HOW DO YOU CAPTURE THE EPHEMERAL?

A PITT LAB JUST DID.

CANCER STEM CELLS FROZEN IN TIME.
**OVER THE TRANSOM**

**PITT SIGHTINGS**
I joined the Brady Urological Institute at Johns Hopkins recently and in just two months ran into three other Pitt med classmates: Yvette Kasamon (MD ’99), an attending in medical oncology; Devin Sanders (MD ’99), attending in pediatric anesthesia and critical care; and Ken Gage, a resident in radiology after a long stint in the lab finishing his MD/PhD at Pitt in 2007. Who knows how many more of us are here?

Stephen Schatz (MD ’99)
Baltimore, Md.

**RECENT MAGAZINE HONORS**

IABC Pittsburgh Golden Triangle Award of Excellence, Magazines

IABC Award of Excellence, Feature Writing (J. Miksch, “The Investigator’s Path”)

IABC Award of Honor, Publication Design (E. Cerri)

Pittsburgh Black Media Federation Robert L. Vann Media Award Magazine Features, Third Place (C. Zinchini, “Twins”)

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

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**FRIEND US**

OMG, the SOM is on FB!
Check out the School of Medicine’s new Facebook page for the scoop—news headlines, reunion updates, videos, and photos, including this pic from Match Day 2010. The about-to-be MD jumps for joy moments before presenting with acute 😊.

http://www.pittmedfb.pitt.edu
DEPARTMENTS

OF NOTE 3
Cracks in HIV’s armor.
Stimulating funding.
From bench to bassinet.

CLOSER 7
At the heart of the dance.

INVESTIGATIONS 8
Piggy in the middle.
A tail of Huntington’s.

ATTENDING 32
Married, with science.

MATCH RESULTS 35
Where do they go from here?

ALUMNI NEWS 36
Seeing the world.
Cross-border commute.

LAST CALL 40
Trailing spouses in the lead.

CONTRIBUTORS
A native of Dallas, Texas, Pitt Med’s new associate editor, ELAINE VITONE [“Traffic” and other stories], earned her MFA in 2006 from the University of Pittsburgh and embarked on a freelance career that saw her work published in this magazine, Ladies’ Home Journal, GQ, and oldhouseweb.com. In between assignments, she and her husband, photographer and Carnegie Mellon University professor Dylan Vitone, had been restoring a home in Pittsburgh’s Highland Park. Since joining Pitt Med full-time, Elaine’s sanding and spackling have been limited to weekends. She says she relishes her new job because the medical school “is just fascinating and always changing.” And, being that her mother and father are in the medical field, “I also have something to discuss with my parents.”

How do you capture the ephemeral? Hire a preschooler. Our art director, ELENA GIALAMAS CERRI (who did work for organizations such as J. Crew and Elle in New York for 10 years before joining us), searched for the perfect rainbow to illustrate the idea of the transitory for the cover. To make sure the painting would have a true childlike quality, she enlisted ANTONIO CERRI, her 5-year-old son (shown right). Antonio sat down with his mom and his grandmother, artist FRAN GIALAMAS. “My mom was with us, and we were laughing about it. We told him, ‘There’s no black in a rainbow!’” says Elena. Antonio enjoys going to art openings with his mom and exhibited a piece himself recently at Fein Art Gallery in a multigenerational show with his grandmother. (His paper bag sculpture sold there for $2.)

COVER
A doctor at Children’s Hospital of Pittsburgh of UPMC has developed a cell line that could fundamentally change cancer treatment. (Illustration: Antonio and Elena Cerri, © 2010.)

FEATURES

B.F. and A.F., Before Ferg and After Ferg 12
A century of orthopaedics at Pitt.
BY MICHAEL FITZGERALD

Traffic 18
New Pitt recruit Alexander Sorkin blends caution and inspiration in a quest to sort out how cells usher in the good guys and shut out the bad ones.
BY ELAINE VITONE

How Do You Capture the Ephemeral? 22
It’s generally agreed that cancer stem cells are difficult to study effectively. Ed Prochownik might have just made it a whole lot easier.
COVER STORY BY JOE MIKSCH

Very Carefully 27
Industry and academic medicine are partners by necessity. How should they work together?
BY SHARON TREGASKIS
In an April 1 article in the *New England Journal of Medicine*, Harvard’s Michael Chernew and others describe the current projections for health care spending in this country as a path to “financial Armageddon.” As I see it, the single-most important strategy that we can take in reducing the cost of health care is to address the cultural notion and imperative, seemingly unique to Americans, that the more we spend on drugs, devices, and procedures, the greater the likelihood that we can immortalize ourselves—even when there is no scientific evidence in support of the care being delivered. This conceit is fostered both by patients and physicians and is a consequence, I believe, of our great national success in powering our global stature through investment in high technology.

There are many examples of how we throw money around. Although our own Bernard Fisher established 25 years ago that breast cancer is a systemic disease and usually should be treated by lumpectomy and adjuvant chemotherapy, some surgeons still perform radical mastectomies when the breast could be preserved. Although research shows that it is generally safe to have vaginal births after an earlier caesarian section (VBAC), expecting mothers have to hunt to find a willing obstetrician and hospital in this litigious society. Although certain complex spinal surgeries tend to lead to more complications than traditional treatments, their frequency jumped 15-fold between 2002 and 2007 among the elderly with questionable effectiveness in reducing pain and at great cost.

The list of dubious treatments goes on and is not confined to surgical procedures. (Consider the frequent use of antibiotics for viral upper-respiratory infections.) At Pitt, we are about to launch a major comparative effectiveness research initiative in which statisticians, epidemiologists, and clinical researchers will work with health-policy experts. The effort will include new clinical trials and also the mining of existing literature. Yet, absent a paradigmatic cultural shift, we are on course to continue to spend money on health care needlessly. This will compromise, if not doom, “health care reform.” In fact, costs will increase even more as 32 million more people gain health insurance coverage with no assurance that they will be treated with evidence-based medicine.

From a more philosophical perspective, I wanted to share the above haiku by the 19th-century Japanese poet Issa, written after the death of two of his young children. The intellectual knowledge of the transitory nature of life (symbolized by dew) does not stem a father’s grief. Of course, yearnings for immortality and a life free of suffering are part of human nature. (And the drive to heal and make whole motivates those of us who are physicians.) Even in cultures more comfortable with the inevitability of decay and death, people struggle with these yearnings. My intention is not to quash hope, but to implore us to revisit our standard practices with newfound humility—so that medical miracles can happen, without overtreatment and crippling waste. So that, “above all, we may do no harm.”
A Mighty Mouse

The good news is that the thymus produces T cells, prime players in the immune system. The bad news is that as we age, the thymus degenerates, leaving the immune system compromised.

Abbe de Vallejo—a PhD associate professor of pediatrics and immunology at the University of Pittsburgh and faculty member at Children’s Hospital of Pittsburgh of UPMC, the University of Pittsburgh Cancer Institute, and the McGowan Institute for Regenerative Medicine—is studying a mouse with a particularly robust thymus. De Vallejo’s mice live at least 30 percent longer than his control rodents.

“These mice are different from the others in that, even as they age, their thymuses remain intact and [the mice] remain fertile,” de Vallejo says. “They are not sickly animals.” His results were recently published in Proceedings of the National Academy of Sciences.

