samarasinghe had ever administered it before on anyone.)

"I was terrified of losing her," Franco revealed to a reporter later.

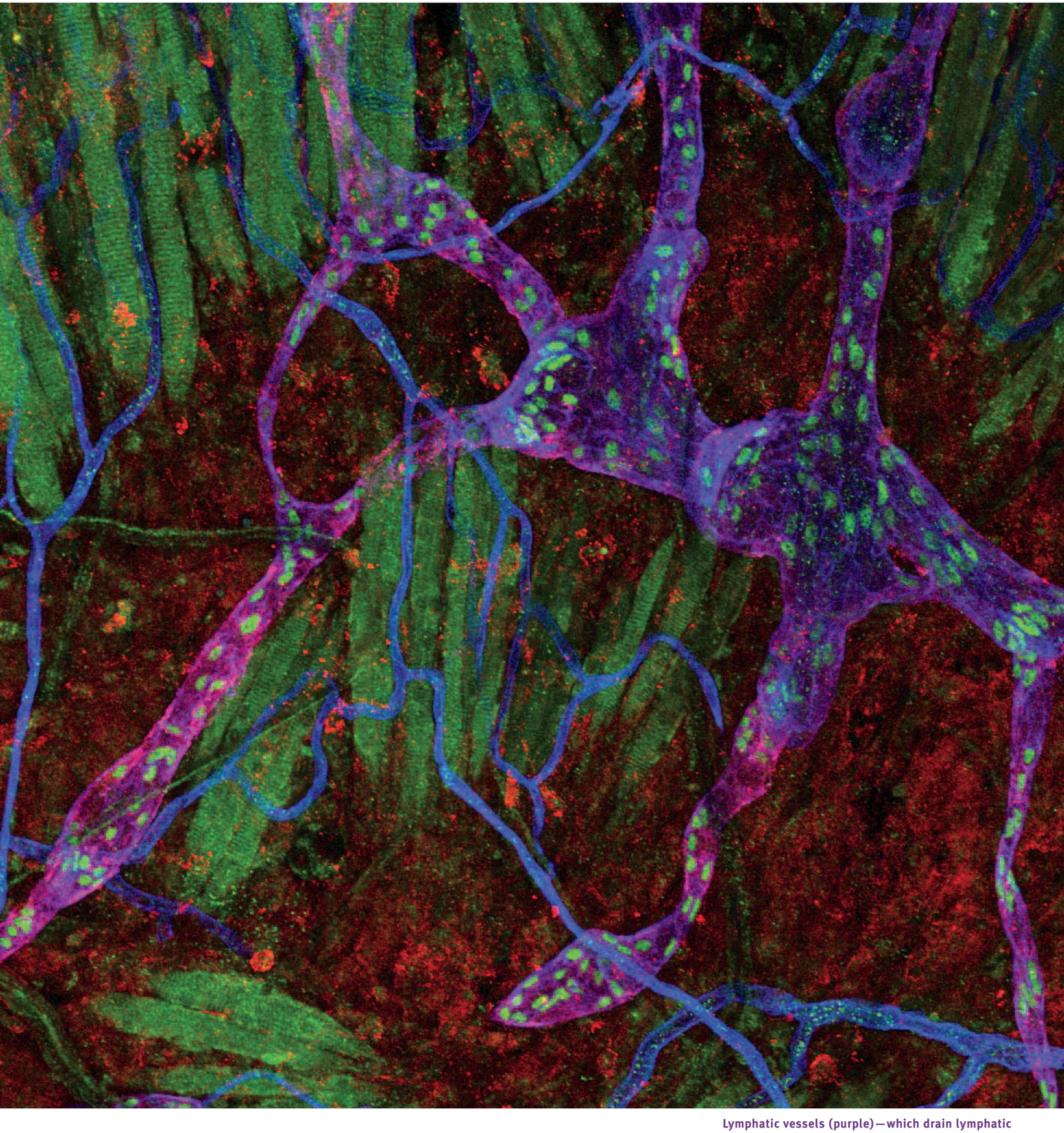
Gradually, the color returned to the woman's face, and paramedics arrived with an AED to shock her heart back into rhythm before she was rushed to UPMC Shadyside's ER.

The woman collapsed on a Sunday morning last November, as Franco and Samarasinghe were driving to Giant Eagle in Shadyside. Where South Negley crosses the Port Authority East Busway, a group of people huddled around the woman were yelling for help. Franco and Samarasinghe pulled over and intervened. It turned out that the woman was a KDKA news anchor and mother of three, Susan Koeppen (shown above, flanked by the students), who suffered from a defect of the mitral valve, which facilitates the flow of oxygenated blood in the heart. She had gone into cardiac arrest while on a run with friends. (She was training for a half marathon.) In March, the now-40-year-old Koeppen underwent open-heart surgery to repair the faulty valve, then made a full recovery, and resumed her position at the news desk in May.

Samarasinghe and Franco are in the medical scientist training program; they will finish their MDs this fall and then pursue postdoctoral work before starting residencies. Both have PhDs in neuroscience. Franco hopes to enter emergency medicine; Samarasinghe recently decided on neurology. Franco has been pursuing research on marathon runners and heart health. She conducted a pilot study during the Pittsburgh Marathon that she hopes to replicate in other races around the country. (She pursued the study with the help of executive vice chair of emergency medicine Clifton Callaway, an MD/PhD who is the Ronald D. Stewart Professor of Emergency Medicine, and Dave Hostler, a PhD research associate professor of emergency medicine.) The encounter with Koeppen has made the work even more meaningful to Franco.

—by Hayavadhan Thuppal
—Photo by Martha Rial

Explorations and revelations taking place in the medical school



Lymphatic vessels (purple)—which drain lymphatic fluid from tissue—next to blood vessels (blue)

THE FAMILY THAT ASSAYS TOGETHER

THE GENETICS OF LYMPHEDEMA REVEALED AT A REUNION | BY ALLISON A. CURLEY

Nearly two decades ago, Pitt's David Finegold (BS '68, MD '72, Res '75), professor of pediatrics and medicine, and Robert Ferrell, professor of human genetics in the Graduate School of Public Health, were chatting over a cup of coffee. Finegold mentioned that his wife, physiatrist Judith Esman (Res '87), worked with patients with lymphedema, an often-disabling retention of fluid (usually in the limbs) that results from abnormal drainage of the lymphatic system. Ever the curious geneticist, Ferrell asked his usual question: "Is it ever inherited?" As it happened, Esman was treating a father and his twin daughters for Milroy's disease, a hereditary form of lymphedema. In fact, many members of this family were affected, and they were willing to participate in research. Finegold and Ferrell couldn't pass up the opportunity to study an obscure disorder that was clearly genetic, and so they set out to identify the genes underlying Milroy's disease.

Some days later, the researchers rented out a local fire hall and hosted a family reunion. At one end of the hall were cookies and coffee and at the other, blood draws and clinical exams. The team collected DNA samples from 40 family members; others mailed in samples later. Such was the beginning of the largest-ever genetic study of heritable lymphedema, the Pittsburgh Lymphedema Family Study, which now includes more than 300 families worldwide.

Three years in, Finegold and Ferrell identified the first-known causative gene, which codes for a protein named VEGFR3 and is important in the development of the lymphatic system. They went on to find three more of the seven known causative genes—and have pinpointed the genetic culprits in about a third of the families they've studied.

The lymphatic system is a network of vessels that collect fluid from tissue throughout the body and deliver it to the bloodstream and lymph nodes. Hereditary (or primary) lymphedema, in which the system develops abnormally, occurs in roughly one in 6,000 people.

Far more common is secondary lymphedema. Secondary lymphedema occurs in about 30 percent of women treated for breast cancer; for many years, doctors assumed it was a result of the trauma of surgery, chemotherapy, or radiation. But not everyone in treatment gets lymphedema, so Ferrell and Finegold reasoned that trauma probably isn't the only cause. They suspected that genes played a role in this form of lymphedema, too, and set out to prove it. "If we're right, and we can identify a subset of women who are going to be at risk, we can potentially start preemptive treatment, such as massage and compression garments," says Finegold.

Secondary lymphedema occurs in about 30 percent of women treated for breast cancer.

In April, the team published results of a study that examined several candidate genes in a population of women with secondary lymphedema following breast cancer treatment. They found that these women—but not healthy women or those with breast cancer who hadn't experienced secondary lymphedema—had mutations in the gene coding for connexin 47 (Cx47). The researchers had previously implicated the gene in primary lymphedema.

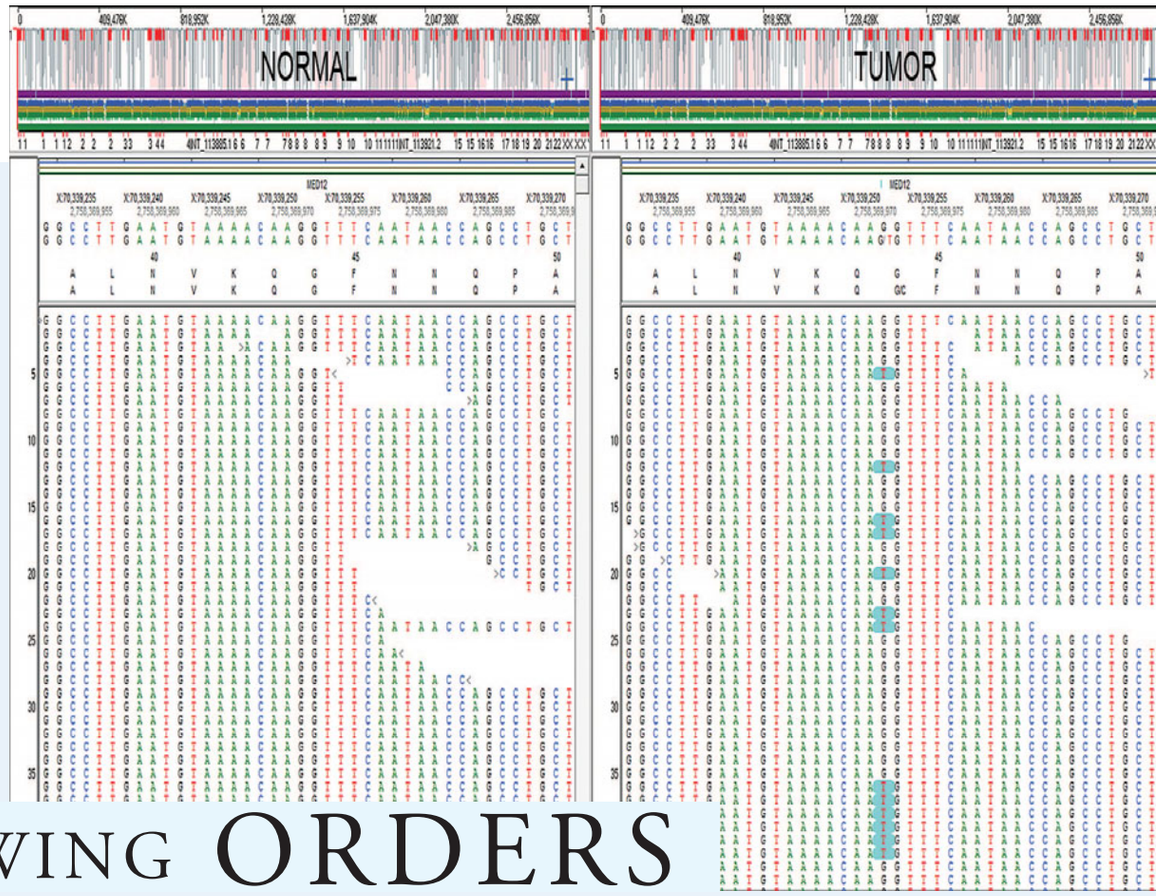
Drawing on the expertise of research assistant professor of cell biology Catherine Baty, who joined the team in 2008, the researchers also examined the functional consequences of the Cx47 mutations. Connexins are the primary components of structures called gap junctions; recent evidence suggests they are important in the movement of lymph fluid. The investigators reasoned that the deficits resulting from the mutations may be subtle, because patients don't develop the condition until after the insult of cancer treatment. Using cultured human cells with mutations introduced, they showed that proteins trafficked normally to the cell surface but exhibited other functional impairments.

Ultimately, the team hopes that knowledge of the underlying genes could lead to a cure. In fact, drugs modifying the function of connexins are already available; they were initially developed for cardiovascular disease.

The findings could also have implications for wound healing among other conditions linked to fluid imbalance, says Ferrell. He calls lymphedema a "window on lymphatics" and a way to identify genes that are important in the functioning of the lymphatic system as a whole. ■

JENNY M. KARLSSON, CENTER FOR BIOLOGIC IMAGING

"CAPTAIN" GENE
A NEW TARGET
FOR FIBROID THERAPY
BY DANA YATES



RAJKOVIC LAB

JUST FOLLOWING ORDERS

LEFT: Genome sequencing of normal uterine tissue. RIGHT: Highlighted letters show a genetic change on the X chromosome. A single gene mutation, MED12, causes fibroid tumor growth—it was found in 70 percent of the fibroid samples Rajkovic studied.

The National Institutes of Health reports that, by age 50, half of all women will have fibroids. Consisting of muscle cells and other tissues found in and around the wall of the uterus, fibroids cause no symptoms for some women. For others, however, fibroids can lead to a range of problems. They include frequent urination, lower back pain, heavy menstrual bleeding, painful sex, a sensation of fullness or pressure in the lower abdomen, miscarriages, and premature labor. In extreme cases, fibroids can weigh up to 100 pounds, causing severe disfigurement. Fibroids are the leading cause of hysterectomies in the United States.

But what causes them? A discovery made by the University of Pittsburgh's Aleksandar Rajkovic indicates that, for the majority of women, a single gene mutation is to blame.

Rajkovic, an MD/PhD and associate professor in the School of Medicine's Department of Obstetrics, Gynecology, and Reproductive Sciences, is division chief of genetics at Magee-Womens Research Institute. He is also the senior author of a study that identified the genetic pathway that contributes to the development of uterine fibroids. The team's findings were published in the online journal *PLoS One* in March.

"Right now, the only treatment for fibroids involves surgically removing them from the uterus. But that solution isn't perfect," he says. "For approximately 50 percent of women, the fibroids come back, and redoing the surgery is associated with even more complications." Among them, infection, loss of the whole uterus, and death.

As a gynecologist who is familiar with those risks, Rajkovic is focused on finding noninvasive ways to eliminate fibroids. Using genome-sequencing technology, Rajkovic's group figured out the exact order of the chemical building blocks of fibroid and healthy uterine tissues.

"We wanted to know if there were differences or genetic changes in the tissues that allowed fibroids to grow," he says.

By examining the fibroid and normal uterine tissues from five women who had undergone hysterectomies, the research team learned that three of the women had fibroids with mutations in a gene called MED12. A regulatory gene, MED12 acts like a captain, telling the genes downstream what to do.

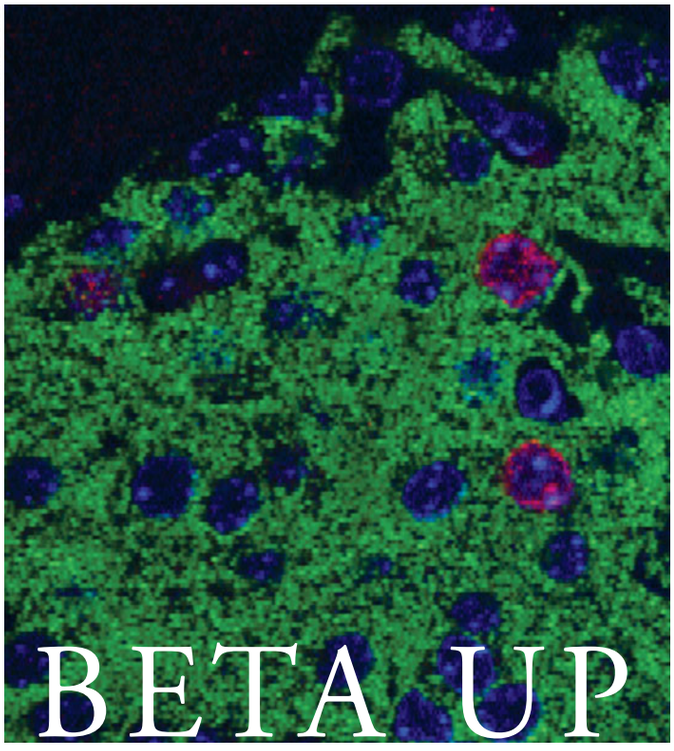
The researchers broadened their exploration and turned to a biobank for additional tissue samples, looking for the MED12 mutation in 143 uterine fibroids. The results: approximately 70 percent of the samples contained the mutation, whereas normal uterine tissue samples did not.

"Ultimately, we hope to target the other players that MED12 regulates," says Rajkovic.

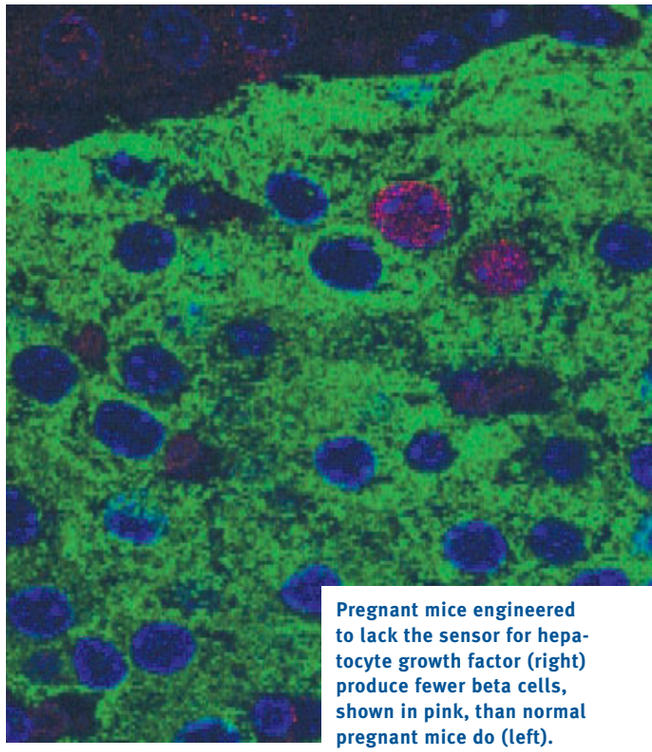
"They are the major carriers of the information that MED12 is trying to convey, and we could modify their function pharmaceutically."

Rajkovic's research group is now exploring the mechanism between MED12 and other genes that take orders from it. To that end, the researchers are working with mice with modified MED12 genes. The team also wants to determine whether the MED12 mutation makes fibroid regrowth more or less likely after surgical treatment.

And what about the fibroid samples that lack the MED12 mutation? In those cases, Rajkovic speculates, multiple genes may be involved, interacting with environmental factors to spur fibroid growth. Future research studies will investigate that process, but Rajkovic is still busy unraveling the MED12 mystery. ■



JUAN CARLOS ALVAREZ-PEREZ



Pregnant mice engineered to lack the sensor for hepatocyte growth factor (right) produce fewer beta cells, shown in pink, than normal pregnant mice do (left).

BETA UP

CAN HGF STRIKE OUT GESTATIONAL DIABETES?

BY MELINDA WENNER MOYER

For an expectant mother, a diagnosis of gestational diabetes—which afflicts 135,000 pregnant women in the United States every year—can be terrifying. For the remainder of her pregnancy, she must carefully monitor her blood sugar as well as her baby's size to minimize the risk of labor difficulties and stillbirth. Further, she and her baby will always be at heightened risk for type 2 diabetes. Historically, researchers have understood very little about the cause of gestational diabetes, but a new study by a team led by Adolfo Garcia-Ocaña, a PhD associate professor of medicine at the University of Pittsburgh, suggests that the difference between a healthy pregnancy and a diabetic one may boil down to problems with a single liver protein and its molecular sensor.

This protein, called hepatocyte growth factor (HGF), has actually been a longtime interest of Garcia-Ocaña's. It was discovered in 1990 by Pitt's George Michalopoulos, MD/PhD and chair of Pitt's Department of Pathology. Soon after arriving at Pitt in 1997, Garcia-Ocaña wondered: Given HGF's ability to induce cellular growth in tissue, could the protein be used to grow more beta cells (found in the pancreas) in people with type 1 and type 2 diabetes—diseases characterized in part by a paucity of beta cells? In 2000, Garcia-Ocaña genetically engineered mice so that their beta cells over-produced HGF, and the mice grew more and bigger beta cells than normal mice did. HGF, it seemed, played an important role in beta-cell growth and replication.

It occurred to Garcia-Ocaña that beta-cell growth was also an important aspect of a healthy pregnancy. "A mother adapts to enhanced metabolism during pregnancy in a way that increases the number of insulin-producing cells and increases the amount of insulin that's being produced by these cells," he explains. After delivery, her body kills off the extra beta cells. He knew from research published in 1995 that during pregnancy, HGF levels in the body skyrocket. "So we thought, *Hmmm. Maybe HGF plays a role in gestational diabetes.*" Perhaps the condition arises when HGF is unable to do its job, he imagined.

In order for pancreatic cells to respond to HGF, they have to express its sensor, c-MET, on their surface. Garcia-Ocaña wondered what would happen if HGF couldn't communicate with c-MET during pregnancy. To find out, he genetically engineered female mice to be unable to produce c-MET on their beta cells. Then he watched what happened.

At first, the mice did just fine. They seemed perfectly normal. But then, when they became pregnant, "the expansion of insulin-producing cells was blunted, and insulin secretion was also diminished," he explains.

In other words, "These mice developed gestational diabetes."

When Garcia-Ocaña studied the mice further, he discovered that their bodies prematurely killed off beta cells during late pregnancy, too.

Garcia-Ocaña and his collaborators—who include the School of Medicine's Cem Demirci, Sara Ernst, Juan Carlos Alvarez-Perez, and Gabriella Casinelli, among others—published the findings online in March in *Diabetes*.

He doesn't yet know whether women who develop gestational diabetes tend to have problems with HGF or c-MET or both. So his team will analyze blood samples from this population to find out more.

Another unanswered question is whether HGF and c-MET affect beta-cell growth directly, or do so by way of additional proteins or receptors.

Garcia-Ocaña wonders whether doctors might one day treat or prevent gestational diabetes with therapies that regulate abnormal HGF/c-MET signaling.

He's considering the implications for type 1 or 2 diabetes, as well. Boosting the growth of insulin-producing beta cells might treat or prevent those disorders, too. ■



NOT QUITE CATCHING UP WITH
ROBERT FRIEDLANDER
BY DAVID R. ELTZ

EVERY MOVEMENT COUNTS

Robert Friedlander is, among other things, a neurosurgeon. Whenever he is working inside someone's brain, excising a brain tumor or fixing an artery, he is in a state of heightened awareness. In his line of work, wandering just a millimeter off could mean nicking a nerve, clipping a blood vessel, altering lives. "Every movement counts," says Friedlander, who is chair of the University of Pittsburgh's Department of Neurological Surgery.

That philosophy seems to apply to all aspects of his life. Friedlander has made every movement count in a career in which he has not only helped patients with his surgical talents, but also made important discoveries about programmed cell death and how interrupting that cascade of death may one day translate into treatments for patients with neurological diseases.

Growing up in Caracas, Venezuela, Friedlander knew early that he wanted to be a doctor and a scientist. In high school, he read an influential *Scientific American* paper on oncogenes, which convert normal cells into cancer cells, by MIT's Robert A. Weinberg. Yet, higher education

Robert Friedlander is thought to be the first neurosurgeon to do research on cell-death pathways.

PHOTOGRAPH | JIM JUDKIS

wasn't a tradition in his immediate family. His Jewish grandfather had escaped from Pinsk, Russia, after half his family was murdered in pogroms. At 15, his grandfather fled with the equivalent of $30 in his pocket and made his way to Cuba, eventually ending up in Venezuela with a wife from Brooklyn via an arranged marriage that would produce Friedlander's mother. Friedlander's paternal grandparents had escaped the Nazis prior to World War II to what would become Israel. His father eventually visited Venezuela, where he met Friedlander's mother at a high school dance and stayed to marry her.

Friedlander's parents encouraged their son to pursue his dreams. Two of Friedlander's uncles had left Venezuela to become doctors in Boston. When he was just out of high school, Friedlander applied to Brandeis University near Boston, figuring an American education would give him the best opportunities. "That's where things happen," he says.

He was wait-listed.

Friedlander had learned to speak English from his grandmother. But realizing he needed to improve his writing and reading skills in the language to get into Brandeis, he took a six-month English course in Boston. Once finished, he was accepted into Brandeis and enrolled in an ambitious dual bachelor's and master's program in biochemistry. Friedlander soon discovered he needed to improve in other areas. His first test was in calculus; he got a C+.

"I said, *Hmmm … that's not going to get me into medical school.* It was a wake-up call," says Friedlander, who buckled down, pushing himself like never before.

Between 1985 and 1987, Friedlander worked in the lab of Michael Newman, a PhD and an assistant professor of biochemistry. In Newman's lab, Friedlander learned to grow cells in tissue culture to try to understand how a normal cell became a cancer cell.

"He was always coming back to me and making suggestions and going above and beyond what the typical undergraduate would do in pursuing research," says Newman, now executive vice president of research and development at Vaxiion Therapeutics in San Diego.

Friedlander finished both his bachelor's and master's degrees in three-and-a-half years—while working with Newman and attending classes every summer in Boston—and was accepted into Harvard Medical School. At Harvard, Friedlander wanted to continue to do research. Initially, having read Weinberg's paper on oncogenes years earlier, he was interested in studying cancer. (Cancer had run in Friedlander's family.) But he also recognized that the fields of genomics and cell biology were taking off.

When Friedlander started rotations during his third year of medical school, he considered a surgical subspecialty, but the grueling hours and years of training required made him hesitate. One of his mentors, Charles McCabe, then the director of the surgical clerkship at Harvard, told Friedlander a parable about what could happen if he chose an easier path in medicine.

McCabe said: *You could choose something else and have a good lifestyle, but if you don't like what you're doing in your practice, you're going to hate waking up. You're going to hate going to work. You're going to come home maybe at 5 o'clock and be in a bad mood. And you're not going to be nice to your wife and your kids.*

Or, McCabe told Friedlander, he could pursue training that might take two or three years longer. He would have the rest of his life to become the kind of physician and researcher he wanted to be. And he'd be doing what he loved.

Friedlander took his mentor's advice. He graduated from med school in 1991 and started a seven-year residency in neurosurgery at Massachusetts General Hospital. He worked through his residency, contemplating whether to become either a neurovascular or brain tumor surgeon. Then, something else caught his attention. During a neurosurgeon update course, Friedlander attended a talk by MIT professor H. Robert Horvitz, the founder of the emerging field of cell death.

He had planned to become a stroke researcher, but all of a sudden he was a famous ALS researcher.

"It was one of those lectures ... where your heart starts beating really fast, and you're really excited about something. Something that all of a sudden opens your eyes," Friedlander says.

Friedlander was hooked by Horvitz's science. After the talk, he approached him to ask how he could research cell death. Horvitz put him in touch with Junying Yuan, an assistant professor at Harvard who at the time had a research lab in Massachusetts General. Yuan had discovered the caspase 1 pathway (a dying cell's executioner)—the first insight into the molecular mechanism that regulates apoptosis (programmed cell death), which is crucial to many biological processes, including embryogenesis. (Horvitz, who earned a share of the Nobel Prize in Physiology or Medicine in 2002, has credited Yuan with doing a third of the work that earned him the award.)

Yuan took Friedlander into her lab in 1994. Their first goal was to understand the basic mechanisms of cell death.

"When Robert first came on board, he was just a fellow who had never done any research [like this] before," says Yuan, now a professor of cell biology at Harvard. "I was really worried about him because most people in my lab were much more advanced in terms of science."

But Friedlander caught on fast. At the time, scant evidence implicated activation of the caspase cell-death pathway in neurological diseases. Figuring he was eventually going to become a stroke researcher, Friedlander, with Yuan, created a transgenic mouse model (it made a protein that blocked cell death in the brain and spinal cord); then he made the mouse have a stroke. When he did, he saw that caspase was indeed activated in neurological disease. He also discovered that if he blocked the pathway with a drug, he could protect the mouse from suffering massive cell death during a stroke and shield the mouse from neurological damage.

Working from that model, Friedlander began to think about inhibiting cell death in amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease. Other researchers had created a mouse to study ALS using the mutant SOD1 gene, which had been identified as a cause of ALS. If the gene overexpresses its protein, the mouse's motor neurons would die, and the mouse would end up with progressive neurodegeneration, then die. This disease course is similar to what happens in humans with familial ALS. Friedlander took his cell-death-resistant mouse and crossed it with the ALS mouse. The offspring lived longer. This was the first time a scientist had been able to extend the life of an ALS mouse. The results were published in *Nature* on July 3, 1997.

But the research part of his residency was ending. Yuan was moving her lab to Harvard, and he'd have to return to the hospital staff. Yet Friedlander wasn't about to give up on his studies. So he secured a small grant from the Muscular Dystrophy Association and his own small lab to

continue the studies while going back to a rigorous house staff schedule. Friedlander was able to show that blocking the gene coding for a protein called ICE in the caspase 1 pathway in an ALS mouse slowed progression of the disease, and the mouse lived longer after getting the disease.

Here was another crossroads. He was trying to finish his residency and to become a stroke researcher, but all of a sudden he was a famous ALS researcher. "That was not the plan," he says. "But if you see an opportunity, you take it."

Around the same time, other researchers had created a transgenic mouse to study cell death in Huntington's disease, which affects muscle coordination and leads to cognitive decline, psychiatric problems, and eventual death. Nancy Wexler, president of the Hereditary Disease Foundation, had seen Friedlander's *Nature* paper on ALS. She had a representative from the foundation give him a call, asking, "Would you like to do research on Huntington's?"

Years earlier, Wexler had started research near Lake Maracaibo, a brackish body of water in the eastern part of Venezuela, home to the world's largest concentration of people with Huntington's disease. Wexler eventually discovered the gene that causes Huntington's disease, and her work led to the creation of a genetic test for the disease.

The foundation gave Friedlander his first big grant. Meanwhile, the chair of Harvard's Department of Neurosurgery offered him a tiny lab, "with the ceiling falling off," and Friedlander started research on Huntington's disease. By then, he was the chief resident at Massachusetts General Hospital.

His Huntington's research produced results similar to those he'd found in ALS: The caspase 1 cell-death pathway was activated in Huntington's disease. Blocking the pathway when breeding the Huntington's mouse with the model Friedlander had created (that inhibited cell death in the brain) made the offspring live longer. So did delivering a caspase inhibitor drug to the brain. The results were published in *Nature*. Here again, Friedlander got a diseased mouse model to live longer when no one else could.

After completing his residency in 1998 and taking a position at Brigham and Women's, Friedlander went on to use mice to make the first findings that the caspase family of cell-death pathways was activated in many neurological diseases, as well as in head trauma and spinal cord injury.

Around the same time, other researchers had used minocycline—an antibiotic used for decades to treat acne and rheumatoid arthritis—to evaluate stroke. Friedlander wanted to see how the drug worked in his mice. He tried it in mice with traumatic brain injury, then his ALS mice, and finally his Huntington's mice. In each case, the animals were protected from damage and lived longer.



AMERICO TORRES/AFP/GETTY IMAGES

Venezuela's Lake Maracaibo area is home to the world's largest concentration of people with Huntington's disease.

He would eventually show that caspases don't just abruptly kill off a damaged cell. Their activity in one cell is essentially contagious, prompting the secretion of toxic substances that make neighboring neurons too sick to work properly.

Despite his success at the bench, Friedlander hasn't yet been able to demonstrate the same results in clinical trials. He has worked with others to develop drugs to block the caspase family of cell-death pathways, yet none of the drugs has worked in humans.

Friedlander says part of the problem is in the challenge of translating research from mice into humans. Although disease in mice mimics disease in humans, transgenic mice are essentially identical; they have the same disease, the same mutation. Humans, however, are not all the same. Mutations and injuries in humans vary from person to person.

Friedlander, who became chair of the neurological surgery department at Pitt in June 2010, has since been looking for other drugs that might work better than minocycline. He is collaborating with Robert Ferrante, professor of neurological surgery, whom Friedlander recruited to Pitt last year from Boston University.