—Joe Miksch

FOOTNOTE

Pitt med supports the Pittsburgh South Side’s Birmingham Free Clinic in myriad ways. The most entertaining effort, though, is likely the student-led annual benefit auction. This year’s items included handbags, coats, sports tickets, personal-training sessions, an invitation for eight to the annual Lotze/ Harvey Crab Fest (hosted by Associate Dean for Student Affairs Joan Harvey and Professor Michael Lotze), an oil change (parts and labor offered by fourth-year student Andrew Farkas), and hula lessons (courtesy of first-year student Ka’ohimanu Dang).
Her newest job has J. Nadine Gracia (MD '02, Res '05) advising top government officials on health policy—you could say it’s taken her back to her roots. A first-generation Haitian-American, Gracia traveled this spring to Haiti as chief medical officer for the U.S. Department of Health and Human Services (HHS) Office of Public Health and Science, a position she assumed this year. Gracia was part of an HHS delegation helping the effort to rebuild from January’s devastating earthquake by taking stock of the country’s health care system. Before taking the job at HHS, Gracia was a White House Fellow. She spent part of her fellowship year in the office of first lady Michelle Obama working on her childhood obesity initiative. While at Pitt, she was the national president of the Student National Medical Association. Gracia is the med school’s 2010 commencement speaker.

On rebuilding Haiti
Part of my role is strategizing ways we can help with some of the longer-term needs of Haiti. It’s about how you build a strong health care system—which includes the physical infrastructure, such as the hospitals, clinics, laboratories, and pharmacies—but it’s also about having a comprehensive health workforce.

On returning to the country where her family is from
Being involved in the recovery process has meant a great deal to me—not only in my role at HHS, but also for me as a Haitian-American. It reinforces what I find to be important and what my passions are—to advocate for and serve the most vulnerable and underserved.

On working with HHS
I provide public health and policy guidance to the assistant secretary of health on such topics as childhood obesity, adolescent health, global health, environmental health, climate change, autism, epilepsy, and the White House Council on Women and Girls. We synthesize the science with public health and prevention. It’s an exciting time. To be able to work in the new administration on such important health issues that impact various populations is a great opportunity.

Her question for us
What do you hope the world will be like in 20 years, and what are you doing now to make that a reality? — Interview by Reid R. Frazier

A Big Share of Stimulus-Fund Grants for Pitt
Given that National Institutes of Health (NIH) funding has stagnated since 2003, federal stimulus grants have come at a good time, wrote Arthur S. Levine, the University of Pittsburgh’s senior vice chancellor for the health sciences and dean of the School of Medicine, in a recent letter to President Obama and the U.S. Congress.

Distributed by the NIH as part of the American Recovery and Reinvestment Act of 2009, the agency’s stimulus grant program was created to kick-start advances in biomedicine, behavioral science, and public health research. Of the $8.2 billion in total NIH research funding under the recovery act, Pitt received an ample share—$140 million spread among 305 grants as of May. At that time, the University’s stimulus funding from federal sponsors totaled $173 million, and grants are still being approved.

The NIH funds will support investigations in cancer, liver disease, heart disease, infectious diseases, traumatic brain and spinal cord injury, diabetes, Parkinson’s disease, obesity, mood disorders, among others.

Levine noted that Pitt is deeply appreciative of the stimulus funding, which he sees as a life raft for the research programs of many top-notch investigators.

“However,” he added, “in order for our research to be translated into new therapies, new products, and new jobs, continued, stable funding of NIH is essential.”

—Elaine Vitone

The stimulus funding is seen as a life raft for the research programs of many top-notch investigators.
CARDIAC CRIB NOTES

One percent of babies are born with congenital heart defects. In many cases, why that’s so is a mystery.

Cecilia Lo, a PhD and founding chair of the Department of Developmental Biology, is looking for answers as she leads Pitt’s portion of the six-year, $100 million National Heart, Lung, and Blood Institute’s nine-site Bench to Bassinet Program. As the name suggests, Bench to Bassinet is intended to quickly move insights gained into the nature of congenital heart defects from the lab to the clinic.

Lo says that Pitt’s portion of the work will consist of screening mutant mice to discover the core genes—likely a few hundred—that play a role in congenital heart disease. Fetal ultrasound will help Pitt investigators watch malfunctioning hearts as they develop in the mouse mutants.

“In the future, we can use this knowledge to prescreen patients for mutations in genes involved in congenital heart disease,” Lo says. “The longer-term possibility is that by understanding the genes that underlie heart disease, we can develop better therapies.” —JM

Doors Opened

A series of case studies recently featured at Falk Library were not of the medical variety but the biographical — stories and images of African American surgeons from far and wide who overcame adversity to become leaders in their field. The exhibition, “Opening Doors: Contemporary African American Academic Surgeons,” was a collaboration between the National Library of Medicine and the Reginald F. Lewis Museum of Maryland African American History and Culture. It ran from November 2009 through January 2010.

“It’s important that students coming along behind [these surgeons] know that there are role models out there,” says Paula Davis, assistant vice chancellor for health sciences diversity. Visitors to the exhibit included Pitt’s Premedical Organization for Minority Students and students from the new Pittsburgh Science and Technology Academy. “We hoped people would leave with a new sense of attainability,” says Davis.

Not to be outdone, the School of Medicine complemented the exhibit with a similar display highlighting pioneers with Pitt ties. Among them: Ala Stanford Frey (Res ’04), among the very first African American women to become a pediatric surgeon, and Velma Scantlebury-White (Fel ’88), former Pitt associate professor of surgery and pediatrics, and the nation’s first African American woman to become a transplant surgeon. —Ben Korman

FLASHBACK

History gives us much to chew on. And, in this case, to chew with. George Washington’s dentures —made of ivory and human and animal teeth and wired to lead plates—are on display until July 18 at Pittsburgh’s Senator John Heinz History Center. The president’s real teeth were destroyed by mercuric chloride, a common ingredient in 18th-century medicine and purported yellow fever cure. In addition to the incisors, molars, and bicuspids, the traveling show also features “forensic figures” of Washington at 19, 45, and 57 created by a team led by Pitt professor of anthropology and history and philosophy of science Jeffrey Schwartz.

FLASHBACK

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**Appointments**

Since patenting a new computer-aided method for detecting lung nodules from CT scans as a medical student at the University of Chicago, Ty Bae has drawn on his engineering background to solve problems in the field of radiology. The result has been eight additional patents and the discovery of new imaging biomarkers that grew from nearly two decades of research and clinical work. The University of Pittsburgh MD/PhD professor of radiology and bioengineering and director of the Imaging Biomarker Lab has recently added chair of the Department of Radiology to his title. As chair, Bae is intent on fortifying and advancing the department’s research portfolio.

Pitt’s new chair of the Department of Neurological Surgery, Robert Friedlander, comes to the University from Boston, where he served as professor of surgery and vice chair of neurosurgery in Harvard Medical School, as well as associate director of cerebrovascular surgery at Brigham and Women’s Hospital.

Friedlander begins his tenure at Pitt in June. His clinical interests are the surgical management of aneurysms, arteriovenous malformations, carotid disease, and brain and spinal cord tumors. The surgeon’s laboratory work has resulted in new approaches to limiting the impact of cell death in a variety of neurological diseases, such as ALS and Huntington’s. He is a member of the American Society for Clinical Investigation and associate editor of the *Journal of Neuroscience and Neurosurgery*.

Alexander Sorkin is now the School of Medicine’s Richard B. Mellon Professor and Chair of the Department of Cell Biology and Physiology. He comes to Pittsburgh from the University of Colorado Health Sciences Center.

Sorkin would like the department to focus on “the fundamental issues of cell biology,” including the basics of how cell components interact and relate on the molecular level. His own research delves into the cell’s endocytotic and postendocytotic activity. Research coming out of his lab is changing conventional thinking about protein signaling. His work has implications for understanding drug addiction, as well as head and neck and lung cancers. (See our p. 18 story.)

At the UPMC Stroke Institute, director Lawrence Wechsler has built a team of experts to advance stroke research and treatment. The institute serves as the stroke team for 15 hospitals via tele-medicine, a system that allows doctors to consult on, diagnose, and treat patients remotely. The MD professor of neurology and neurological surgery now assumes the position of chair of the Department of Neurology. He hopes to partner with other departments in future studies to improve understanding of the biological mechanisms of neurological disorders, treat the depression that often accompanies neurological disease, and improve quality of life after stroke. —TE and JM

**HEAD AND SHOULDERS ABOVE THE REST**

Jack Schumann wins teaching awards like Pitt’s men’s basketball team wins games. The PhD associate professor of neurobiology at Pitt and member of the school’s Academy of Master Educators is considered the cream of the crop by his anatomy students from the Class of 2013. In recognition of his pedagogical prowess, they recently gave him an anatomical model of the human head, neck, and shoulder musculature. A team of students raised cash to buy the model. Getting the needed money was no problem. “The students rushed in and almost knocked down the PBL [problem-based learning] room door” to support the idea, says first-year student Michael Liggon. The school’s Office of Medical Education chipped in, as well. The model now resides in the Anatomy Museum in Scaife Hall, but it also has a place in Schumann’s heart: “It was one of the greatest honors I’ve received in my life,” he says. —JM
Robert Kormos, University of Pittsburgh professor of surgery and director of the UPMC Artificial Heart Program, is not a ballet dancer. Yet the surgeon found himself onstage in February performing in Heart (Function vs. Emotion), Maria Caruso’s first full-length ballet, at Pittsburgh’s Byham Theater.

It happened this way. Dennis McNamara, Pitt professor of medicine and director of Heart Failure/Transplantation at the UPMC Cardiovascular Institute, was having a conversation with Caruso, the dance group Bodiography’s founder, artistic director, and choreographer. (McNamara’s daughter performs with the Pittsburgh-based ballet company—and her dad has as well.) McNamara noted that Bodiography occasionally touches on medical themes. Perhaps some of his patients’ stories could serve as inspiration for a new work, he suggested.

Caruso was intrigued. Soon she met with a half-dozen heart transplant patients who had been treated by McNamara and gave them a homework assignment of sorts: Bring her three physical gestures and three tangible items related to their experiences with heart disease. Some spoke of their struggles with illness, others the prospect of living with another’s organ inside them.

Kormos came in to consult—“A lot of it had to do with helping translate motions we use in surgery and do those in an exaggerated but legitimate fashion so that they can be seen by the audience,” he says—and eventually was persuaded to perform. (Caruso and Kormos are shown above during a dress rehearsal. McNamara did not appear in the production.)

“There were two things that made me reluctant to do it,” he says. “One … I’m your typical, overweight male; and standing onstage with fit, beautiful women was a challenge to my body image,” Kormos says with a laugh. “And, two, I didn’t want to distract from the dancers or the message.”

The message, Kormos and Caruso say, is one of struggle and recovery—of people who neared death and persevered.

—Joe Miksch

—Photo by Eric Rosé
David Cooper and Massimo Trucco grafted pig islet cells into the livers of monkeys to treat diabetes. Three months after the transplant, the cells of the pig present in the monkey liver (pictured here, nuclei in blue) continue to produce insulin (red).
In the quest for effective diabetes treatments, the University of Pittsburgh's Massimo Trucco and David K.C. Cooper are searching for the perfect pig.

Trucco, Pitt's Hillman Professor of Pediatric Immunology and chief of immunogenetics for Children's Hospital of Pittsburgh of UPMC, and Cooper, professor of surgery with the School of Medicine, have transplanted beta islet cells from genetically modified pigs to successfully treat nonhuman primates with diabetes. As reported in the December issue of the American Journal of Transplantation, the islets from one species functioned well in another—up to a year in the case of one monkey.

“There are 2 to 3 million people with diabetes in the United States,” says Cooper, an English immunologist who came to Pittsburgh a half-dozen years ago from Massachusetts General Hospital.

“And in the past 10 years, there have been fewer than 1,000 human-islet transplants—even though these kinds of transplants are effective—because there aren’t enough donors. This is where xenotransplantation research can really make an exciting difference.”

In mammals, including humans, insulin production takes place in the beta islet cells of the pancreas. Normal metabolic breakdown of sugar is impossible without the hormone insulin. Although insulin-replacement therapy has saved the lives of many people with diabetes, strict glycemic control can remain elusive. Complications of uncontrolled diabetes include improper circulation, leading to lower-limb amputation, blindness, and kidney failure.

Finding an effective, abundant source of islet cells for transplantation would help people with diabetes produce the insulin they need. Pigs, already a source of heart valves for human transplant, may have the inside track.

“What’s quite remarkable about what Massimo is doing is that he's on the verge of several different kinds of strategies to try to ameliorate type 1 diabetes,” says David Perlmutter, Vira I. Heinz Professor and Chair of the Department of Pediatrics at Pitt. “Certainly it's very exciting to have xenotransplantation possibly be an option.”

Cooper is chair of the scientific advisory board for Revivicor Inc., a Blacksburg, Va.-based regenerative-medicine company that produces transgenic pigs. The company has modified the pigs to make their organs more acceptable for transplantation into humans. UPMC is a significant shareholder and collaborator with Revivicor.

One genetic modification gives the pigs a human cell-surface protein called hCD46, which regulates a portion of the immune response. Results show that manipulating the hCD46 pathway may be protective against rejection.

For the study, Trucco, Cooper, and their colleagues isolated these altered pig islet cells and infused them into a small number of monkeys. portal veins carried the cells into the liver, where sufficient numbers of them engrafted to maintain function and appropriately regulate glucose metabolism without the need for diet changes or insulin administration.

Trucco and Cooper write that with additional work, “a safer immunosuppressive regimen might become available for use in human transplant.”

Revivicor has modified other pigs as a-gal (galactosyltransferase) knockouts. Without the a-gal gene, these pigs lack a critical cell-surface sugar molecule that humans and primates do not have, but normal pigs do. This modification again reduces the effect of the primate immune response.

There are still many avenues to explore. Trucco group member Nick Giannoukakis, associate professor of pathology and immunology at Pitt, is looking at ways to block specialized immune cells called dendritic cells to help suppress the immune response. Another immunogenetics colleague, Pitt's Jon Piganelli, associate professor of pediatrics, is working on a new compound to block inflammation.

“We are looking for a good agent that is not toxic to islets,” says Trucco. “We are trying to tackle the problem from all corners,” the genial Italian adds with a grin. “If we can find the right immunosuppressive cocktail, then all we will need is a sterile place to produce the pigs.”

Find pigs with an appropriately human-compatible genetic makeup, add the right immunosuppressive regimen, “and the game will be over,” Trucco says.

Or almost over. Trucco and Cooper, or other researchers, will still need to address a few issues. Massive numbers of islet cells are necessary for transplant, and one monkey required two transplants to maintain sufficient glucose control. Initial die-off of transplanted cells is substantial, and immune-response-related inflammation causes blood clotting, requiring a careful balance of coagulant and anti-coagulant medications.