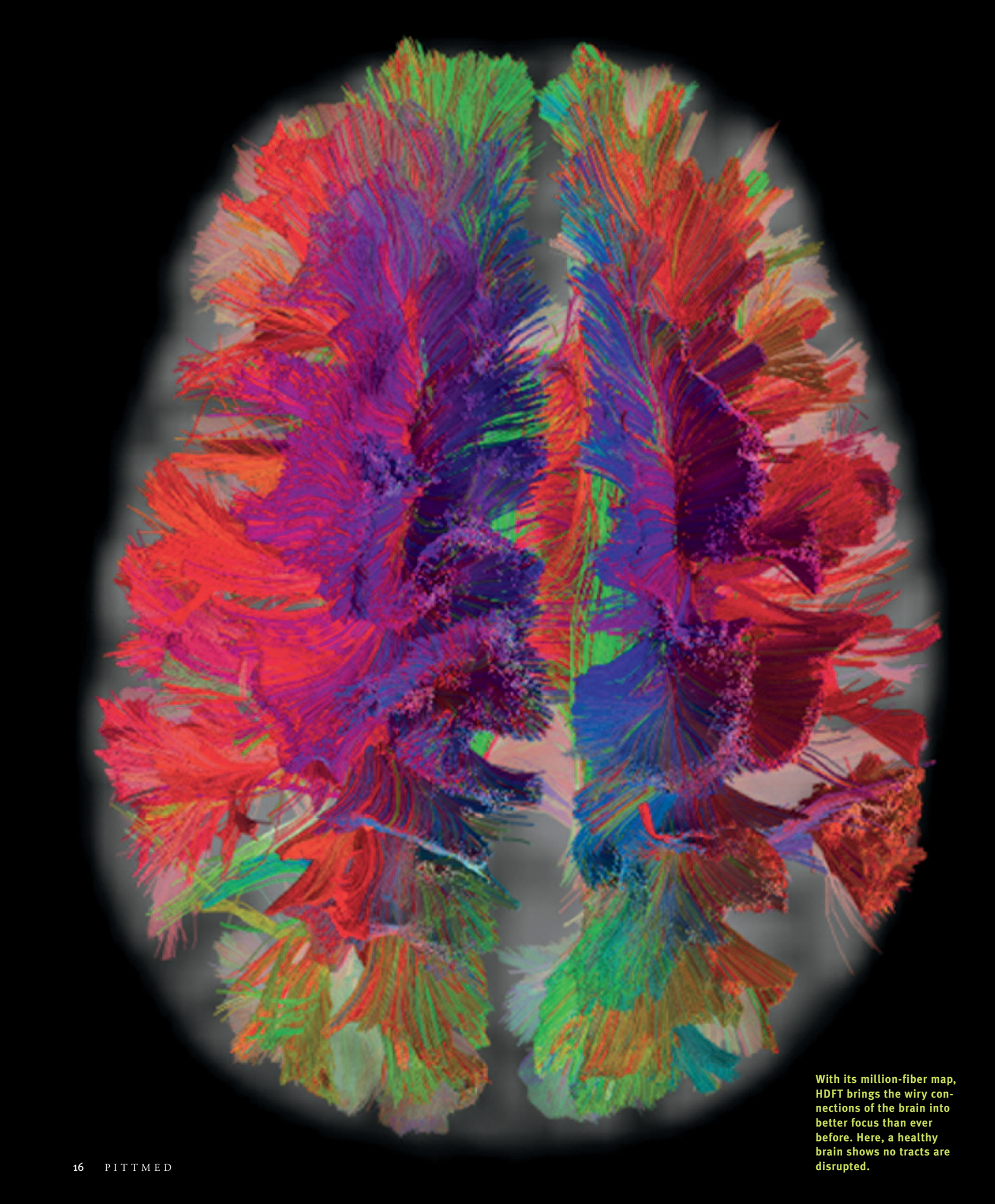
In recent years, both Friedlander and Ferrante have started to think about changing the way clinical research is done. They believe researchers should stop trying to see whether just one therapy can help patients and consider drug cocktails instead. "Much of the target-centric approach that science has taken over the past 50 years really hasn't worked, because we're only homing in on one particular aspect of a disease," says Ferrante. "The current approach is to look at polytherapies. … We're finally taking that approach to patients with chronic neurodegenerative disorders."

Friedlander is currently the only neurosurgeon on the advisory council of the National Institute of Neurological Disorders and Stroke. He's also a recipient of the Society of Neurological Surgeons' H. Richard Winn MD Prize, one of many honors recognizing his contribution to science and medicine. Her Royal Highness Crown Princess Katherine of Serbia, who is known for her humanitarian projects, says, "there's not enough recognition in the world" for Friedlander.

Friedlander and his wife, Eugenia, met the princess about 11 years ago. Since then, Princess Katherine, who helps people in her country get medical care, often calls on him to assist with patient cases: "I think he was born to save lives," she says. "Every day of our lives we are grateful to God that we have gone through this life and not missed meeting him."

Friedlander, so aware of making the most of his time, says Pitt has everything he was looking for in a chair opportunity: visionary institutional support from the medical school and medical center, a vibrant neuroscience community, an institute dedicated to academic drug development, and the largest and busiest neurosurgery department in the country. Pitt is also the home of many innovations, including transnasal (entering through the nose rather than opening the skull) endoscopic skull-based procedures, the Gamma Knife, microvascular decompression, and—among the latest—high-definition fiber tracking, which is an enhanced MRI technique that for the first time allows doctors to see connectivity of brain areas in 3-D (see cover story). And his department has been recognized for its unusual productivity in basic science.

"The opportunity here is once in a lifetime," says Friedlander. ■



With its million-fiber map, HDFT brings the wiry connections of the brain into better focus than ever before. Here, a healthy brain shows no tracts are disrupted.

A NEW TECHNOLOGY ALLOWS DOCS TO SEE MISSING CONNECTIONS IN THE BRAIN

BY JENELLE PIFER

MISSING LINKS

Imagine you're talking to a coworker about what you'd like to eat for lunch—a salad. You can see the salad in your mind—the greens, the cherry tomatoes, the dressing on the side. You can visualize the word, anticipate the consonants rolling around in your mouth. You go to say it aloud—*salad.* But the word you know, can see, can feel, can practically taste, escapes you. What's that thing called again? You start to feel like you're losing it.

This was one symptom presented by a recent stroke patient seen by Juan Fernandez-Miranda, an MD and assistant professor of neurological surgery at the University of Pittsburgh and director of Pitt's Surgical Neuroanatomy Lab. "He has expressive aphasia," says Fernandez-Miranda. "He has trouble articulating words."

The patient underwent an MRI, which confirmed the damage was concentrated in the left, language-storing side of the brain. "Some of the areas of the left hemisphere are smaller than normal," says Fernandez-Miranda. But that's really all the MRI could reveal—a thinning of white matter. What the picture didn't show was the nature of the damage: which connections were broken and what exactly was blocking the word's passage from brain to mouth. "Language is a dynamic process, so you need to understand the connectivity between areas to understand the problem."

A new technology developed at Pitt is making that connectivity clear for the first time.

IMAGES | SCHNEIDER LAB

High-definition fiber tracking (HDFT) runs data from a top-end MRI machine through computational software so that, instead of producing a flat, black-and-white scan of tissue, it generates intricate 3-D images of connective fibers in the brain. Formerly, scientists could only study these connections during post-mortem dissection, or in vague detail through less-precise scans. Now, brain connectivity can be measured, much more thoroughly and accurately, in live patients.

"In warfare and in medicine, it's hard to defeat an enemy you cannot see," says Pitt professor of psychology and neurosurgery Walter Schneider, a PhD, whose team developed the technique. "That doesn't mean you don't try and do things, but it's certainly quite difficult."

Doctors and neuroscientists around the world might use a scanning technique called diffusion tensor imaging (DTI), which measures the movement of water through the brain. The idea is that by watching the way water flows, you can determine the shapes of the fibers it runs through.

The problem lies in the mathematics: DTI software can't account for instances where the fibers cross. And fibers cross all the time. So when the technology detects water moving in one direction and then another, it simply takes the average. The resulting scans show the major stems of fiber tracts—a valuable and revolutionary breakthrough—but the details are still hazy and can lead to inaccurate diagnoses.

"A fuzzy image doesn't help you any clinically," says Schneider, also a senior scientist in Pitt's Learning Research and Development Center. "[DTI] had the right intent but wasn't powerful enough to accomplish the goals that were intended."

Doctors need a technology that can follow a fiber through its crossings, so five years ago Schneider and Sudhir Pathak, a programmer in his lab, set about refining the math. They'd alter the computational method, scan a brain, and show the image to Fernandez-Miranda, one of the world's preeminent neuroanatomists. "He'd say, 'Well, that's good, but it's wrong,'" recalls Schneider.

Fernandez-Miranda knew enough about fiber tracts from studying dissections to know when the maps were off. Year after year the method got better. "Juan would say, 'Hey, you got this one right. How about this one?'" says Schneider. By September 2010, the technique was so precise it could out-predict Fernandez-Miranda. "We could noninvasively get fiber tracts that were better than what he could do with cadaver tissue.

"At that point we hit a critical point of utility and quality, and a lot of the clinical work began," Schneider says.

Everyone has the same 40 major fiber tracts, connecting certain parts of the brain to others, but—like the way arms and eyes differ in size and shape—the way each tract's fibers connect can vary enormously. So studying cadavers could only go so far in helping doctors understand what might be happening in their own live patients.

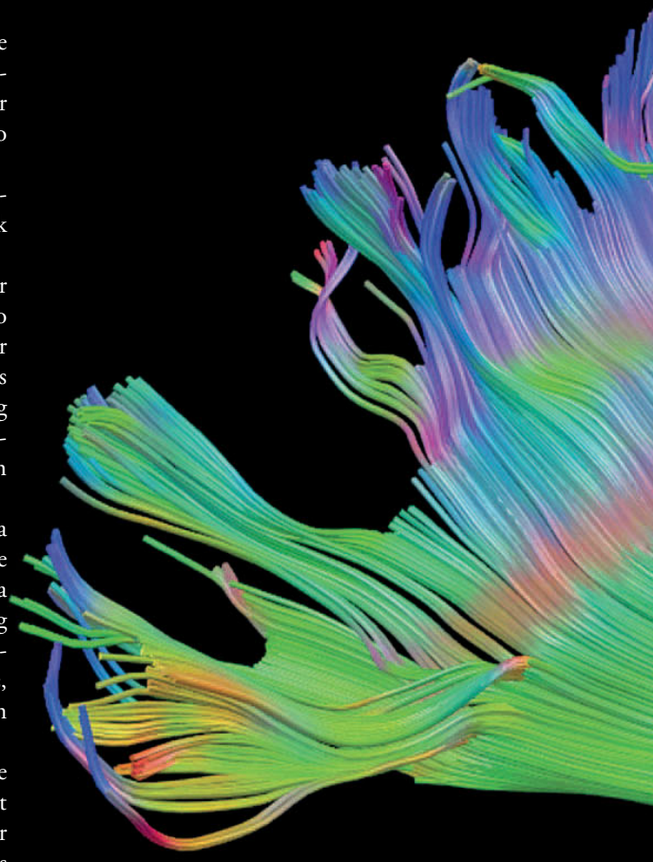
Now the Schneider lab partners with a team of basic scientists (researching things like vision, language, and attention), as well as a team of 10 neurosurgeons who are applying HDFT in the clinic to help people with conditions as diverse as traumatic brain injuries, tumors, autism, and Alzheimer's. More than 120 patients have been scanned so far.

"For surgery, the application is much more immediate," says Fernandez-Miranda. A recent patient, for example, presented with a tumor in the left corticospinal tract, which controls movement. A traditional MRI clearly revealed the location of the tumor, but not what surrounded it.

"I have a tumor here," says Fernandez-Miranda, pointing to a mass on an MRI. "But do I have motor fibers here, or not? How about inside the tumor?" HDFT revealed that only a few fibers passed through the tumor and that most of the important ones had been pushed toward the outside of the skull. Knowing this, they determined that the best approach was from the midline.

In presurgical planning, HDFT can also present patients with the profound opportunity to choose which side effects they'd prefer to deal with. A surgeon can say, for example: If we approach this way, we risk losing mobility; if we go in that way, we might compromise mood control. "Now we have a basis from which to have a meaningful discussion with the patient," says Schneider.

One of Schneider's primary partnerships at Pitt is with David Okonkwo, an MD/PhD, associate professor of neurological surgery, and clinical director of the Brain Trauma Research

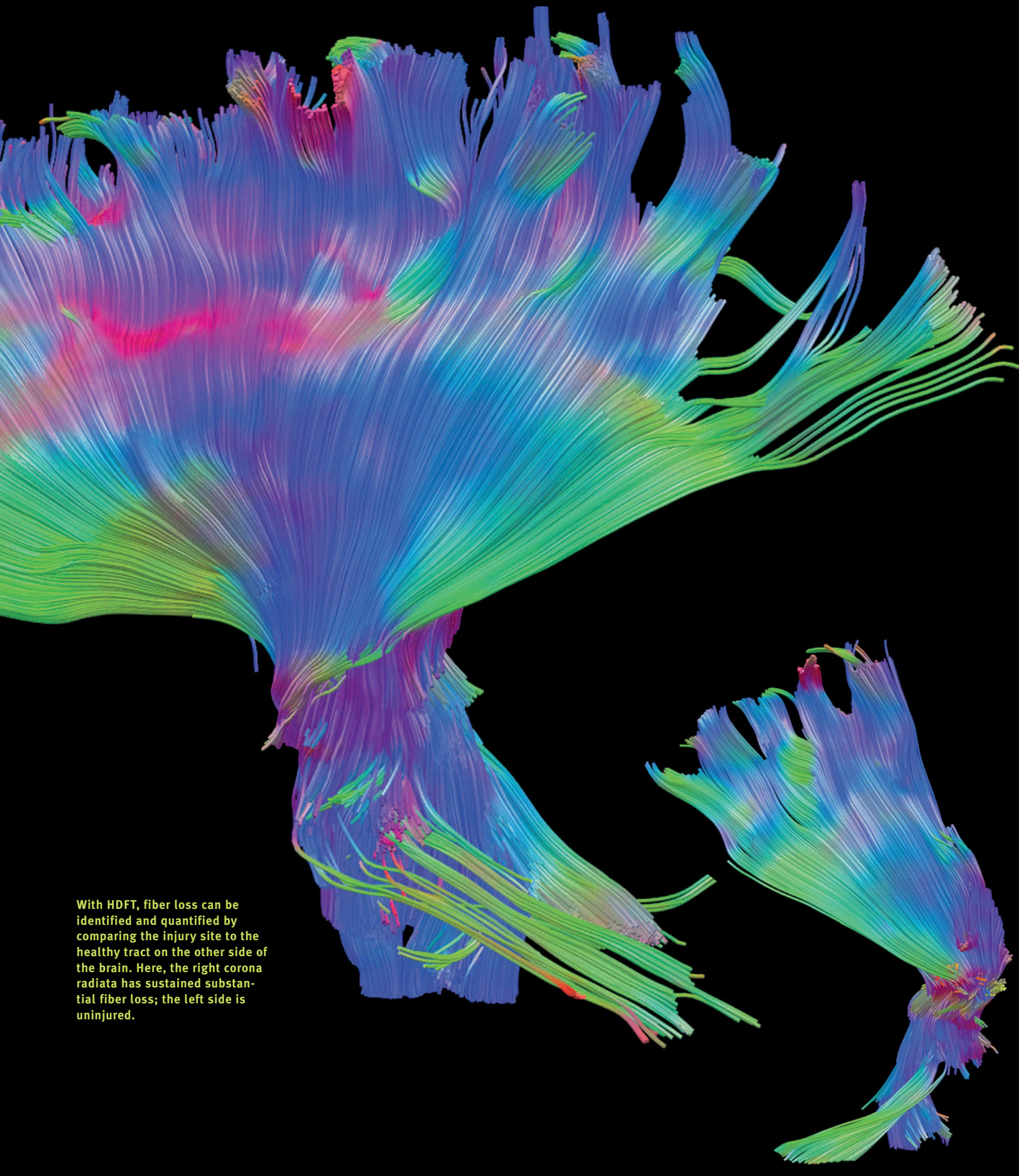


Center. They are using HDFT to guide treatment of traumatic brain injury. In the United States, TBI occurs in 1.7 million people annually and is the most common cause of death between ages 2 and 35. In most TBI cases, an MRI doesn't show doctors much—maybe some swelling or bleeding, but not the actual damage. This leads to a diagnosis that doesn't tell patients, with much certainty, what's wrong or how they can expect to heal.