“But we’re not seeing the typical rejection that we used to see. The key is getting better pigs,” says Cooper. “I’m optimistic that xenotransplantation will be effective long before we can use stem cells for something like this.”
Right around the time Bino John was recruited by the University of Pittsburgh School of Medicine’s Department of Computational and Systems Biology, he decided that he needed to engage in a new field. He would become an experimental biologist—adding the wet bench to the digital world of in silico experimentation. “Bad idea,” said his colleagues, pointing out that he had just landed a job in a good department. “Wait until you have tenure,” someone suggested, implying that his plan would risk his career before he’d even gotten it off the ground.

But on a shelf next to a blooming yellow Phalaenopsis orchid in John’s office sits a photo of his mother. Her death from liver cancer in 2005 at the age of 54 motivated him to pursue molecular biology so that he could work more directly on cancer.

John didn’t heed the advice of his colleagues. Instead, he began setting up a molecular biology lab and hired an experimental biologist postdoc. That’s when the bad idea ran smack into bad luck. It turned out that the postdoc, Zhihua Li, broke out in a rash when exposed to low-level radiation—a very unusual reaction. The workhorse of a molecular biology lab, the northern blot test, uses radioactive probes to separate out bits of RNA from tissue. To accommodate Li, John’s lab had to invest significant time refining northern blot techniques without radiation before they could begin pursuing their target: a short stretch of genetic material called microRNA (miRNA).

MiRNAs are chains of nucleic acids about 22 nucleotides long. Discovered in 1993 and initially thought to be unimportant, miRNAs are now known as key regulators of genes, turning them on and off. Dysfunction of miRNA has been linked to many diseases, including cancer. On John’s northern blot, the miRNA they were working on showed up as a dark band that revealed its 22-nucleotide length. But something unexpected turned up, too. On this very sensitive northern blot they had devised, there was a faint, but distinct, band of about 15 to 17 nucleotides—significantly smaller than even miRNA.

This is the point in the story where the scientist’s luck turns. Much like the once-ignored miRNA, these short RNAs turned out to be common and active regulators of gene expression, John’s team found. They dubbed them “unusually small” RNAs (usRNAs).

Partnering with professors Yuan Chang and Patrick Moore of Pitt’s cancer virology program, John has discovered these usRNAs in both human tissue and in samples of the herpes virus that causes Kaposi’s sarcoma. In late 2009, the team described usRNAs in the Journal of Virology. “There were two myths we broke in that paper,” says John. The first was that any RNA that was only 15 nucleotides long (a 15-mer, to a molecular biologist) could randomly match to several places in the genome, so it couldn’t possibly be important for regulating any specific part of that genome.

“He clearly established this as a very important area,” says Yoel Sadovsky, a professor of obstetrics, gynecology, and reproductive sciences, the Elsie Hilliard Hillman Professor of Women’s and Infant’s Health Research, and scientific director of the Magee-Womens Research Institute. Sadovsky and Pitt’s Jean-Francois Mouillet, of the Division of Fetal Medicine, found usRNAs in placental tissue; Sadovsky is collaborating with John to explore their function in embryonic development. “I think this is going to be the next frontier—to identify if there is a different function, different origin, or different process for these usRNAs,” Sadovsky says.
In 2004, Ronald Wetzel, professor of structural biology, had cause to stop and scratch his head. Scientists had known for decades that the one in 10,000 people who suffer from Huntington’s disease, a neurodegenerative disease that affects muscle coordination and cognition, make a mutated form of the protein huntingtin (HTT), which has a tail composed of many repeats of the amino acid glutamine. In his lab in Biomedical Science Tower 3, Wetzel had been focusing on this polyglutamine tail, as it is called, in isolation, convinced that it was key to the disease; after all, eight other known neurodegenerative diseases are characterized by proteins with similar polyglutamine repeat sequences. Wetzel’s lab’s work suggested that the tails seen in Huntington’s as assembled in a relatively slow, stepwise fashion to eventually form messy protein complexes that accumulate in the brain and possibly play a role in disease development.

But one day in 2004, his lab obtained new results that suggested that these tails aggregated very differently—and in a much more complex fashion—in the presence of an extremely short, seemingly unimportant amino acid sequence found at the tip of the tail in HTT. This little fragment, called HTT-NT, seemed to change the behavior of the polyglutamine sequence completely, producing “entirely different kinds of results,” Wetzel recalls.

Protein fragments containing HTT-NT attached to polyglutamine were found to form protein aggregates so quickly that the reaction was almost impossible to study.

“It just knocked our socks off,” he recalls. “We’ve spent the past five to six years trying to figure out what is going on.”

The fruits of Wetzel’s labor were published in the April 2009 issue of *Nature Structural & Molecular Biology*. His paper elucidates how this short amino acid sequence “communicates” with the polyglutamine sequence to alter the aggregation pathway and produce the protein clumping that may be key to the disease.

“It turns out that these sequences are talking to each other, communicating shape information in a way we don’t yet fully understand,” Wetzel explains.

His experiments suggest that first the polyglutamine tail aids in altering the shape of HTT-NT. Then, the altered HTT-NT segments of a number of HTT molecules assemble, forming a core. This in turn brings the polyglutamine tails of these molecules close together. The result: big protein clumps.

It’s still unclear what, exactly, these protein clumps do to Huntington’s patients. The idea that clumping somehow plays a critical, mechanistic role in Huntington’s has been controversial, Wetzel says—in part because of the complexities his lab has discovered in the aggregation pathway. He suspects that HTT can make many different types of protein aggregates in the brains of people with Huntington’s, and that they have different degrees of toxicity.

“They’re not all created equal,” he says—and this complicates the task of identifying the key toxic material.

More recently, Wetzel’s group found that modifying two amino acids in the small HTT-NT sequence (the serines at positions 13 and 16) has a suppressive effect on the ability of the HTT protein fragments to clump in test-tube experiments.

Previous work had shown that these serines were sometimes modified inside mammalian cells by the addition of phosphate groups, a modification often used by cells to regulate protein behavior. When Wetzel’s collaborators bred mice containing the disease-causing, expanded polyglutamine repeat form of HTT, in which the two serines had been replaced with amino acids that mimic phosphate-modified serines, the mice did not get sick.

“It’s just amazing to me that you can make a potentially very sick mouse normal by changing these two serine residues,” he says.
On June 15, 1910, Chancellor Samuel B. McCormick (third from the left) laid the cornerstone for Pennsylvania Hall, then the new home for the School of Medicine. (The building was torn down in the late 1990s and replaced by a residence hall of the same name.)
In the late 1940s, when Albert “Ferg” Ferguson was a young orthopaedic surgeon at Harvard Medical School and Boston Children’s Hospital, he often saw children with dislocated hips. Their joints had been pushed out of alignment at birth, during breech deliveries, but the problem usually wasn’t apparent until the children tried to stand. The protocol was to not attempt corrective surgery until the child turned 5. “Nobody dared do it,” says Ferguson.

“The delay caused all kinds of damage to the kid, not just in terms of mobility, but psychologically, socially, and every other way,” Ferguson recalled in a 2002 story for this magazine. “He couldn’t play with other kids, couldn’t walk right, was left out.” It was damaging to the parents, too, who were left wondering whether their children would ever walk properly or at all.

Ferguson felt compelled to do something and developed a new surgical approach that minimized scarring and didn’t cut through muscle. He seated the hip where it belonged and pulled down the joint’s lip, which had been pushed up by the hip dislocation. He began operating on children as young as 2. The procedure worked, granting newfound mobility to these toddlers. Eventually orthopaedic surgeons throughout the country adopted Ferguson’s technique and the practice of operating on young children.
Innovations like this got Ferguson noticed and prompted an offer to chair the Department of Orthopaedics at the University of Pittsburgh School of Medicine.