"Having an ambiguous diagnosis is really problematic," says Schneider.

"It's okay to say, 'You have swelling in your head. It's a head cold, and it'll clear up in three days.' But not to say, 'We don't know, you may never work again in your life.'"

Because doctors can't see what's broken in the brain, they rely on outward manifestations—the symptoms—to determine therapy. Recently a patient with TBI (who'd flipped his ATV, end-over-end) presented with limited



With HDFT, fiber loss can be identified and quantified by comparing the injury site to the healthy tract on the other side of the brain. Here, the right corona radiata has sustained substantial fiber loss; the left side is uninjured.



mobility in his arm, hand, and leg. Traditionally he would have started intensive physical therapy in each area, in the blind hope of regaining function. But with HDFT, his doctors can be more realistic, and strategic.

By mapping what percentage of a given fiber tract is damaged, Schneider can determine whether or not function is likely to return. For the patient in question, HDFT revealed projection to the hand was 97 percent lost, to the arm 67 percent, and to the leg 60 percent. Although he could still move his arm, the man's club hand would likely never heal. "People can get over losing a limb: They understand it. They grieve the visible loss. They move on," Schneider says. "You do nobody any good to tell them to work hard at something that's impossible. We need to know how much is left so we know how best to invest hard but limited hours of rehabilitation to bring back function."

The good news: Even though the patient couldn't move his leg at the time, Schneider knew he had enough fibers remaining to walk again. "That's going to take months of hard physical therapy," Schneider says. "We would tell a patient, 'It's not going to be easy, but we have scientific evidence that suggests it's going to come back. It's still okay to work on the hand but concentrate on the leg.'"

The technology can monitor how well a particular therapy works by keeping track of which fibers regrow. It's probably not possible to grow a new fiber if all the fibers of a tract are gone, Schneider says, but it is possible to increase the size of an existing fiber. "If you have a dirt road, we can make it into a highway. If you don't have the dirt road, we can't."

In the case of Fernandez-Miranda's stroke patient mentioned at the start—he'll likely begin language therapy similar to what would have been prescribed without HDFT. But with HDFT, his doctor can see, in detail, whether the therapy is changing anatomy. "You can first understand better the disease," says Fernandez-Miranda. "By doing that, eventually, I think we'll be able to design better therapies."

While HDFT is more accurate than any other technique available, there are still blind spots. "We can detect a 20 percent loss of a tract, but it has to be a reasonable size tract," Schneider says. There are some tracts where if you lose 1 millimeter, you'll never come out of a coma. "We aren't that good yet," Schneider says.

"We've made enormous improvements in the last three years, but we certainly haven't run out of ideas." His goal, Schneider says, is to make what his team developed 18 months ago obsolete. ■



The left arcuate tract connects areas of the brain responsible for understanding language and expressing it. The damaged tract of a stroke patient (right) is visibly thinner than the normal one (left), which explains why the patient can find the right word but can't say it.

THREADS OF LANGUAGE AND A VIEW OF TEMPLE GRANDIN'S BRAIN

As news spread about Walter Schneider's HDFT technology, autism activist Temple Grandin caught word. She wanted to have her brain scanned. Until that point, the new and immensely precise scanning technology had not been used to examine the brain of anyone with autism. "We were able to look at what might be different in terms of her fiber tracts," Schneider, Pitt professor of psychology and neurosurgery, says.

There are three subclasses of people with autism: those who never learn a language system at all; those who repeat what they hear without understanding meaning; and those who are capable of language but at times have a hard time verbalizing, even though they know what they want to say. Grandin is among the latter. (Grandin, who has a PhD in animal science, now lectures widely on autism as well as animal behavior and has written six popular books.)

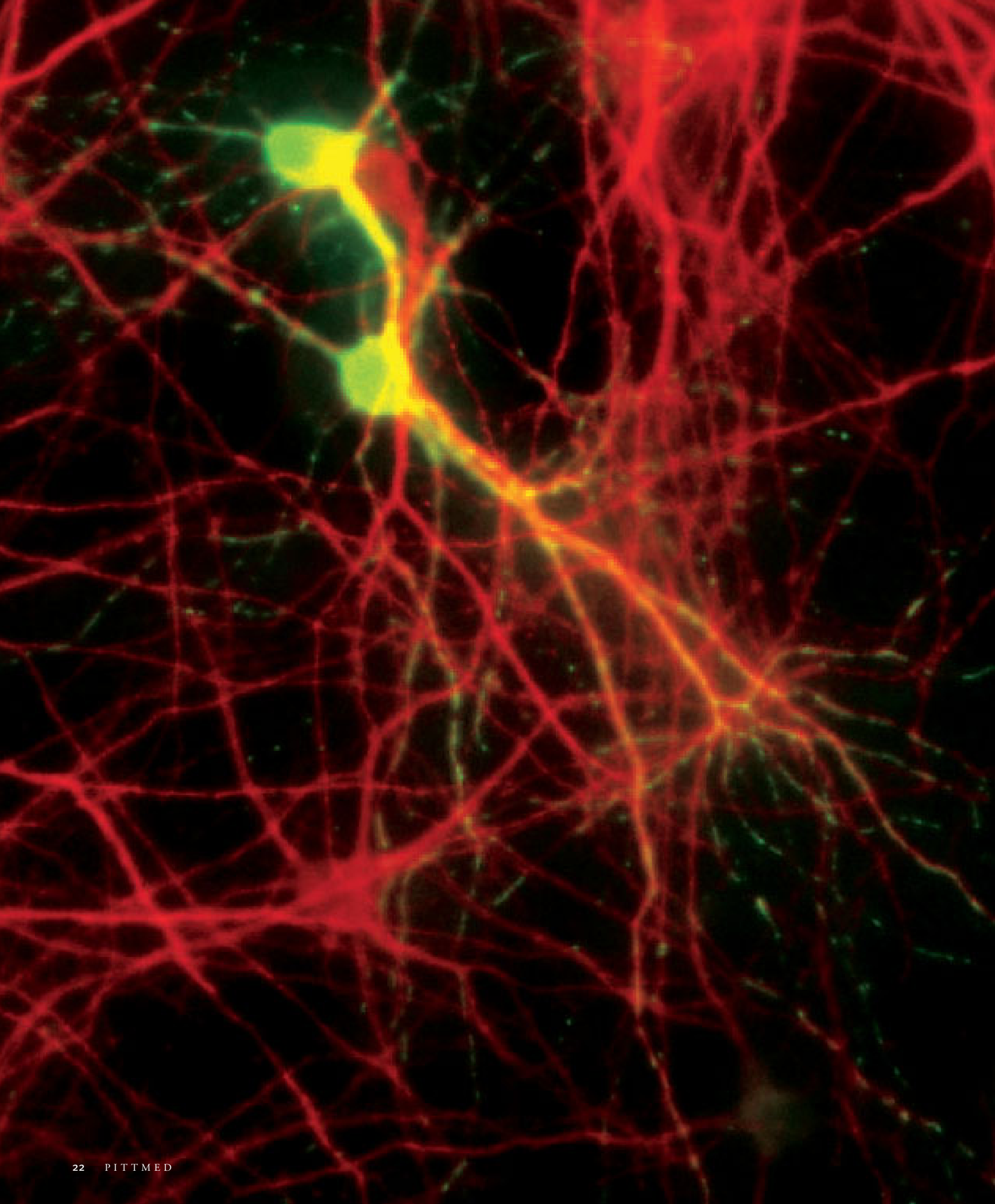
Upon reading the scan, Schneider saw that fibers in Grandin's motor system—in regions thought to control repeating what you hear and naming what you see—were barely there: The tract was more than 90 percent smaller than a control subject's. "I told Temple, 'Your language may have been hanging on by a thread,'" says Schneider. "It was enough, with intense training, to grow it."

Yet Grandin had four times as many fibers connecting her visual system and frontal cortex, "potentially supporting her high visualization abilities," says Schneider.

The two hope to partner on a project to map the brains of people in all three subclasses. So far only four patients with autism have been scanned using HDFT.

Typically, parents notice symptoms of autism when a child is between 18 months and 2 years of age. "The highest priority should be to establish effective communication as soon as possible," says Schneider, whether that communication is verbal, pointing, or otherwise, to minimize psychological damage and stimulate language and cognitive abilities. HDFT can help decide which method to choose.

"The prize is to get a very early diagnosis so that you can speed the development of functional capability to be much, much earlier," says Schneider. *—JP*



THE MITOCHRONICLES: PART 2

BY JOE MIKSCH

MITOCHONDRIA'S MANY MISSIONS

In the first half of this series, scientists were going gaga over the likely role of mitochondria, a long-neglected organelle, in cancer. Pitt mitochondriacs are also tackling Parkinson's disease, heart health, and a devastating childhood disease. Here, you'll read stories of resurrection, vital dances, and very sick flies.

The addicts of America needed a fix. War in poppy-producing Afghanistan and Turkey made it tough to get the real stuff. In 1976, a graduate student in chemistry, a Maryland man named Barry Kidston, tinkered around in his home lab and mixed up a super-potent synthetic called MPPP.

The drug had been around since the 1940s and, back then, had 70 percent of the potency of morphine. Through Kidston's labors, he made it even stronger and, therefore, all the more desirable to addicts. Then, in 1977, the 23-year-old injected some of his "home brew" as he often had in the past. But something went wrong. Within three days he developed symptoms of Parkinson's disease.

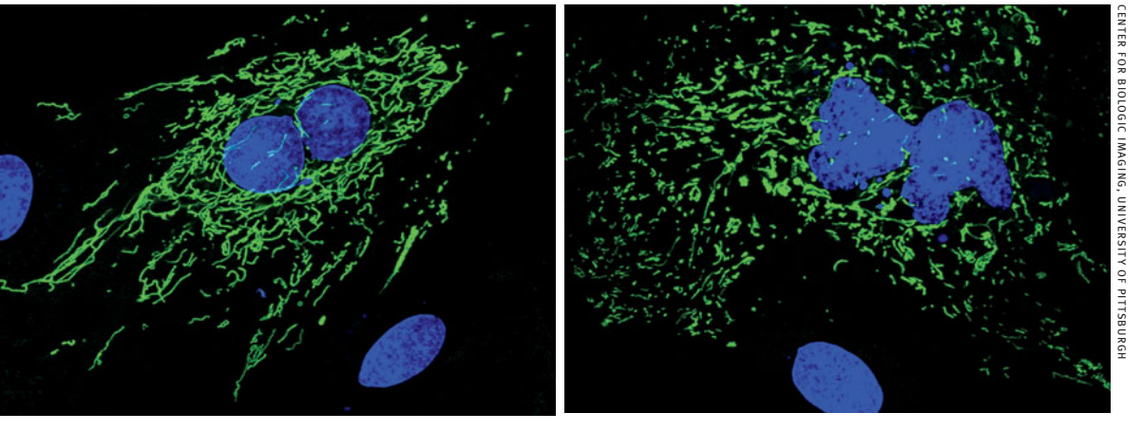
In 1982, 42-year-old George Carillo arrived at a hospital in San Jose, Calif. He was bent, twisted, drooling, and mute. His muscles were frozen. Six similar cases followed. Doctors became detectives. All seven Parkinsonian "frozen addicts" were found to have used a synthetic opiate called China White.

Members of Charleen Chu's lab have found that mutations that cause Parkinson's disease decrease the number of mitochondria (green) in dendrites (red), which are vital for receiving signals in the brain. This image shows mitochondria in healthy neurons.

RUBEN DAGDA AND CHARLEEN CHU

Then, a toxicologist involved in the California case recalled Kidston's misadventure. Though it wasn't big news at the time, authorities who examined Kidston's lab found a very nasty impurity—MPTP—in the batch that had rendered him ill. Six years later, that same impurity was found in the garage-lab-made California China White.

And thus began an explosion in Parkinson's research. Investigators found that when the brain metabolizes MPTP, the byproducts include a toxin called MPP+. This MPP+, they eventually learned, attacks mitochondria—especially the beginning of the electron transport chain, what's known as complex I. This group of enzymes is associated with the mitochondria's best-known role: producing energy for the cell. Later, researchers would discover that complex I is inhibited in all cases of Parkinson's, even in the rare inherited form.



CENTER FOR BIOLOGIC IMAGING, UNIVERSITY OF PITTSBURGH

Mitochondria, the green stuff, fusing (left) and undergoing fission (right). Fusing mitochondria are longer; fissioning ones are shorter; and the entire process is vital for cellular health.

As the disease progresses, mito dysfunction kills off the dopamine-producing neurons in the substantia nigra, a part of the brain that controls voluntary movement.

Enter Pittsburgh's mitochondriacs.

The University of Pittsburgh's J. Timothy Greenamyre—MD/PhD UPMC Endowed Professor of Neurology, chief of Movement Disorders, and director of both the Pittsburgh Institute for Neurodegenerative Diseases (PIND) and the American Parkinson Disease Association Advanced Center for Parkinson's Disease Research at Pitt—was among those intrigued by the relationship between toxins, mitochondria, and Parkinson's.

"In the '80s, mitochondria research was a backwater," says Greenamyre, whose investigations of the organelle stretch back to that decade. "People thought they knew everything there was to know—that mitochondria make ATP [fuel for cells]. It's turned out to be much more complicated than that."

In the late 1990s, while he was on the faculty at Emory University in Atlanta, Greenamyre began thinking that it might be useful to create a better animal model of Parkinson's. He had a particular interest in replicating the manner in which damaged mitochondria create conditions that make neurons interacting with dopamine susceptible to the disease. He started with a naturally derived pesticide called rotenone, which was known to cause mitochondrial damage and remains one of several environmental factors thought to cause Parkinson's.

Sure, other researchers had met with some success; but their techniques were limited. First off, the dominant approach at the time—injecting rotenone directly into a mouse's brain—indeed killed dopaminergic neurons, but it also obliterated plenty of other brain cells not implicated in Parkinson's. You might expect that a random and nonspecific brain cell death would result no matter what toxin was injected directly into the brain, especially in such high doses. Further, because of the injection method, such models damaged mitochondria only in the brain. Greenamyre and his colleagues believed, and emerging literature suggested, that Parkinson's patients had systemic mitochondrial damage, not just damage to the mitochondria in their dopaminergic neurons.

Greenamyre and his Emory group examined cells from humans—Parkinson's patients. They determined the degree to which mitochondrial function was inhibited and then slowly but surely found the right level of rotenone, administered intravenously, to replicate in mice what they had found in people. Success here produced systemic mitochondrial dysfunction, hit only dopaminergic neurons, and produced Parkinsonian symptoms in the mice. Even more useful: The mice developed tangles of alpha-synuclein proteins (the same proteins that aggregate in the brains of human Parkinson's patients) called Lewy bodies. The resulting paper, published in 2000, remains the most cited in *Nature Neuroscience*.

"This model was the first proof of concept that generalized mitochondrial dysfunction could lead to very specific neural degeneration," Greenamyre says. "And since then the genetics of Parkinson's disease have really advanced. Now we've found several genes that, when mutated, affect the mitochondria and produce Parkinson's."

The common thread, then, is that regardless of whether a particular case of Parkinson's is spurred by environmental toxins such as rotenone or genetic mutations accumulated over time, mitochondria remain central.

"That's true in many, probably the majority, of Parkinson's cases," Greenamyre says. "If you're thinking about the pathogenesis of Parkinson's, you can start the degenerative process in numerous places. In some cases, it starts with the mitochondria, in some cases not. But mitochondria will play a vital role in the disease at some point."

Charleen Chu is confident that Greenamyre is right. So much so that the MD/PhD professor of pathology and PIND member is looking at five models of Parkinson's, all of which affect the mitochondriac's favored organelle. To Chu, regardless of whether the models involve neurotoxins or mutated genes, the upshot is that something is quite wrong with mitophagy, the process by which damaged mitochondria are safely destroyed. Or, if it's not mitophagy per se that's gone awry, it's the related and equally important cellular step of generating new mitochondria to replace the bad ones that have been eaten up.

"We've studied the recycling of mitochondria for some time," Chu says. "And the question we're faced with is, 'Well, if mitophagy is good for you, why, in some cases, does it cause neuronal cell death?'"

In the spring, Chu and colleagues published a paper in *Cell Death & Disease* that gives some inkling of an answer. She found that there are

times when mitophagy outpaces a neuronal cell's ability to regenerate mitochondria. "In any recycling process, it's not good enough to degrade the damaged stuff," she says. "You have to rebuild." Neural cells require and burn more energy than other types of cells, making them particularly dependent on mitos. When there aren't enough mitos, there's not enough energy; calcium is mishandled; death comes calling and causes, in this case, neurodegenerative diseases like Parkinson's.

The discovery was based on a slightly counterintuitive observation: Inhibiting ERK, a protein vital to cellular proliferation, resulted in recovery of healthy, functional mitochondria. You see, neurons don't proliferate, and slowing down mitophagy gave them time for mitochondrial repair.

"When we inhibit ERK, not only do we slow down degradation, we boost biosynthesis, and the cells are completely protected," she says. "In our other studies—we've used three genetic models and two toxin models—although mitochondria are all impacted differently, all these processes feed into this cycle of damage-mitophagy-resynthesis."

One path to a possible treatment for Parkinson's and like diseases is obvious: maintain the balance between the destruction of ailing mitos and the generation of healthy replacements. But doing so isn't easy. Bennett Van Houten, a Pitt cancer researcher featured in the first installment of the Mitochronicles, calls mitochondrial degradation over time the "rust of life." As time passes, he suggests, mitos might just accumulate too much rust; and the balance between death and resurrection, the intracellular circle of life, then becomes intractably screwed up.

Chu puts it this way: "Even with increased damage, as long as the cycle is able to roll, you might be able to compensate for it, and maybe that's why diseases like these don't present until decades have passed."

Rolling. An interesting word choice in the realm of mitochondria. The conventional wisdom, for quite a while, was that these organelles were static. They just hung about in the cell's interior and produced ATP. That view turned out to be wrong. Mitos are not only very active; but movement, it is now known, is vital for mitochondrial health. Further, the process by which mitos meet each other, swap genetic material, and separate could have a significant role—when it goes wrong, that is—in the progression of Parkinson's.

Sarah Berman (PhD '98/MD '00), a PIND member and assistant professor of neurology, became interested in mito dynamics and Parkinson's as a grad student here at Pitt. During her training, she studied reactive oxygen species (ROS), the nasty stuff that mitochondria make when the energy production process has gone bad. The idea was that ROS was one of the factors that accounted for the slaughter of dopamine neurons in Parkinson's.

By Berman's grad student days, this was important and interesting, but no longer a groundbreaking concept. The body of evidence was strong suggesting that trouble with complex I and, subsequently, mitochondrial respiration, was a precursor to the development of Parkinson's. Berman, in her own lab, decided to delve a bit more deeply into a different aspect of mitos and Parkinson's.

"What I study is not so much respiration, but mitochondrial dynamics," she says. "It sounds like an obscure sort of thing, but the fact that mitochondria divide and fuse together and get transported up and down neurons, this is really critical—in neurons, in particular."

Neurons, Berman says, are different from other cells in that they require more energy to work, thereby increasing the importance of mitochondrial health. (Not that it is unimportant in other cells.) Further, she says, the process of fission and fusion, the movement of mitochondria from the cell body all the way down the axons to the synapses, seems to be absolutely crucial to the life of the neuron.

"If you take away the ability for them to divide, they don't get down to the synapses, and the synapses don't work right," she says. "That's really intriguing, because one of the things that happens in Parkinson's is that it's not the cell bodies that die first, but the long axon terminals. Something is happening very far away from the cell body, and then the cell dies."

Berman uses an in vitro version of Greenamyre's rotenone model to reveal the music that makes mitochondria dance up and down axons.

Her hunch and hope are that, if she can find a way to alter the fission and fusion processes, to keep them healthy, "maybe then we can develop a corrective therapy we can use before cells die and Parkinson's develops."

Sitting in her office, Berman brings up a movie showing fission and fusion in real time. Mitos blink red and are tagged with a photoactive green fluorescent protein. When a pair fuses, yellow flashes on the screen.

"See!" she says excitedly.

"When the membranes merge and the contents get mixed up, the whole thing turns yellow. Then you see it divide into two, and that's fission. You can monitor and quantify these events, and it's neat. I mean, the geeky scientist that I am, I look at this and think, *It's so cool!*"

In the lab, Berman manipulates the proteins responsible for fission and fusion. Something a bit unexpected happened after Berman started playing with those proteins—something that could, down the line, prove to be an important step in preventing cell death in Parkinson's before the process really gets going.

"When we add a fission inhibitor to the rotenone model—and I wasn't sure which way this was going to go—it turned out to be protective. And if we prevented fission, we didn't lose the [axons]. Maybe we can alter the neuropathology, but we don't know why this is protective.

"Yes, this is exciting," Berman continues. "But at this point we have many more questions than answers."

Whether a particular case of Parkinson's is caused by toxins or genetics, mitochondria remain central.

In the world of mitochondria research—still a pretty young field—questions abound. Sruti Shiva has taken questions about the organelle's role—with the aid of nitrite—to heart. As in heart attacks. Shiva is investigating how mitos, exposed to extra nitrite, protect cells from damage when blood, and the oxygen it carries, floods back into organs after a period of deprivation.

For the past decade or so, it's been known that nitrite, which is native to our bodies and also found in green, leafy vegetables, plays a role in cell signaling. (It had previously been considered nothing more than a physiologically inert product of nitric oxide.) What's new, out of Shiva's lab, is confirmation that increasing the amount of nitrite in the bloodstream can increase the number of mitochondria in a

cell. (Shiva's "cell of choice" comes from the heart.) And a boost in the number of mitos has been shown to facilitate adaptation to high altitude, increase energy efficiency, lengthen lifespan, and ease weight loss.

An emerging bit of Shiva's research (which the PhD assistant professor of pharmacology and chemical biology does as a member of the Vascular Medicine Institute), though, skips over the number of mitochondria generated by the introduction of extra nitrite. Rather, she has examined how nitrite spurs mito activity, leading to a series of cellular events that offer protection to cells stressed by a lack of oxygen and its subsequent reintroduction in the wake of a heart attack.

"What we've found is that, if you give a small dose of nitrite (pre-heart attack), you get a small burst of ROS [those unpleasant reactive oxygen species] from the mitochondria," she says. "This actually turns on a signaling cascade that signals for more protection. It somehow causes a cell to increase its production of antioxidants (counteracting the damaging reactive oxygen species released by a stressor) and bump up protective signaling messages."

Animal studies, Shiva says, have shown a massive reduction in organ damage.

Pursuing and understanding the mechanisms by which nitrite and mitos convey cytoprotection are, naturally, preconditions to bringing any related therapy to the clinic. Thus far, it appears that when nitrite is administered before or during ischemia and reperfusion, it keeps the now obviously vital mitochondrial complex I from going off the rails. Keeping that first step in ATP production on point, it seems, reduces the production of ROS and bolsters production of the antioxidants that tame those ROS that are released.

The takeaway, Shiva says, is that a little more of something that's already inside us can help our mitochondria protect our hearts from a second, and profoundly damaging, insult in the wake of a heart attack.

"So we went from having very little interest in mitochondria to *BOOM*."

Children with mitochondrial encephalomyopathy (ME)—which causes seizures, headaches, strokes, lactic acidosis, dementia, and, typically, death before age 20—are not born with evidence of the disease.

"You're born and deemed healthy at birth and then at some point later—in severe cases we're talking days or weeks after birth—the disease develops," says Michael Palladino. "And being diagnosed with primary mitochondrial encephalomyopathy is pretty much a death sentence, particularly in its [very early] childhood-onset form." The Pitt associate professor of pharmacology and chemical biology notes that when faced with ME, clinicians prescribe cocktails of vitamins and other supplements, but, "No one has any real confidence that those are anything near a cure or even of any therapeutic value." Yet the disease is horribly painful, he says, and "a child could linger for a couple of months, a couple of years, maybe more."

Palladino has developed the only animal model of ME with a mitochondrial DNA (mtDNA) mutation; he uses *Drosophila*, the fruit fly. There are about 200 different such mutations that cause ME, which affects one in 11,000 children. Until Palladino's flies came along, it was difficult to study the disease.

The mutation in Palladino's flies causes them to have poor motor control and exceedingly short lives. It was serendipity that led Palladino to this particular strain. He and members of his lab were studying a fly model of neurodegeneration. (He is also a member of PIND.) The process of sorting out its genetic makeup led to the discovery that a mutation of the ATP6 gene in the fly's mitochondria was also causing symptoms akin to the rare but devastating MEs that affect humans.

"And this put us in a beautiful place," Palladino says. "There's all this interest in human primary mitochondrial encephalomyopathies, but no one had a model system of them. So we went from having very little interest in mitochondria to *BOOM*. We had to become experts in this pretty quickly, because we had a novel resource that no one else in the world had."

The most important feature of the model, says Palladino, is the fact that endogenous mitochondrial diseases are progressive. Yes, the basics can be studied in vitro, but to get the full picture of how such diseases take root and devastate over time, you need to look at a living creature.

So with a compelling and unique model, Palladino has set off to find some sort of viable treatment for the disease. And he's made some progress.

The first front is pharmacological therapy. Drug screening has yielded a handful of compounds that somewhat improve the condition of Palladino's sick flies.

"The drugs we've identified do make the animals better—they live 5 to 8 percent longer, and we've seen a 10 to 15 percent improvement in locomotor function," he says. "But the thing about pharmacological therapies is that these are such complex diseases that few people think there's going to be a magic pill that fixes them. The rationale is that mitochondria do so many important things that there can't be just one target. A large cocktail of drugs probably wouldn't even work."

Knowing this led Palladino to aim closer to the source: mtDNA. Scientists have become adept at inserting and removing components of nuclear DNA, but they've had less success directly affecting the mitochondrial genome. So although he knew his target, he was unsure about the best weapon to deploy. Palladino chose allotropic expression. The idea here—and this is a technique developed about 15 years ago at Columbia University—is that while no one knows how to directly manipulate mtDNA, it is possible to tweak the nucleus. Before inserting a gene into the nucleus, a researcher can attach chemical directions that will drag the protein, generated by the gene in the nucleus, into the mitochondria.

"We've made some huge improvements to the efficacy of this process," Palladino says. "We're getting 10 to 15 percent rescue in longevity and 35 to 45 percent improvements with locomotor function.

"Within a year or two, we're going to have some real successes here. Our mutant's disease is so incredibly severe—worse than it ever is in humans—and we're very excited about the levels of improvement we've seen so far. Nevertheless, we're pushing for a 40 to 50 percent improvement in longevity.

"We'd like to achieve that before we publish, and I think we can."

Palladino is so excited about the therapy's potential—an excitement that seems both natural and a possible consequence of the espresso machine in his office—that he's already in the early stages of planning for clinical trials.

Why so optimistic? "Why not?" Palladino asks. "It keeps you motivated!" ■

For further mitochondrial motivation, visit www.upci.upmc.edu/trmad/



Nationally, the ecosystems that support getting scientific discoveries into the clinic have been pretty fragile. A few years ago, the NIH stepped in to help.

CAROL HAVENS/GETTY IMAGES

SURVIVAL OF THE FUNDED

BACK FROM THE BRINK OF EXTINCTION

BY ELAINE VITONE

It begins with a good idea. With a little luck and a lot of sweat, this idea grows into a fully realized and hard-won laboratory discovery. Then, with more luck and, yes, more sweat, that good idea in basic science could develop to become a human trial and gestate for a while, experimentally, in the clinic. And, with time, effort, resources, and sweat, sweat, sweat, it could prove its worth—improve patients' lives—and gain acceptance in the medical community. Eventually, our brave young idea could mature into an advancement that improves human health on a grand scale.

This is translational science—a bit of a buzz term, really. Simply put, it's the process by which researchers work to bring new science to the clinic. One key group of researchers on whom we've relied to do this—physician-scientists, the MDs who

both treat patients and study their ailments—are a vanishing breed. And with their staple food—federal research funding—in such short supply, it's no wonder.

Not only that, but medical research has become extremely complex. This has made it more difficult to learn all the skills needed "on the job," as Elias Zerhouni, former National Institutes of Health (NIH) director, notes in a 2005 *New England Journal of Medicine* op-ed. Increasingly, translational and clinical research relies on technology and on specialization in multiple areas. Thus, game-changing discoveries in medicine often emerge from novel partnerships—people from disparate disciplines coming together to dream up entirely new approaches to old problems.

Of course, the business of getting hatchlings out of the lab and into the clinic requires money to support the professionals who undertake years of study and training. It requires money to staff and sustain labs. Money to recruit patient volunteers; collect samples from them; and crunch, troubleshoot, and interpret the data. Biomedical and behavioral research eats funding as insatiably as a round-the-clock noshing newborn.

But what's even more costly? Scientific inertia. Good ideas stuck forever in the nest.

The stakes are high. Zerhouni notes in his 2005 op-ed that this country's medical and public health practices "must undergo a profound transformation in the coming decades if we are to succeed in providing access to care for all Americans at reasonable costs."

In 2006, the NIH created a special set of funds to support the delicate ecosystem that scientists who do this work need to thrive. Among their longest-running awardees is the University of Pittsburgh–based Clinical and Translational Science Institute (CTSI). Pitt and its local partners have received some $150 million for its CTSI since 2006. Today, CTSI supports hundreds of researchers by funding pilot studies, core laboratories, statistical support, regulatory assistance, study-volunteer recruitment, education for researchers at all stages of their careers, and more.

In addition to doing its level best to incubate physician-scientists and their partners, CTSI has helped make Pitt a hospitable environment for getting great ideas into the clinic.

Robert Arnold, the Leo H. Criep Professor of Patient Care and professor of medicine, says CTSI resources have been invaluable in supporting his own translational science efforts. And, more importantly, the institute's education programs (18) deserve credit for Pitt's success in attracting a number of stellar junior faculty and fellows to his department.

"To go someplace that has a fabulous group that has organized mentoring and meetings every month, where people get to present their research, where they have grant reviews and they urge people to involve statisticians early in their project? That's a great way to make sure the project is structured so that it's most useful and most likely to get good results.

"There are few places in the country that have that. It's so hard to get funded. These are the things that help people succeed."

Throughout the last six years, CTSI has provided crucial support in such discoveries as the possible gene-regulation role of usRNAs (small strands of RNA once dismissed as molecular junk) and the part polyomavirus plays in Merkel cell carcinoma.

A few years ago, CTSI helped a team of researchers try an experimental treatment for paralysis—a brain-computer-interface device, in its first-ever human test drivers (patients with epilepsy who volunteered to have their neurological signaling studied during hospital stays for seizure-mapping). CTSI seed money and regulatory support helped the researchers land an NIH grant, and, long story short, the researchers' hard work culminated in October in an exciting moment: A man with paralysis moved a robotic arm with his thoughts, reaching out to his girlfriend's hand for the first time in seven years. (See our Investigations story in the Spring 2012 issue.)

And the good ideas keep germinating. Here are just a few examples of translational science research coming of age here at Pitt.

Finally Airborne

Twenty years ago, Don DeFranco and Selma Witchel (MD '78, Fel '83) began their translational science journey at, of all places, a little league game in Churchill, Pa. They were sitting on the sideline—each had a son in the game that they were pretending to watch.

"We were taking turns to see who was at bat," admits Witchel.

"We were both reading articles," says DeFranco, "and I looked over, and her article had words that I recognized."

Ever since, DeFranco, a molecular endocrinologist and professor and vice chair of education in Pitt's Department of Pharmacology and Chemical Biology, and Witchel, associate professor of pediatrics and director of the pediatric endocrinology fellowship program at Children's Hospital of Pittsburgh of UPMC, have wanted to collaborate on their common ground—glucocorticoids and steroid physiology.

Often, in response to sepsis and traumatic brain injury, blood levels of free cortisol—a steroidal hormone that (among other functions) keeps inflammation in check—increase. For good reason: Inflammation can be a critically ill patient's undoing. But some patients have much lower total cortisol levels than others. So, in the 1970s, researchers tried administering drugs related to cortisol (synthetic glucocorticoids) to patients with lower levels of the hormone; the researchers found that some improved. But in the coming years, other studies showed that there were too many complications, including infections and high blood sugar. The practice has been debated in the literature ever since, its favor swinging back and forth like a pendulum.