The surgeon would go on to remake orthopaedics at Pitt. Among other notable achievements, Ferguson’s program trained at least 30 department chairs for other institutions. The historical timeline for Pitt orthopaedics is now split into two eras: Before Ferg and After Ferg.

B.F. was a quieter and less storied time, but also one of inventiveness.

In 1909, Honus Wagner and the Pittsburgh Pirates won their first World Series, playing in brand-new Forbes Field (now the site of Posvar Hall). It was just a year after Western University of Pennsylvania formally changed its name to the University of Pittsburgh, moved from Observatory Hill to Oakland, and adopted the panther as its mascot. And David Silver, a 36-year-old orthopaedic surgeon, began teaching at Pitt.

Silver, a local orthopaedic surgeon who trained in Harvard and in Europe, taught at the behest of Thomas Shaw Arbuthnot, the medical school’s new dean. Arbuthnot, a physician from one of Pittsburgh’s leading retailing families, was in charge of remaking the school during a time of dramatic reform in medical education nationally. Arbuthnot was intent on making the school among the very best. He had some success recruiting top medical talent to Pittsburgh. He upgraded entrance standards. (Starting in 1911, applicants needed at least a year of college. They would need two by 1913.) Also in 1910–11, the medical departments moved from Polish Hill to a newly constructed building in Oakland, Pennsylvania Hall, located next to where Pitt stadium would be built. (The old Pennsylvania Hall was demolished more than a decade ago; a new residence hall of the same name now occupies the site.)

When Silver joined the faculty, medical students studied orthopaedics in their fourth and final year, a year dedicated to clinical work. He lectured once a week for an hour. Immediately afterward, Henry Thomson Price, also new to the faculty that year, hired to teach “Children’s Diseases,” administered an hour long quiz. Clinical instruction was split between Allegheny General Hospital and Children’s Hospital of Pittsburgh.

Silver is considered the father of orthopaedics at Pitt; he laid the groundwork for the program to achieve department status. Yet other orthopaedists preceded him. C.B. King, one of the 1886 founders of the medical school’s antecedent, West Penn Medical College, was its clinical professor of orthopaedic surgery. Also preceding Silver was Stewart LeRoy McCurdy, professor of orthopaedic surgery at the Western University of Pennsylvania; McCurdy stayed on the Pitt faculty after the name change and Arbuthnot-led reorganization, with appointments in the dental and medical schools. McCurdy was noted for both roles in his obituary in the 1936 Report of the Chancellor to the Trustees.

McCurdy drops off the list of the School of Medicine’s orthopaedics surgery faculty after Silver’s appointment. As the years roll on, however, a growing register of names join Professor Silver as lecturers and demonstrators in the annual catalog. One of those names is that of Paul B. Steele, who joined Silver’s practice in 1917 and would eventually succeed Silver as head of orthopaedic surgery at Pitt.

Silver’s photograph in the 1933 edition of The Owl, the University’s yearbook, shows a dapper man with a trim mustache, peppy hair combed back and parted in the middle, and circular glasses. Silver headed Allegheny General Hospital’s orthopaedic department for 30 years. He ran the D.T. Watson Home for Crippled Children in Sewickley from 1919 until 1944, not long before it would serve as the site of Jonas Salk’s first clinical trial for the Pitt polio vaccine. Silver also headed the American Orthopaedic Association in 1916–1917, shortly before he served as a lieutenant colonel in the U.S. Army during World War I (65 percent of the med school’s faculty served in World War I in some capacity). The professor also established two Pitt traditions: He was loyal to the medical school, endowing a chair in his name, and he was an active researcher—most notably, while consulting for the army. Silver invented a three-part artificial leg made of fiber and rubber.

Arbuthnot’s reforms secured an A-plus rating for the medical school and widespread acclaim; yet the dean struggled with raising the funds to continue to build on these programs and eventually retired in 1919. Silver and many of Arbuthnot’s other early key hires were a source of constancy for the school. The orthopaedist taught until 1940 and then appears to have handed the reins to his partner and longtime colleague, Steele. (There is no record of how the transition occurred.)

Steele was “a powerful and potent man,” recalls retired plastic surgeon Ross Musgrave (MD ’43). Musgrave wanted to do his residency at Allegheny General. But Musgrave says when Steele found out that Musgrave’s uncle worked at Allegheny, he red-lettered his name.

After graduating from medical school in Baltimore in 1914, Steele interned at Allegheny General in 1915–16, after which Silver hired him. The next year, the 26-year-old Steele shipped off to Great Britain as part of the Second Orthopedic Unit. Steele went to France in 1918, serving at the bloody battle of Château-Thierry, and he eventually received the U.S. Army’s Silver Star. After being discharged in 1919, Steele came back to Pittsburgh and helped Silver organize the Watson Home, beginning his long surgical career.

Steele published little, but his ingenuity was apparent in the O.R., and the surgeon was quick to share his ideas. H. Andrew Wissinger, who graduated from Pitt in 1952 as an undergrad and as an MD in 1956, knew of Steele’s reputation, though he did not meet him while he was in medical school. He met “Still” at the 1957 American Academy of Orthopaedic Surgeons conference at Chicago’s Palmer House hotel. Wissinger was in the navy and went in uniform. When Wissinger walked into a bar at the Palmer House, he heard a shout: “Hey, sailor! Come over here, and we’ll buy you a drink!” It was Steele, holding court at a table in the corner of the bar.

“He was pretty smart,” Wissinger says. “I
got a kick out of him.” Wissinger himself was famous within the city for his excellent surgical technique. He says he picked up a couple of things just from listening to Steele. Wissinger attended Steele’s talks to local groups and eventually used a Steele idea for fusing wrists to help patients suffering from rheumatoid arthritis. “It was quick and easy, and it worked,” he says. “He was one of those guys who had good ideas but never got around” to writing them up and submitting them to journals.

Steele does get credit for his method for treating avascular necrosis of the femoral head when it occurs in children, usually because of Perthes disease. In 1928, Steele developed a technique that involved hollowing out the femur and filling it with bone grafts. *Who’s Who in Orthopedics* (Springerlink 2005) notes that “in [Steele’s] hands the results seemed to be better than those reported by others.”

Steele was also credited with developing a barrel-stave graft for ununited fractures and bone cysts. The *Who’s Who* entry reports that Steele originated at least six other surgical procedures, ranging from a novel treatment for scoliosis to fixing a fracture of the patella without entering the joint. None of these have been published in journals, nor did Steele formally track outcomes.

Despite being chair of the orthopaedics department from 1940 to 1953, Steele did not have much interaction with Pitt medical students. Musgrave says that when he was in medical school from 1940 to 1943, most orthopaedics surgery was taught by a Steele associate named John Best. George Gilmore (MD ’52), who grew up in Steele’s neighborhood, remembers him giving only a lecture or two and otherwise being uninvolved. Some of that may have been a factor of time: Steele was on staff at eight hospitals in Pittsburgh, one in Erie, Pa., and also at the D.T. Watson Home.

In 1953, Ferguson was convinced to come west from Harvard and become Pitt’s David Silver Professor and Chair of Orthopaedic Surgery. It was a major coup for the school as it aspired to transform itself from a training ground for local physicians to a nationally renowned institution. The dean at the time was William McElroy; yet Ferguson says he was lured by Edward McCluskey, head of Children’s Hospital of Pittsburgh and later vice chancellor of the schools of the health professions. Ferguson recalls McCluskey as an unsung hero of the medical school’s new focus.