Today, glucocorticoids are again used in these critically ill patients, albeit in smaller doses than they were 40 years ago. Yet the debate has hardly been put to rest. "Some patients it helps, some patients it doesn't," says DeFranco. "There's still no consensus about how to best evaluate for adrenal insufficiency during clinical illness."

DeFranco and Witchel thought: Rather than the amount of total cortisol in the bloodstream, wouldn't it be more helpful to know how cortisol interacts with these patients' immune cells—how well it's doing its job, at the molecular level?

Interdisciplinary collaborations are among the hardest to get off the ground. To win a federal grant, you need pilot data to prove your idea has wings, and that takes money. Ideally, you have a larger effort to draw on—a big, preexisting, funded study that dovetails into a little spinoff study. First-of-their-kind, fledgling ideas generally aren't so lucky.

Such was the case with DeFranco's and Witchel's brainstorming. Then they heard about a CTSI pilot fund for investigations exploring new territory and promoting new research partnerships. Right around the same time, Cristina Candido-Vitto (Fel '09), then a fellow, expressed interest in doing the legwork for such a project. The team applied for and received their award in 2008 and, after years of talking about it, finally got to work.

The researchers studied white blood cells taken from pediatric critical-care patients (using very small samples, collected while

DANIEL J COX/GETTY IMAGES



What's more costly than the business of moving breakthroughs from the lab into the clinic? Scientific inertia. Good ideas stuck forever in the nest.

other blood draws were already being taken, so as not to interfere with care). They looked at what was actually going on within the cell: Were glucocorticoid receptors in the right places, in adequate numbers? Was cortisol binding to them in the cytoplasm, then moving to the nucleus—all-important steps that enable a molecule to give the cell its marching orders?

They found that the glucocorticoid receptor protein maintained some function—it was indeed binding to the hormone and moving from the cytoplasm to the nucleus. However, in these critically ill patients, the level of receptors and their ability to bind were decreased in the early stages of illness.

"It looks like these kids don't have the capacity to respond to glucocorticoid therapy," says DeFranco.

"The physiologic significance of the decreased number of receptors is unclear. ..." says Witchel. "[Still] they're missing part of the effector mechanism they need to get a response."

The team has written a review article on the topic. They hope their findings might eventually contribute to a better blood test and take

the guesswork out of who stands to benefit from anti-inflammatory hormones, what dosage is beneficial, and how long patients should continue the therapy.

Before CTSI's pilot-funding program and others like it across the country, there were no federal mechanisms to bring good ideas like DeFranco and Witchel's to fruition. Apart from a few very targeted grants, there was virtually no way to fund a mini-proof-of-concept project to demonstrate whether a study was worthy of funding. It was classic chicken and egg.

"Without CTSI," says DeFranco, "this would have been just another dinner conversation."

Different Feathers

Say you are unlucky enough to have a bad fall, or a run-in with a piece of construction equipment, or any of the other cringe-worthy scenarios that could eventually land you in recovery from orthopaedic surgery, waking up with what arguably amounts to the worst of the worst of post-op pain. The good news is that you live in a time when there are drugs available to keep you comfortable. For most people, opioids are very good at lulling a profoundly traumatized body.

But for some people, they're so good that the body neglects one all-important function: breathing.

At that point, an alarm sounds—a signal that your blood-oxygen level is too low. The team of nurses caring for you leaps into action. They'll lift your chin and draw your jaw uncomfortably forward—to open your airway and, more importantly, to annoy your groggy body into breathing again. If they have to, they'll put an endotracheal tube down your throat.

If all else fails, you'll receive what's called an opioid rescue. Naloxone, a common option, will nix that whole not-breathing thing for a full hour. Problem is, it will also get rid of what you, on that most unlucky day, want most: pain relief.

Genetic and other factors that contribute to how well opioids manage individuals' pain have been widely studied—but not the risk factors for respiratory depression. Which means we have absolutely no way of knowing who is in for a particularly rude awakening after surgery.

"I did the math," says Will Lariviere, assistant professor of anesthesiology and neurobiology in the School of Medicine, "and it turns out there's a quarter-million Americans getting a naloxone rescue for profound respiratory depression each year—and that's based on conservative estimates."

Lariviere is an expert in the responses to pain and analgesia and the interactions between stress and pain systems—in animal models. But how respiratory depression looks in the clinic never really came to life for him until a few years ago, when a colleague introduced him to nurse anesthetist Rich Henker, a professor and international education coordinator for acute and tertiary care in the School of Nursing. They got to discussing recovery in the postoperative environment.

"Every time we met," says Lariviere, "I would realize, *Oh my gosh, the nurses are running around like crazy trying to keep people breathing.*"

"Will brings new perspective to my clinical [experience]," says Henker. "I don't think about it. I'm like, *Well, no, that's just what we do.*"

The problem with opioid-induced respiratory depression has been cited numerous times in nursing literature. And now, thanks to a 2009 CTSI pilot grant, this unlikely pairing of a bench scientist and a nurse anesthetist is finally confronting a problem that peer-reviewed literature aimed at MDs has yet to address: A side effect of analgesia, respiratory depression, is actually dictating the quality of care that some patients receive.

Lariviere is hunting for relevant genetic targets in animals; Henker is testing for those targets in humans—orthopaedic-surgery patients with lower-limb fractures, to be precise. So far, they have identified several distinct genotypes that respond uniquely to opioids, either in terms of analgesia, respiratory depression, or both. They have presented their findings nationally and published twice in *Biological Research for Nursing*. Their work is ongoing while they apply for larger grants from the NIH.

The goal, says Henker, is to tailor analgesia for optimal effects. Who needs more opioid, who needs less? And whom can they flag, based on genetic risk factors, as a patient who would fare much better on a nonopioid medication?

"The goal is to try to get rid of pain for these people."

Eagle Eye

Melanoma is unique among cancers in that it's right there where you can see it—a new mark on your skin, a visual reminder that you've got to get it checked out. The rub is in the getting-it-checked-out part. Most often, you'll see a primary care doc, who then has to decide whether to call a dermatologist. Who will then decide whether you need a biopsy. Which will take time to process in pathology. And all the while, the clock is ticking.

"Melanoma can grow from a curable lesion to an incurable one while you're waiting for an appointment," says Laura Ferris, an MD assistant professor of dermatology.

False-alarm biopsies cause patients undue expense, not to mention discomfort and worry, and that thought weighs heavily on the mind of your front-line clinician. But what if there were a virtual second opinion available, a tool to aid in the determination of whether to biopsy you right then and there?

Ferris is working with Mahadev Satyanarayanan, professor of computer science at Carnegie Mellon University, on a new use for his Web-based application, dubbed Diamond. The application can take any image you give it, compare it to others in a database, and display the ones it most closely resembles. Diamond has already been deployed in a number of ways, from clarifying mammogram results to spotting terrorists in video-surveillance footage.

Ferris has uploaded some 1,000 images of UPMC patients' skin lesions with known biopsy results (with patient identities removed). Funding from CTSI's Novel Technologies Core—which supports new biotech efforts—allowed the researchers to hire a programmer to harness this resource for melanoma screening. Once complete, this latest iteration of Diamond will be able to find the image best resembling a new lesion's unique features—shape, color, pigment patterns, blood vessels, and so on. In addition to its great potential as a diagnostic aid for both primary docs and dermatologists, it's a promising dermatological teaching tool.

And yet it almost didn't happen.

Ferris and Satyanarayanan began the project at a privately funded laboratory. That arrangement fell through when it became clear that their mission—to make Diamond open-sourced, for anyone to use and benefit from—didn't jibe with that of their sponsor.

CTSI's Novel Core was uniquely suited to the project, says Ferris. "There's really not a lot of funding to help you sit down and build something like this from scratch." ■

CIDDE/JOE KAPELEWSKI



Since its establishment six years ago, CTSI has enabled investigators to conduct 5,200 studies.

CTSI: A BIRD'S EYE VIEW

The University's Clinical and Translational Science Institute (CTSI), a National Institutes of Health (NIH)–funded effort, helps get clever ideas off the ground. With its support, Pitt has become an incubator of physician-scientists and others engaged in bringing promising discoveries to the clinic, where they can help patients. Here are a few ways CTSI is feeding the flock.

• CTSI's Institute for Clinical Research Education has grown into one of the premier clinical and translational research training programs in the country, now offering 18 academic career-development programs for grad students, med students, residents, fellows, postdocs, and faculty in all phases of their careers. For example, in 2011, CTSI's PhD Program in Clinical and Translational Science graduated its first three students. Another 11 are in the queue. (The Institute has even engaged more than 9,000 high school students. CTSI runs a mobile science lab—it's a truckload of fun.)

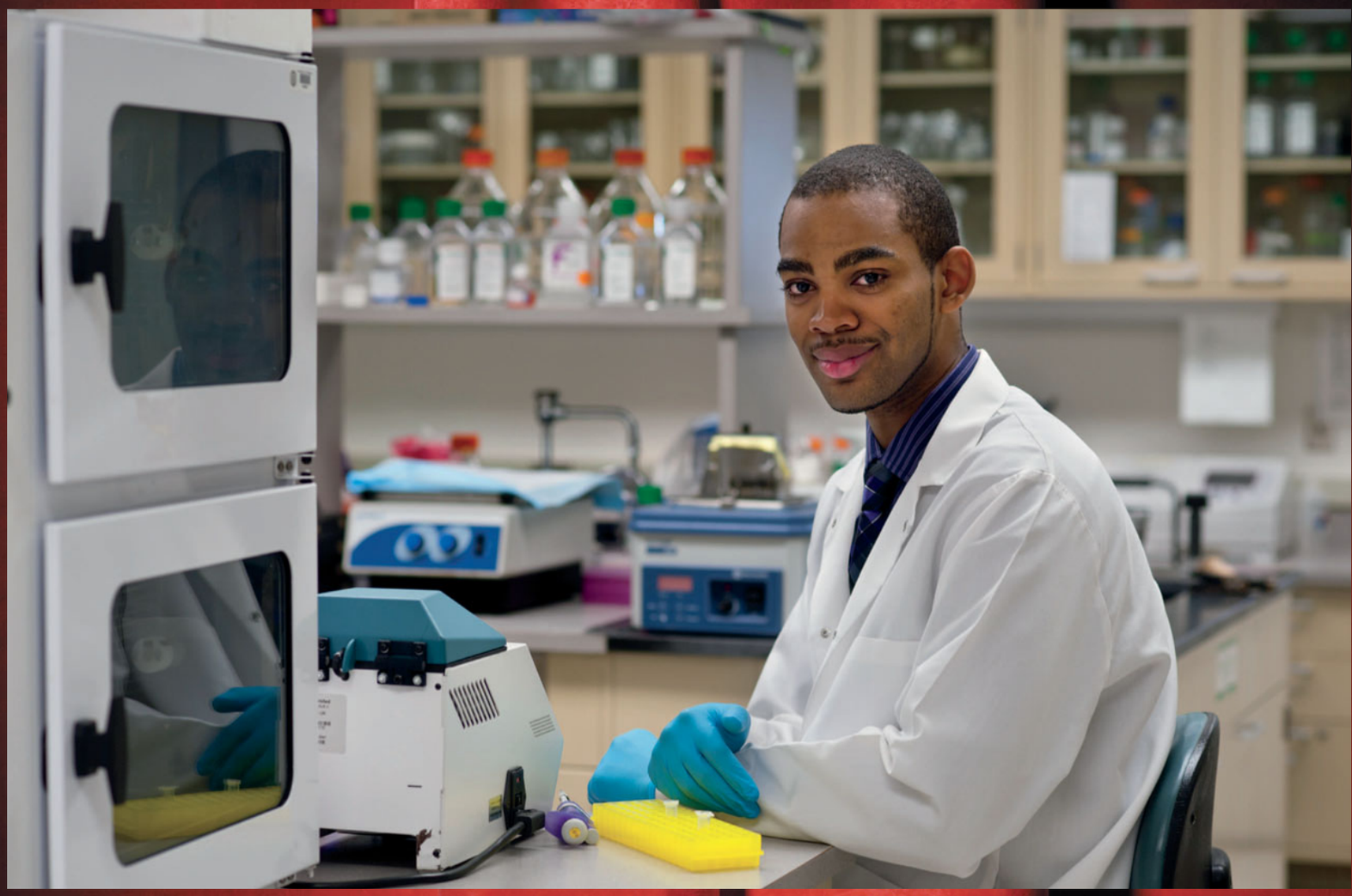
• In the past six years, CTSI programs enabled 2,100 investigators to conduct 5,200 studies.

• Last fiscal year, CTSI-funded facilities provided quantitative analysis of more than 6,000 clinical samples, bioinformatics analysis for 43 studies, and assistance with regulatory compliance for 69 investigators.

• Each year, CTSI fills more than 150 requests for assistance with study design, biostatistics, and epidemiology support.

• ProDy, a free and open-source molecular-systems-modeling software package (developed by Pitt's Ivet Bahar with CTSI support), has been downloaded more than 10,000 times in the past two years.

• At last count, there were more than 34,000 people enrolled in the CTSI Research Participant Registry. *—EV*



Franklyn Boothe is one of hundreds of young people who spent the summer working with School of Medicine researchers.

SUMMER TO REMEMBER

CURIOSITY PIQUED AT PITT

BY JENELLE PIFER

PHOTOGRAPHY BY MARTHA RIAL

If during high school or early in your undergraduate years you decide you want to become a doctor, the first thing an advisor will likely tell you is: *You're going to need to do a lot of research.* That's what happened to Franklyn Boothe, an undergraduate and senior at Pitt. *Research*, he thought back in 10th grade, *it sounds interesting. But what is it?*

"It's this mysterious thing you're supposed to do," says Boothe, "but they don't tell you exactly what it entails."

Having spent this summer (his second in a row) studying how antipsychotic drugs work in schizophrenia, Boothe knows this: "You just have to start small and ask a lot of questions."

He got his start in the lab with David Lewis, an MD, director of Pitt's National Institute of Mental Health–funded Conte Center for the Neuroscience of Mental Disorders, chair of Pitt's Department of Psychiatry, and UPMC Endowed Professor of Translational Neuroscience. Boothe is one of 15 undergraduates participating in the Conte Center's summer research fellowship. Lewis says he hopes the program will engage students both "intellectually and affectively" by showing them the path discoveries take to become treatments, as well as "the importance of developing new treatments from a human perspective." Fellows attend weekly lectures on faculty research, as well as clinical sessions where they interact with patients face to face.

The latter was eye-opening for Boothe. He met high-functioning schizophrenia patients and patients so overwhelmed by delusions they couldn't maintain relationships or hold down jobs. "It really puts things in perspective and gives a face to what you're working for," he says. "It's easy to lose track of why we're sitting in a lab and pipetting for several hours. It's to try and improve people's lives."

Boothe's first days in the lab were among his toughest. "It's kind of like being thrown into a quantum physics class when you've never taken physics before," he says. He had to acquire the lingo, memorize the protocol, and master new techniques.

This summer, however, he's working almost independently. He's designed an experiment to help determine how mitochondria change in schizophrenia. The Lewis lab had already defined an abnormality that may cause less energy to be produced, fewer neurons to fire, and problems to occur in systems like working memory. Still, Boothe says, there could be confounding factors. Not enough research has been done into how antipsychotic drugs affect mitochondria, and researchers can't say, with certainty, that it's the disease causing the change, not the drug. Boothe's preliminary data indicate the drug is not responsible.

It's the first major study he's conducted from start to finish. "It's been really gratifying to not only be able to do this on my own but to get good results," Boothe says.

The big picture, Lewis says, is that mental illnesses and addictive disorders account for 40 percent of all the years lost to premature death from disability in the United States. "The problem is big," he says, "and we need the best and the brightest now and in the future to consider it."

For a career path as demanding as research, students have to take some initiative, says Pitt's Guy Salama, a PhD. In other words, they need to knock on some doors.

And the busy scientists on the other side? They need to be willing to answer.