The Before Ferg era ended without fanfare. Ferguson doesn’t remember ever meeting Steele. Stationed in Children’s Hospital, he quickly went to work building his department. Today, the Ferguson days are remembered as sort of a Camelot for Pittsburgh orthopaedics. Right away he hired Mary Cosgrove, who would be his assistant (some would say department cochair) for all of his 33 years at the University. Ferguson’s wife, Louise, says he took advantage of a chance to build a program “the way he thought it ought to be done.”

Ferguson believed in McCluskey, even though McCluskey outraged many doctors by banning smoking at Children’s Hospital. (Ferguson smoked a pipe then and still does.) So Ferguson helped recruit other talented doctors (among them, Jack Myers for medicine and Hank Bahnsen for surgery). He established a research lab, a rarity in orthopaedics departments at the time. Ferguson, who will be 92 in June, says he started a lab because research was important, and he thought it would help him attract good residents if he could offer them a year in the laboratory.

Ferguson’s charisma, more than any lab, helped him recruit. In April 1955, a colleague and occasional patient of Ferguson’s, Jonas Salk, became a national celebrity for heading the Pitt team that developed a vaccine for polio. (Ferguson’s young sons were among the early test subjects.) That boosted Pitt’s reputation and Ferguson’s recruiting, too.

Some of Ferguson’s hires helped him draw Henry Mankin (MD ’48) back to Pitt from the University of Chicago in 1960. “Ferguson put together a really superb program,” says Mankin. “He was himself superb. It wasn’t the University that did it for him. He did it for the University.”

Mankin himself was an exceptional instructor—“probably the most outstanding teacher of orthopaedics and orthopaedic surgery I have ever known,” says John Perri (MD ’59, Res ’66). The surgeon-scientist did groundbreaking work on articular cartilage. Mankin also has been a significant supporter of the school: He endowed the chair today held by Pitt stem cell researcher Johnny Huard and has served on a number of Pitt committees.

Ferguson says that “we were just really, really lucky” in drawing talented residents and clinicians with a bent for research. But Ferguson’s charisma and vision helped, as did his love of people—his former residents say they still hear often from Ferg. (He sends holiday cards with illustrations of his original paintings.)

Ferguson’s greatest legacy may be the dozens of department chairs whom he helped train. Mankin says Ferguson had a gift for getting people interested in academics and for keeping out of their way.

Mankin was asked in 1966 to become head of orthopaedics at New York’s Hospital for Joint Diseases (now part of New York University’s medical school). He says, “I told Ferg, ‘Listen, I’m very happy here.’ But he said, ‘Go! This is your chance to become an academic giant. Do it!’”

Mankin would go on to chair orthopaedics departments for more than 30 years, one of several such long-serving Ferguson protégés. The record holder at 35 years and counting is Robert D’Ambrosia (MD ’64, Res ’70), who has trouble with the idea that he has
chaired a department for more years than Ferguson. He runs the orthopaedics program at Louisiana State University in New Orleans. (Ferguson also inspired at least two former residents, D’Ambrosia and Edward Hanley, to take up painting.)

The 1960s and 1970s were heady years for orthopaedics at Pitt with docs like Mankin and William Donaldson Jr. (MD ’43, Res ’50), who was the first surgeon in Pittsburgh to succeed in correcting spine curvature in a scoliosis patient. Ferguson himself led the use of titanium and other metals in joint replacement. His lab also did early work in what we now call tissue engineering.

Ferguson also brought in Pitt’s first woman to train in orthopaedics, Mary Williams Clark (Res ’72), then hired her as a faculty member. Even so, Clark remembers that at one point when she was on the faculty, he asked her whether it would be okay to bring in two women as residents one year. She replied, “You always take more than one guy.” Ferguson made both offers. Today, Pitt has a notably diverse faculty, and in the most recent class, a record five (of eight) residents were women.

For all Ferguson’s success in building the reputation of Pitt orthopaedics, he still relied on many non-staff surgeons. He only had three full-time staff until 1980, when he asked Edward N. Hanley (Res ’80) to become part of the department after finishing his residency and also added Mark Goodman (MD ’79). The bigger department then moved to new quarters in the Falk Clinic.

Ferguson’s approach to recruiting trainees was based more on intuition than application strength. He was used to bending rules when he felt the need. For instance, he sent D’Ambrosia off for six months with Andy Wissinger to get up to speed on surgical technique and also allowed him to finish his residency six months early to help establish an orthopaedics program at the University of California at Davis.

In 1986, at 67, Ferguson retired. His departure coincided with a shift in medical school culture. Then-dean Thomas Detre was elevating the importance of research across the medical school. It was becoming harder for doctors to follow a three-pronged approach—i.e., clinical care, teaching, and research—notes Hanley, now chair of orthopaedics at Carolinas Medical Center in Charlotte, N.C. Hanley served as Ferguson’s interim replacement while a search committee looked for a permanent chair.

Tabbed to take over after Ferguson was James Herndon, then chair of orthopaedics at Brown University. Herndon, now the chair emeritus at Partners Health Care and still the William H. and Johanna A. Harris Professor at Harvard Medical School, remembers being wowed by Pittsburgh’s beauty as he drove in from the airport for his first interview. Herndon was impressed with Pitt’s orthopaedics program and Ferguson’s foresight in such things as setting up his lab. “I just took it to a different level,” Herndon says.

In particular, Herndon greatly expanded the staff, bringing in multiple specialists and increasing the number of residents. He concentrated his far-flung department at what is now UPMC Presbyterian and a few community hospitals, and he encouraged all of the faculty to be more involved in research. In part, Herndon was looking at the writing on the wall—the National Institutes of Health (NIH) was awarding grants to fewer than 10 percent of applicants. By the 1980s it had become much harder for practicing clinicians to best full-time researchers for federal funds. Herndon also wanted to expand the Ferguson lab into bioengineering and biomechanics.

Under Herndon, Pitt’s orthopaedics department ranked among the top five NIH grant recipients for orthopaedic surgery departments, more than doubled in faculty size, and tripled in clinical volume. Herndon was close to completing an MBA at Boston University when he came to Pitt and managed to finish it despite having to fly to Boston once a week for a while. He eventually became involved in reorganizing UPMC, which was growing by buying and integrating

**TOP RIGHT:** Current chair Freddie Fu (left) with former chairs James Herndon (center) and Ferguson. **RIGHT:** The 1982 resident class meets with Ferguson (back to camera). Clockwise from front left—Fu, Dean Bennett, Robert Weiss, Linda Thompson, William Pekman, Thomas Rago, Dan Johnson, and Mickey Moritz.
practices, including specialty practices.

After a decade at Pitt, Herndon was lured away to Harvard Medical School and Partners Health Care. Among other Pitt rising stars, Harry Rubash (MD ’79, Res ’84), now chief of orthopaedics at Massachusetts General, followed. This time, the medical school picked a Ferguson protégé, Freddie Fu, to lead orthopaedics.

Herndon “put the department into the modern era,” says Fu (MD ’77, Res ’82), who joined the orthopaedics faculty in 1982 and has been at Pitt ever since. “It was a little bit difficult for some people who were in the old-time mood; they were not used to it.”