"People who have decided to dedicate their lives to research are few and far between, so you have to cater to them a bit and encourage them. Otherwise, it's not going to happen," says Salama, who is a professor of cell biology and mentor in the Pittsburgh Research and Investigation Summer Experience (PRISE) program, a summer cardiology fellowship for undergrads.

Zane Kalik, a rising senior at Youngstown State University (YSU) and current PRISE fellow, came knocking early on. "It doesn't matter where you start, just get a good research foundation as early as possible," says Kalik, who started in an environmental biology lab as a freshman.

When he was a junior at YSU he caught Salama's attention. Kalik's mentor Carl Sims, a former Pitt postdoc with Salama who later joined the faculty at YSU, had recently died. Kalik had been so well trained he was able to pick up where Sims left off. Kalik was using equipment that allowed him to study electric currents in the heart, and how they sync to create irregular heartbeats called arrhythmias. Salama was impressed and invited the budding researcher to speak at Pitt's Cardiovascular Institute.

When Kalik heard about the PRISE fellowship—funded in part by the American Heart Association—he applied, was accepted, and spent the summer at Pitt researching a new drug to prevent atrial fibrosis.

"The cardiac action potential is a symphony of ion currents," says Kalik, now in his second year with PRISE and one of six fellows. "All those currents work together to generate our heartbeat, and it's a very beautiful process." But this electric chorus can get thrown out of whack when deposits of collagen develop in the atria because of injury or aging. (This is called fibrosis.) The heart can then become highly susceptible to atrial fibrillation, the most common arrhythmia. A hormone called relaxin, however, seems to prevent this; Kalik is trying to figure out how.

"Zane is really unusual. He's just totally devoted. He spends an enormous [number] of hours to try to crack a difficult nut," says Salama. Kalik's typically in the lab between 12 and 15 hours per day, a habit he attributes to his former mentor Sims. Kalik says the more cells he can study, the better his data.

"*A summer*—a lot of people say—*it's not enough time.* I think it is," he says. "You just have to use the time, and you have to really work at it."

The Chang-Moore lab at Pitt—a tumor virology lab run by National Academy of Sciences members Patrick Moore and Yuan Chang—took in a high school student this summer. It was the first time it had done so. The researchers had decided to participate in the Doris Duke Foundation



Birdy Assefa



Zane Kalik

Academy for Clinical Research, an eight-week program for young people from underrepresented and disadvantaged groups. Program director Michael Lotze, Pitt professor of surgery and assistant vice chancellor, health sciences, remembers when he first sidled up to the research pair with the idea: "They said, 'Make sure you give us a good one.'"

Birdy Assefa, an enthusiastic 16-year-old, did not disappoint.

She found out about the program through the Jack Kent Cooke Foundation, which connects highly motivated students with new opportunities as early as the seventh grade. Assefa met with her advisor there. "I told her, 'I'm interested in research, and I want to know what that is.'" Her advisor directed her to Pitt.

This summer Assefa immersed herself. Working alongside Chang at the bench every day, Assefa studied a virus called the Merkel cell polyomavirus (MCV). The Chang-Moore lab had recently discovered that MCV causes an aggressive type of skin cancer called Merkel cell carcinoma, but the team is still working to unwrap the biochemical pathways responsible.

"It's really interesting, and there's so much to be done [in cancer research]," says Assefa, who attended lectures and worked alongside 37 other scholars in this program and the University of Pittsburgh Cancer Institute Academy. Assefa, who's originally from Ethiopia, came to America at age 10 and now attends high school in Arlington, Va.

"She had the personality to be inquisitive," says Chang, "She just came in with that and leaves the lab with that." Chang remembers one early interaction when Assefa was learning to manipulate DNA: "She said, *You know what they show in* CSI *[the TV show]? Does it really happen that way?*"

What's great about the Doris Duke program, Chang says, is it harnesses students' enthusiasm and teaches them what science is really about.

Assefa now speaks fluently about the project and her plan to go to med school one day.

Lotze spearheaded the Doris Duke program at Pitt many years after spending two pivotal summers in high school programs himself: "One at Northwestern University, where I ended up going to college and medical school," he says, "and the other at Strong Memorial Hospital in Rochester, N.Y. My first summer after high school I worked in an operating room, and I ended up becoming a surgeon."

Beginnings, he says, are really important. ■

NOT SO LAZY DAYS

The School of Medicine and partners offer summer research and enrichment opportunities for students 16 and older.

UNDERGRADUATE

- **Center for Neuroscience at the University of Pittsburgh Summer Undergraduate Research Program**
- **Conte Center for the Neuroscience of Mental Disorders Undergraduate Research Fellowship**
- **Models of Infectious Disease Agent Study (MIDAS) Summer Research Program, *MIDAS National Center of Excellence***
- **Pittsburgh Center for Kidney Research**
- **Pittsburgh Research and Investigation Summer Experience (PRISE) for Undergraduate Students, *Cardiovascular Institute***
- **Pittsburgh Tissue Engineering Institute Summer Internship Program**
- **Pittsburgh Tuskegee Prostate Training Program, *Department of Pathology***
- **Summer Premedical Academic Enrichment Program, *Student Affairs/Diversity Programs***
- **Summer Undergraduate Research Program, *Departments and Divisions of Cell Biology and Molecular Physiology, Cellular and Molecular Pathology, Immunology, Molecular Genetics and Developmental Biology, Molecular Virology and Microbiology, Molecular Pharmacology, and Molecular Biophysics and Structural Biology***
- **TECBio, *Department of Computational and Systems Biology***

HIGH SCHOOL

- **Doris Duke Foundation Academy for Clinical Research**
- **Medical Explorers, *Student Affairs/Diversity Programs***
- **Pittsburgh Tissue Engineering Institute High School Summer Research Internships**
- **Summer Premedical Academic Enrichment Program, *Student Affairs/Diversity Programs***
- **University of Pittsburgh Cancer Institute Academy, *Departments of Biomedical Informatics and Computational and Systems Biology, Hillman Cancer Center, Women's Cancer Research Center***
- **University of Pittsburgh Health Career Scholars Academy**

For more information: www.howscienceworks.pitt.edu or Office of Science Education Outreach, M525A Sciafe Hall, 412-648-9572.

People and programs that keep the school healthy and vibrant





BRIAN MATHIE UPMC

The new Mario Lemieux Center for Blood Cancers will be on the fourth floor of the Hillman Cancer Center.

LEMIEUX CENTER NEARS COMPLETION

BLOOD CANCER TREATMENT AND RESEARCH, IN ONE PLACE

BY JENELLE PIFER

It was in the middle of his greatest season with the Pittsburgh Penguins that Mario Lemieux was diagnosed with Hodgkin's lymphoma. That same year the hockey star (now cancer free) created the Mario Lemieux Foundation, which raises money for cancer research in Western Pennsylvania. In 2010, the foundation presented the University of Pittsburgh Cancer Institute (UPCI) and UPMC CancerCenter with $3 million, closing a fundraising campaign to build a new treatment facility. UPMC then stepped in with an additional $10 million investment for the Mario Lemieux Center for Blood Cancers, now nearing completion.

"We are thrilled that [Lemieux's] name, which we associate with success, is going to be associated with our center," says Nancy Davidson, the MD director of UPCI and Pitt professor of medicine.

The center, set to open this December, will occupy the fourth floor of the Hillman Cancer Center and serve an estimated 25,000 patients a year. Employing a mixed-use design, it will offer comprehensive diagnostic and treatment services and access to clinical trials.

"The center will allow us to bring together, in one place, the practitioners, researchers, and support services that are wrapped around the care of individuals with blood cancers in our region. It'll help us to really optimize care," Davidson says.

From a patient's perspective, this means being able to enter the center and receive complete treatment services in one place. Usually, Davidson says, "you have to go to this office to see the doctor, and you have to go somewhere else for your blood drawing, and a third place to check out." What UPCI wants is that when patients check in, they're sent to the right place, and everything—physicians, therapists, staff to draw blood—comes to them.

This patient-centered focus also extends to the site's operating hours, says Stanley Marks (MD '73, Res '76), director of clinical services, chief medical officer for UPMC CancerCenter, and clinical professor of medicine at Pitt. "Many of the patients who have these cancers, especially those who have leukemia or those undergoing bone marrow transplant, they're in a situation where they require care almost every day for long periods of time."

Typically these patients are treated in the inpatient setting, he adds. But the Lemieux Center is joining a nationwide push to try to bring as much medicine as possible into the outpatient setting, which helps outcomes, minimizes hospital complications, and improves quality of life for many patients. To do so, the center will be open 12 hours each day, with weekend hours, too, so services are continuously available to those who need them.

The design also means more synergy for new research: Researchers' offices are intermingled with treatment rooms. "We always want to be doing this in oncology. We are not satisfied with where we are in the treatment of almost any kind of malignancy, and blood cancers are no exception," says Davidson.

Mario Lemieux, chair of the Mario Lemieux Foundation, says, "The translational research component of our new blood cancer center will help us take one step further toward reaching our goal of finding cures for cancer." ■

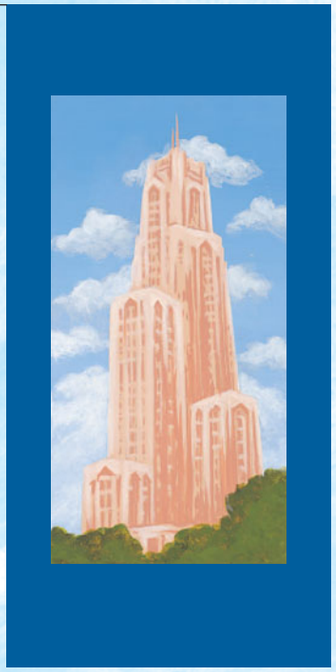
BOOSTER SHOT

It's not the most common husband/wife origin story, but **Noel Gillette** and **Lynn Daugherty Gillette** (both MD '60) met in med school over a shared cadaver in anatomy class.

Noel Gillette, who practiced in Monroeville and Wilkinsburg, died in March. He considered himself a lifelong learner and something of a teacher, as well. His donation to the School of Medicine, his own body, will allow him to carry on his teaching role, says the Gillettes' daughter, Susan Gillette Meer.

"This [donation] allowed him to serve his dear alma mater. And, I think, a small romantic side of it is knowing the possibility that friendship, or possibly love, could be found among the medical students in the same way he and my mother found theirs," she says. —*Joe Miksch*

For more information on making a similar donation, go to www.ooas.pitt.edu/content.asp?id=1735



CLASS NOTES

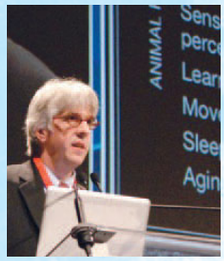
'70s

Ed Boyko (MD '79), a professor of medicine at the University of Washington who has devoted two decades to epidemiologic research, is the VA investigator for the Millennium Cohort Study, the largest prospective health project in military history. Using volunteers' self-reporting as well as Department of Defense medical records, Boyko and his team are evaluating the long-term physical and mental health effects of military service, looking for links between military experience and physical and mental health outcomes in their 150,000 study participants. "The main exposure everyone's concerned about is deployment to combat zones," he says. So far, they've found that in this population (active duty military and reservists, most in their 20s and 30s), PTSD has a strong link to type 2 diabetes—even stronger than the previously established link between depression and type 2 diabetes in the general population.

Boyko is also a principal site investigator for the Million Veteran Program, a VA patient biorepository in the making, which now has more than 70,000 enrollees toward its million-enrollee goal. (Pitt is one of the study's 40 sites, he notes.) Once complete, the biorepository will be a treasure trove for epidemiologic researchers, with blood samples, questionnaires on health and lifestyles, and health care records. "Typically, you need to get permission from regulatory bodies; you need to go out and recruit subjects; and you need to set up your processing and analysis of data. All this could take five years. A biorepository should create considerable savings in time," he says.

'80s

Imagine you could build a new organ from scratch. **David Gerber** (MD '89, Clinical Transplant Fellow '98), professor of surgery, surgical director of liver transplantation, and chief of abdominal transplant surgery at the University of North Carolina School of Medicine, hopes to make that dream a reality. Gerber is researching stem cells and nanotubes to meet the needs of many patients suffering from organ failure. "Our current strategies are not meeting this clinical gap," he says. Tissue engineering has a number of potential applications, including the creation of artificial pancreases to secrete insulin in diabetics or designing vascular grafts to repair blood vessels. Gerber's work in this field is focused on the three-dimensional growth of neo-tissues—he's currently principal investigator for more than 15 clinical trials aimed at better outcomes for kidney- and liver-transplant patients. "The longer-term goal is the development of implantable biologic units," he says.



Small

'90s

Language is among the many things that make us distinctly human. Studying how our linguistic faculties develop is one of the primary concerns of **Steven Small** (Neurology Resident '91), editor in chief of *Brain and Language* and founder of the Society for the Neurobiology of Language. After his residency, Small took on a number of positions in Pitt's Departments of Neurology, Psychology, Communication Sciences and Disorders, and Intelligent Systems, and also was a founding member of the Pitt-Carnegie Mellon University Center for the Neural Basis of Cognition. Now, as professor and chair of neurology at University of California, Irvine, Small studies language and hand-motor recovery following stroke. By observing the natural patterns of recovery, Small has devised various interventional techniques that could speed up the healing process.

A decade ago, only about 10 percent of plastic surgeons were women. But that's changing rapidly, says **Anureet Bajaj** (MD '96). Today, 30 percent of all plastic surgery residents are women. Bajaj, assistant medical editor of *Plastic Surgery News* and chair of the Women Plastic Surgeons Steering Committee for the American Society of Plastic Surgeons, is doing her level best to fuel the fire. The Oklahoma City–based reconstructive and cosmetic plastic surgeon organizes teleconferences each month for the committee, as well as workshop luncheons at the society's annual meeting, covering such topics as time management, legal issues, work/life balance, and social networks and practice. She's now organizing the committee's 2013 retreat, slated for sometime this spring in Las Vegas, Nev.

Sandeep Nathan (Internal Medicine Resident '98), director

FAMILIAL TALES

As kids, neither Susan Dunmire (MD '85) nor Samuel A. Tisherman (MD '85, Res '93, Fel '94) got to watch much of the *Super Friends* or other Saturday morning cartoons. They were off with their dads, Lester A. Dunmire (MD '48) and Samuel E. Tisherman (MD '55), on rounds.

Little Susan and Sam grew up and met decades later at the welcoming reception of Pitt med's Class of '85. They got to know each other. They fell in love. They chose specialties. (Susan is a Pitt associate professor of emergency medicine; Sam a Pitt professor of critical care medicine, as well as surgery.) Surgeon Lester Dunmire died this summer, but the familial medical tale continues as Susan and Sam's oldest, Robert Tisherman (Class of 2017), begins his first year at Pitt med. Robert is the 15th member of his family to do so and represents the fifth generation of a line of Pitt physicians dating back to Lester Haven Bodkin, who enrolled in 1886 as part of the first class to enter Pitt med's forerunner, the Western Pennsylvania Medical College.

Robert and the other Tisherman children have always been surrounded by medicine. When child-care arrangements fell through, Susan says, they put the children in an office behind the ER. "They splinted each other. … My kids learned to build trauma packs from the time they were 5 and 6 years old."

For those who aren't in the know, the family ties can cause confusion. A col-

RIGHT: Sun. BELOW: Asare (right) at the U.S. Capitol last year with former U.S. Congressman Louis Stokes.





of interventional cardiology research and education at the University of Chicago Medical Center, is among a small group of cardiologists who routinely perform coronary angiographies—to test heart health—via the radial artery in the wrist, rather than the femoral artery in the leg. Though the transradial technique is used in less than 10 percent of angiographies performed in the United States, Nathan and others believe it can cut costs, allow for earlier discharges, and reduce patient discomfort. He has taught the technique at national symposia and workshops and hopes that it will soon be a more widely practiced procedure. "There is a learning curve and some associated growing pains, but the potential payoff is huge," he says.

'00s

It's a common refrain in legislation: Health care policymakers often have little to no experience in health care themselves. But **Akua G. Asare** (MD '06) set out to change that as the 2011 American Psychiatric Association Jeanne Spurlock, MD, Congressional Fellow. Last year, Asare put her dual training in general medicine and psychiatry to work on a number of policy issues ranging from mental health to antimicrobial-resistant pathogens. She first became interested in health care policy during her residency in psychiatry at the University of Miami Leonard M. Miller School of Medicine/Jackson Memorial Hospital, when Asare was involved with the Committee of Interns and Residents, a national house staff union that advocates for better working conditions in health care. Though the Spurlock Fellowship kept her from practicing medicine, she says, "It's opened up a different world wherein I can become a change agent on a macro scale."

Smell tests—where people measure their ability to recognize distinct scents—have been featured on *The Dr. Oz Show* as simple and effective indicators of your risk of developing Alzheimer's disease. Finding evidence of this to be lacking, **Gordon Sun** (MD '06) sought to sniff out the truth. The Robert Wood Johnson Foundation clinical scholar at the University of Michigan reexamined the research behind such tests and published a paper this May in *Laryngoscope*, which caught the attention of WebMD and *Medical News Today*. His conclusion? "The evidence is not strong enough to support the regular use of smell tests in predicting the development of Alzheimer's dementia." He notes the correlation between decreased olfaction and Alzheimer's; however, rigorous studies are still needed before smell tests can be used to predict onset of the disease, he says.

'10s

In August 2011, the American Medical Association Foundation awarded **Alana Otto** (MD '12) a $10,000 Physicians of Tomorrow scholarship. Otto was one of only 18 to be presented with the honor last year. The foundation scholarships are given annually to medical students who not only demonstrate excellence within the classroom, but also have shown a commitment to community involvement and volunteering. A regular volunteer with the Allegheny Reproductive Health Center and the Women's Center and Shelter of Greater Pittsburgh, Otto started her pediatrics residency in June at Northwestern University/Lurie Children's Hospital in Chicago. She has also served as a mentor for pregnant teenagers around Pittsburgh. Otto says she looks forward to "the opportunity to be an influential member of patients' lives and communities in addition to providing medical care." As a pediatrician, she wants to make "health care more accessible, relevant, and effective for children."

—Hayavadhan Thuppal and Elaine Vitone





LEFT: The recently deceased surgeon, Lester Dunmire. RIGHT: Two more Pitt med generations—Robert Tisherman is flanked by his parents, Samuel Tisherman and Susan Dunmire.

league of Sam's was once approached by a student worried about an affair. When pressed for evidence, the student revealed seeing Professors Dunmire and Tisherman holding hands. The amused colleague responded, *They've been married for 20 years!*

Another time, Susan reports, she was "talking back" to Sam in the ER: "A resident turned to me and said, 'You can't talk to him that way—he's the attending for surgery.' And I said, 'Yes I can; he's my husband!'"

Robert shares dinner with his parents and sometimes stops by his mom's office to drop off a coffee. Eventually, he'll take classes taught by his parents, which will, in all likelihood, generate more entertaining stories. *—Em Maier*

THE WAY WE ARE

CLASS OF '88

When **Elaine Hylek** (MD '88) thinks about her days at the School of Medicine, she rattles off the names and residencies of her classmates as if she graduated yesterday. Hylek was the class president her first two years and got to know many of her classmates through a number of events: the hayride, the '50s-themed dance, the Scope and Scalpel performances. Today, Hylek is a world-renowned expert in the prevention of stroke and atrial fibrillation, as well as the safety of anticoagulants. She is also the director of the Thrombosis Service at Boston Medical Center, associate director of the Education and Training Division of the Boston University Clinical Translational Science Institute, and professor of medicine at Boston University.

Hylek recalls more than just the name and residency of fellow Pitt meder **Eric Peterson** (MD '88)—she regularly collaborates with him. Peterson is director of the Duke Clinical Research Institute and professor of medicine in the Division of Cardiology at Duke University Medical Center. He studies outcomes research and contemporary management of acute coronary syndromes.



Mosesso

Another classmate Hylek remembers fondly is **Vincent Mosesso** (MD '88, Emergency Medicine Resident '91). The two grew up together on Brinwood Avenue in Baldwin before reuniting at the School of Medicine. Mosesso is professor of emergency medicine at Pitt, medical director of prehospital care for UPMC, and medical director of the Sudden Cardiac Arrest Association, a nonprofit that promotes awareness and treatment of sudden cardiac arrest, as well as support for survivors.

As a med student, Mosesso performed in Scope and Scalpel with Hylek … sort of. "My singing was deemed so bad that I had to lip sync, and another classmate sang from backstage," he says.

Husband-and-wife alums **Ken Washburn** (MD '88) and **Anne Logan** (MD '88) met



Washburn and Logan

at Pitt med. Logan, a pediatrician, has a private practice in Boerne, a Texas Hill Country town the couple has called home since 2000. Washburn is the Valero Distinguished Chair in Transplantation and director of liver transplantation at the University of Texas Health Science Center at San Antonio. An expert in pediatric and adult liver transplantation, he's led a number of clinical research protocols in the field. During the past decade, Washburn has also served on numerous state, regional, and national committees that match organ donors and recipients.



Faro

For **Albert Faro** (MD '88, Pediatrics Resident '91, Pulmonary Medicine Fellow '96), studying and training in Pittsburgh helped him discover his "two loves"—caring for patients with cystic fibrosis (CF) and transplant medicine. (Nearly half of pediatric lung transplant recipients have CF.) As the first president of the International Pediatric Lung Transplant Collaborative, he brought together lung transplant centers from around the world to better serve patients in need. Faro continues his academic and clinical work at the Washington University School of Medicine in St. Louis, where he is associate professor of pediatrics. *—HT*

CHARLES E. COPELAND

NOV. 16, 1931–MAY 8, 2012

Charles E. Copeland (MD '58, General Surgery Resident '63, American Cancer Society Fellow '65, Vascular Surgery and Transplantation Research Fellow '66) was well known for founding UPMC Mercy's burn unit, the first of its kind in Pennsylvania, in 1967. He remained a constant presence there until six months before he died of liver cancer in May. But the 80-year-old's "biggest legacy" is the surgical training program at Mercy, says surgeon Harry W. Sell Jr., a longtime colleague who followed Copeland as the chair of Mercy's Department of Surgery. Copeland, a general, vascular, and trauma surgeon and clinical professor of surgery at Pitt, was among the first local doctors trained in advanced trauma life support in the 1960s and continued teaching residents at Mercy for some 50 years. Apart from a one-year fellowship in Boston, Copeland spent his entire career in Pittsburgh.

It has not been uncommon for former patients to call the burn unit asking to talk to Copeland decades after being in his care. Sell recalls Copeland as the sort of surgeon who gave himself entirely to his profession and his family.

"That kind of person doesn't come along too often," says Sell. "He had a tremendous amount of accomplishments here, and you couldn't tell. He was humble about it." *—HT*

PEARL G. MCNALL

FEB. 3, 1923–MARCH 26, 2012

As an anesthesiologist, Pearl McNall (MD '49, Intern '50, Anesthesiology Resident '52) was known for her precise manner, take-charge attitude, and lifelong devotion to treating patients with myasthenia gravis. She died March 26, at age 89, of congestive heart failure.



Copeland



McNall

"She was the most meticulous, careful anesthesiologist on my staff," says Rick Siker, an MD, longtime friend, and former director of anesthesiology at Mercy. "I would always assign new residents to have at least one week's rotation with Dr. McNall. She would teach them how important it was to be meticulously careful with patient safety."

She is also fondly remembered, Siker says, for once telling a too-curt surgeon who demanded she come to the hospital late one night, "You've got to wait until I get my girdle on."

"She was well known for that comment," Siker says. "One could not dictate to Dr. McNall, and I think it was one of her finest qualities." McNall was the first woman appointed to Mercy's senior medical staff, a position she accepted humbly.

As a young physician, McNall developed an early interest in studying and treating myasthenia gravis, a chronic neuromuscular disease that causes muscle weakness. With Francis Foldes, an MD and cofounder of the Myasthenia Gravis Clinic of Western Pennsylvania at Mercy Hospital, McNall authored numerous studies on myasthenia gravis treatments and protocol, as well as new localized muscle relaxants in anesthesiology. McNall became a physician at the clinic in 1957 and in 1962 was appointed its director. She later served as chair of the Myasthenia Gravis Foundation of America and received its Outstanding Woman of the Year Award in 1974.

Outside of the hospital, McNall was an ardent bridge player, world traveler, and botanist. Her family asks that donations be made on her behalf to the Myasthenia Gravis Association of Western Pennsylvania, to which she remained devoted throughout her career and late in life.

—Jenelle Pifer

IN MEMORIAM

'30s

THOMAS M. BALDWIN SR.
MD '37
MAY 2, 2012

PAUL M. RIKE
MD '38
MAY 10, 2012

'40s

CARL BENNETT BEAN
RES '44
JULY 14, 2012

LESTER DUNMIRE
MD '48
JULY 21, 2012

'50s

JOSEPH G. BURGER
MD '55
JULY 2, 2012

JAMES ANTHONY ROCK
MD '56
JUNE 1, 2012

'60s

NOEL JOHN GILLETTE
MD '60
MARCH 22, 2012

DAVID STELLE
MD '61
JUNE 27, 2012

JOHN R. MISAGE
MD '62
MAY 4, 2012

JOSEPH BRENNER
MD '65
JULY 30, 2012

LORETTA R. LOEB
MD '57, RES '68
MAY 11, 2012

'80s

GERALD BRETT WEISS
MD '87
JUNE 2, 2012

GREGORY S. SHEFFO
MD '89
MAY 27, 2012

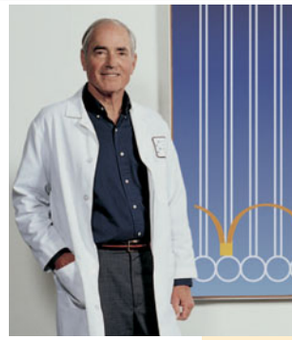
WE KNEW YOU WHEN CHARLES COCHRANE AND THE PITTSBURGH FIVE

BY JENELLE PIFER



1961 *HIPPOCRATEAN*

Pitt med's Department of Pathology in the 1961 *Hippocratean*. That year, the "Pittsburgh Five"—William Weigle, Charles Cochrane (top row, fifth and sixth from the left, respectively), Joseph Feldman, Frank Dixon (front row, third and fourth from the left, respectively), and Jacinto Vazquez (not pictured)—left Pittsburgh for California, establishing the forerunner of today's Scripps Research Institute.



Cochrane

On the afternoon of March 6, 2012, Charles Cochrane sat nervously near the phone in his lab at the Scripps Research Institute in La Jolla, Calif. "You're waiting, waiting, waiting," says the 81-year-old MD and former Pitt professor of pathology. The call he was expecting from the FDA was one that would determine the fate of a project he'd labored on for 25 years. The new drug he'd created was called Surfaxin, a synthetic surfactant that coats the lungs of preterm infants in respiratory distress and helps them breathe. Cochrane knew the potential was enormous.

The phone rang. A colleague spoke: "Charley, in 2 seconds you're going to be very happy." It was the team's fifth attempt, and Surfaxin was finally approved. The drug will be on the market this October.

In 1956, at 25, Cochrane joined a group of up-and-coming pathology researchers at Pitt. "Our department was always rated the best by the students because we were such young cowboys," Cochrane says.

"He displayed a lot of enthusiasm. That resonated with some students," says Richard Trackler (MD '61). "They thought, *He's more like we are.*"

In 1961 Cochrane decided to pursue research full time. He and four others from Pitt—then-department-chair Frank Dixon, Joseph Feldman, Jacinto Vazquez, and William Weigle, a sought-after group called the "Pittsburgh Five"—moved to California to a then-unknown complex called the Scripps Research Institute, where an enterprising hospital director promised to build them a facility and leave them alone. Dixon eventually became the institute's first director and led the research program for two-and-a-half decades.

In 1988, a pediatrician studying the human surfactant—which coats the air sacs in the lungs and helps keep them open—came to Cochrane for help. His team had identified the lipids involved but didn't quite understand its proteins. Cochrane set about isolating them.

"The first thing that struck me was that in our columns for separating the proteins there was precipitation at the top," says Cochrane. Until then, no protein in the human body was known to be insoluble in water. "I couldn't believe what I was seeing," says Cochrane, now professor emeritus in Scripps' Department of Immunology and Microbial Science.

He analyzed the DNA, determined the entire sequence of the protein, and pinpointed which regions were responsible for the surfactant activity. Knowing this, he made a very simple version of the protein, mixed it back in with synthetic lipids, and lo and behold: He'd made an entirely synthetic surfactant.

Infant respiratory distress syndrome is a life-threatening disorder that occurs when premature lungs don't have the proper elasticity to spring back open after exhaling. Surfactants restore the stretch and enable these babies to breathe on their own. Until now, they typically have been given surfactants derived from animal lungs, but Surfaxin has been demonstrated to work equally well, says Jennifer Kloesz, Pitt associate professor of pediatrics and clinical director of the neonatal intensive care unit at Magee-Womens Hospital of UPMC. Surfaxin eliminates risks of impurities inherent in animal products. "And sometimes different religious or cultural groups have concerns with us using animal-derived products," Kloesz says.

Getting approval from the FDA was a long and turbulent process in part because the drug type was so new, Cochrane says. He's now working on an aerosol delivery method, so Surfaxin can be administered in developing countries without ventilators. He's also confident the drug will find new applications, treating diseases like cystic fibrosis and acute asthma in adults.

The four other members of the Pittsburgh Five have since died, and colleagues at Scripps now jokingly call Cochrane "the last of the Mohicans."

"There is something almost mythical about the Pittsburgh Five," says Trackler. "They were the nucleus of the Scripps Research Institute, these cowboys." ■

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THAT'S NOT NATURAL

It would be surprising to find a display about *E. coli x1776* in a natural-history style exhibit. For one thing, it's a bacterium—not exactly the usual dinos-and-Darwin fare. More importantly, it's not *natural*. *E. coli x1776* was invented in a laboratory in 1976 as a safe research organism that couldn't survive outside the lab. Genentech cofounder Herbert Boyer (PhD '63) used *E. coli x1776* in the work that led to mass-produced insulin; his invention of recombinant DNA could be seen as a Promethean moment. But while a lab origin may take it out of the running for natural history museums, it makes *E. coli x1776* perfect for the Center for PostNatural History.

Founded by Richard Pell, associate professor in Carnegie Mellon University's School of Art, with colleagues including lead scientific advisor Lauren Allen, a graduate student in Pitt's Science and Education Policy Program, the center is an archive and public-outreach project that features living organisms that have been altered by humans. From sterilized screwworms to transgenic chestnut trees (engineered to resist chestnut blight), the center keeps documentation and specimens of transgenic living things. It also creates exhibits for its new storefront gallery in Pittsburgh's Garfield neighborhood and for venues as diverse as European avant-garde art spaces and the Smithsonian Museum of Natural History, where Pell was a research fellow in 2010. ***—Justin Hopper***

—Illustration courtesy Center for PostNatural History

CALENDAR

OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

INDIANAPOLIS HEALTH SCIENCES ALUMNI RECEPTION
SEPTEMBER 27
6 p.m.
Indianapolis, Ind.

MUSGRAVE LECTURESHIP
OCTOBER 12–13
J. William Futrell, MD, Speaker

HOUSTON HEALTH SCIENCES ALUMNI RECEPTION
JANUARY 17, 2013
6 p.m.
Houston, Texas

AUSTIN HEALTH SCIENCES ALUMNI RECEPTION
JANUARY 18, 2013
6 p.m.
Austin, Texas

PALM BEACH HEALTH SCIENCES ALUMNI RECEPTION
FEBRUARY 13, 2013
6 p.m.
Palm Beach, Fla.

2013 WINTER ACADEMY
FEBRUARY 15, 2013
Ritz-Carlton
Naples, Fla.
www.winteracademy.pitt.edu

MEDICAL ALUMNI WEEKEND 2013
MAY 17–20, 2013
Reunion Classes:
2003 1998
1993 1988
1983 1978
1973 1968
1963 1958

UPCOMING HEALTH SCIENCES ALUMNI RECEPTIONS
DATES TBA
St. Augustine, Fla.
Atlanta, Ga.
Phoenix, Nev.
Los Angeles, Calif.

For information on an event, unless otherwise noted, contact Pat Carver, 412-647-5307, cpat@pitt.edu

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

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70	5.1	$510	$3,691
75	5.8	$580	$4,268
80	6.8	$680	$4,791
85	7.8	$780	$5,502
90	9.0	$900	$6,190