Fu has both honored Ferguson’s legacy (when his parents correspond with Ferguson, they speak of their shared “son”) and taken Pitt orthopaedics in new directions. The surgeon is a perpetual-motion machine, constantly seeking ways to promote ortho at Pitt. He spurred the building of an innovative sports medicine complex. That expanded another Ferguson legacy—Ferguson was interested in sports medicine, was team doctor for the Pittsburgh Pirates, and had encouraged Fu to start Pitt med’s original sports medicine clinic, which Fu had developed during his years on the faculty. Fu has also expanded the department, now nearly 80 faculty members strong, close to double what it was when he became chair in 1998. He has added both clinical faculty and research staff, aggressively recruiting, for instance, surgeon Constance Chu, a groundbreaking arthritis researcher, from Harvard in 1999. (Chu ranked first among orthopaedic surgeons receiving grants from the NIH last year. She ranked second on the agency’s listing of ortho researchers receiving funds.) A decade later, Fu helped convince the prominent stem cell and tissue engineering researcher Rocky Tuan to leave the NIH and come to Pitt to head orthopaedics research and a new Center for Cellular and Molecular Engineering. Fu himself has been involved in innovative research on the evolution of important ligaments in the leg. He recently was named a principal investigator on an NIH grant for a randomized double-blind study on anterior cruciate ligaments. Fu, one of the world’s top sports medicine authorities, replaces torn ACLs using a “double-bundle” approach that connects the replacement ligament as a double bundle, rather than the single-bundle approach common today. And he had the pleasure, last year, of celebrating a century of orthopaedics in the medical school during a Grand Rounds.

Success brings its own challenges. Orthopaedics has spilled away from its center at UPMC Presbyterian. The sports complex is in one place, the tumor program is in another, pediatrics in a third. Fu says he hopes to address this diaspora by bringing orthopaedics back to one location. In the meantime, Pitt ortho continues to soar: Department faculty captured the Kappa Delta award for clinical research four of the last six years; Becker’s Hospital Review ranked the department among the nation’s great orthopaedic and spine programs; and the department caused the medical center to place among the top 10 hospitals for orthopaedics in U.S. News and World Report’s current ranking.

The Ferguson era started 44 years after David Silver began at Pitt; Fu became chair 45 years after Ferguson. Fu says he has no expectations of changing Pitt orthopaedics as much as Ferguson did.

“I can never be comparable to him,” says Fu. “If I can do half of what he did, I’ll be happy.”
Dopamine transporters (blue)—which help the brain regulate body movement and our sense of pleasure—rest on the surface of a neuron during endocytosis. Membrane-bound compartments (endosomes, red) encase the dopamine transporters in the cell's interior.
Alexander “Sasha” Sorkin has spent decades staking out the comings and goings in our cells—how proteins enter them, how the cells usher in the good guys, how they shut down the bad guys before they can cause trouble. Biologists call this essential process—this busy movement of molecules—“membrane trafficking,” and in a vague sense, the allusion to narcotics commerce seems apt. When molecular deals go south, cells can follow very dark paths, living fast and dying young.

Sorkin investigates two seemingly disparate cell types, following each of them from the first, minor infractions to the worst ends: epithelial cells to cancer (namely head and neck and lung cancers) and neurons to drug addiction. His gift is careful, basic science at its most fundamental level; but unlike many basic scientists, he’s been known to partner with physicians and others who best know how to help those who are all too often caught in the cross fire when trafficking gets ugly: patients.
Previously a professor of pharmacology at the University of Colorado, Sorkin joined the Department of Cell Biology and Physiology as Richard B. Mellon Professor and Chair in March. He hopes to bring to his new leadership role the same passion for collaboration that he has fostered since his rookie days.

“We still need to do a lot of basic science,” Sorkin says. “But it’s time for us to also be direct contributors in diagnostics and drugs—really improve outcomes for people.”

Sorkin has curly, salt-and-pepper hair and speaks with the accent of his native Russia. His colleagues say he’s a joy to work with, thoughtful and congenial—never competitive or aggressive. They call him adventurous and passionate, but cautiously so. He’s not the type who hangs posters of his work outside his office, or even lets on that he’s particularly jazzed about how things are turning out. For all of Sorkin’s many accomplishments, he still walks into each new project making pronouncements like: This will never work. I am sure that we are wrong. This will be a disaster.

“Usually he says these things with a little bit of a chuckle,” says Sorkin’s longtime collaborator Mark Von Zastrow, professor of psychiatry and cellular and molecular pharmacology at the University of California, San Francisco. Von Zastrow suspects that at least part of that trademark-Sorkin pessimism is genuine—just enough to help him as a scientist.

“I think what it means is that he’s willing to be self-critical.”

CANCER’S “GROW HOUSE”

When Sorkin was a postdoc at Vanderbilt University in the early ‘90s, we were just beginning to understand the protein known as epidermal growth factor (EGF), which plays a vital role in cellular growth, reproduction, and differentiation. EGF is also thought to be an essential, driving force in a variety of cancers—patients who have higher levels of EGF in their tumors are more likely to die. (Nobel Prize-winner Stanley Cohen, of Vanderbilt, discovered EGF in 1972. Sorkin was mentored by Cohen’s protégé, Graham Carpenter.)

EGF’s receptor, EGFR, straddles the membrane of the cell. When EGF comes along, the two join, and EGFR “activates,” sending a message to the nucleus: Grow. If too many active receptors are around, cells not only divide more than normal, they also stop dying as part of their natural course. This pattern gives rise to cancer.

The cell’s defense against letting those extra, trouble-making receptors wreak havoc is to “traffic” them—or move them—inside the cellular membrane and into one of its lysosomes (the garbage incinerators of cells), then destroy them. But unfortunately, there are limits to how many excess receptors a cell can dispose of at a time. Ten to 20 thousand, no sweat. One or two million, however, and you’ve got yourself a problem.

EGFR is an approved therapeutic target for head and neck, lung, colon, and pancreatic cancers. Drugs along these lines treat cancer by cutting the EGFR count throughout the body as a whole. These therapies are far easier on the body than chemotherapy treatments, but they’re not perfect. In rare cases, patients have significant side effects. Absent enough EGFRs, tissue that would normally stay healthy through constant cellular regeneration—like that in the intestines, skin, reproductive organs, and liver—can suffer. But more importantly, these drugs only help 10 to 12 percent of patients.

“This is not acceptable,” Sorkin says.

He’s developed cell lines to help him understand what separates the lucky 10 to 12 percent from the rest. His research is giving him a clearer picture of EGFR’s partners in crime: i.e., the proteins—and the amino acids within them—that are involved in trafficking.

Sorkin believes EGF is a player in almost all cases of head and neck cancer and more than 50 percent of lung cancer cases. These are devastating diseases with very low cure rates. However, he believes that in time, it could be possible to save as many as half of these patients—but that depends on the quality of our intelligence-gathering. It’s not enough to know EGFR is involved; we also have to find out when and how. For example, in some cancers, EGFR doesn’t stir up trouble in the initial phase, but it does in metastasis, so in terms of treatment, timing is everything. In other cancers, EGFR is only a good target for patients with a certain genetic mutation.

Jennifer Rubin Grandis (MD ’87, Fel ’92, Res ’93) has been friends with Sorkin for years, having served on several grant-reviewing panels with him. Grandis, who holds the UPMC Endowed Chair in Head and Neck Cancer Surgical Research and is a professor of otolaryngology and pharmacology in Pitt’s School of Medicine, leads the Head and Neck Cancer Program at the University of Pittsburgh Cancer Institute. Sorkin says she’s one of the reasons he decided to come to Pittsburgh. The two plan to collaborate once he’s settled in.

“I think he’s one of these rare basic scientists who is willing to step outside of his comfort zone,” says Grandis. “In Colorado, he sought out collaborators—specifically, clinicians—who were caring for patients with cancers he was studying and trying to figure out how his work could ultimately benefit people with cancer.

“He’s not afraid of saying, ‘I don’t understand that. Help me understand.’”

EAVESDROPPER

As any police detective knows (at least the ones on television), if you want to get a line on your perp’s M.O., there’s nothing like a wiretap. That’s why, in addition to watching the busy molecular comings and goings of membrane trafficking, Sorkin is also eavesdropping. He’s an expert in signaling—the process by which proteins communicate.

Scientists used to think that once a receptor passes through the cellular membrane—the first step on the way to the dumpster—it’s incommunicado. In a paper published in Current Biology in 2000, Sorkin became the first to prove that this assumption was false.

Rather, Sorkin believes the cell’s interior is where most EGFR signaling happens in head and neck cancer, and perhaps a significant amount happens there in the case of lung cancer, as well. Yet, many of the drugs that target EGFRs are only effective against the receptors on the outside of the cell.

Sorkin has used a microscopy technique called FRET (fluorescence resonance energy transfer), a method in which two proteins are marked with fluorescent tags of different colors. When the proteins come into close contact, you can excite the tag on one molecule and watch—in real time—as the energy transfers to the other molecule, causing it to fluoresce during signaling.

To get even more detailed data, Sorkin developed what he calls “Triple FRET,” so that it’s possible to witness this interaction between three molecules, rather than two. This imaging technique has been helpful for scientists in a wide range of research fields—from heart disease to cognitive studies. Sorkin’s colleagues call this feat of ingenuity the work of a triple-threat investigator.

“Sasha is a very insightful and creative scientist,” says Carpenter, Sorkin’s mentor. “He has a broad range of skills. Some people are trained biologists and have trouble getting into chemistry or math. He can do all three.”

At Pitt, Sorkin aims to take trafficking models once again to a new level by develop-
As a chair at Pitt, Sorkin—cell biologist and once-avid climber—will stretch himself beyond his comfort zone.

We used to think that the dopamine transporter remained stationary, embedded in the membrane. But in 1999, Pitt neurobiology chair Susan Amara (she was at Oregon Health and Science University at the time) became one of the first to demonstrate that the transporter can go inside and back—that it, too, is trafficked. It was a revelation in the field.

Amara also discovered exactly how cocaine and methamphetamine affect the brain at the cellular level—essentially, by latching onto the dopamine transporters and keeping them from doing their job. With the dopamine vacuum cleaners out of commission, dopamine runs amok, resulting in thoughts and movements on fast-forward.

By then, Sorkin was already an internationally recognized membrane-trafficking expert. He wondered how applying his knowhow to the world of dopamine-transporter trafficking might help people struggling with cocaine and methamphetamine addiction. There is no pharmaceutical treatment for people hooked on these narcotics, no way to ease the torturous journey back down to sobriety. Additionally, as a visual scientist, he found the highly complex terrain of the brain fascinating. Problem was, he didn’t know anything about it.

As luck would have it, someone who did—a neuropharmacologist who was dying to learn more about the dopamine transporter—happened to be working just down the hall from him. That was Nancy Zahniser, professor and associate dean for research education in the University of Colorado School of Medicine. (She’s also a ’77 PhD graduate of Pitt’s School of Pharmacy.)

“If you drew the two circles of our expertise and interests, there was this tiny little overlap,” says Zahniser. “So that’s how we got together.” The two went on to collaborate for more than 10 years.

Many labs were working on dopamine-transporter research at the time, but Sorkin’s trafficking expertise made him stand out. Together, Sorkin and Zahniser identified the enzyme NEDD4-2 as a component of dopamine-transporter trafficking. Zahniser is sad to see Sorkin go (“Pitt’s gain is our loss,” she says), but she’s glad for him to be in his new home, rich with prospects for new collaborations with Amara and other top-notch dopamine investigators.

Dopamine transporters are notoriously sparse and difficult to pin down. Recently, Sorkin developed a mouse model with tags on its dopamine transporters that made them much easier to study. The project is funded by the National Institute on Drug Abuse. Zahniser is thrilled about what this new tool might mean for the broader field.

For example, eventually she hopes to use Sorkin’s mouse to investigate differences in individual animals’ responses to cocaine. She wonders: Are the animals that have higher numbers of dopamine transporters resistant to cocaine-induced changes in transporter trafficking? And if so, what does that mean? Would a more sluggish pace mean a more addiction-prone brain? And if so, then could the trafficking process be helped along somehow? Could we rescue people from the throes of addiction?

CLIFF HANGER

Back in the former Soviet Union, Sorkin competed with a speed-climbing team semi-professionally from 1975 to 1987 and has been an avid mountaineer since. He has seen the tops of Mont Blanc, Grand Teton, and several peaks along the Caucasus, Tian Shan, and Pamir ranges.

More recently, it’s been harder to fit in as much climbing as he’d like; and since he’s arrived in Pittsburgh, it’s become harder still. When he was offered the job, leaving the mountains of Colorado was one of the hardest parts of his decision.

“When I climb,” he says, “I forget everything else. I’d try to take papers to read in the tent when we’d go on those month-long expeditions, but in all my career, I could never read one page. I could read books, but not scientific papers. It was like I was rebooting my computer.”

The Pitt appointment is Sorkin’s first experience in administration. His move surprised his old friends—and even Sorkin himself—because he prefers to keep a low profile. But Sorkin saw this as another chance to stretch and grow, to leave his comfort zone. And besides, when Pitt’s School of Medicine came courting, the promise of marrying basic science to clinical science on a grander scale won him over. Apparently, some adventures are even more irresistible than cresting a mountain. “In science, you’re always learning something new,” he says, “something that no one in the human race has ever known. It’s like discovering a new island. It might be a small island, but it’s new.”
HOW DO YOU CAPTURE
Sperm meets egg, begetting an embryo. The cells divide, divide, divide, and you get a person. During development, stem cells—undifferentiated lumps of genetic information—become heart, brain, lung, skin, bone, cartilage, whatever they like (pending the influence of all sorts of genetic and chemical signaling in the developing embryo, of course).

A prevailing theory posits that cancers may be driven by a sort of stem cell, as well—one that is seemingly immune to conventional cancer therapies. Scientists would like to study these cancer stem cells, but there’s a problem: They don’t stay stem cells for long. As they rapidly spin off conventional cancer cells, what’s left is their offspring.

It seems that if investigators could figure out a way to kill cancer stem cells, they would be on the path to killing cancer itself. But how do you capture the ephemeral?
John Lazo, a PhD and the Allegheny Foundation Professor of Pharmacology at the University of Pittsburgh, also directs the University's Drug Discovery Institute. There, he has access to a library of 200,000 compounds and the equipment, knowledge, and staff to quickly screen these compounds against possible drug targets. Though it's a bit more complicated than this, the process is something like throwing a whole bunch of stuff at a wall, seeing what sticks, and then studying why whatever stuck, stuck.

“We’ve actually had several faculty members at the University of Pittsburgh come to us with the same question: How can we selectively kill cancer stem cells?” Lazo says.

The question, obviously, is a good one. But Lazo’s drug-discovery team came up against the same problem again and again. Cancer stem cells are transitory, evanescent, and prone to differentiate quickly.

No one had met with success in arresting cancer stem cells, Lazo says, making it more difficult to study how to combat them.

“If you’re attempting to develop approaches that would use high-throughput screening [automated systems that test how a certain biological process reacts to a library of candidate compounds] or high-content screening [automated optical systems that permit measuring the levels or location of substances in cells],” he says, “the one thing you absolutely have to have is a stable cell line so that you can conduct experiments over weeks or months or maybe years.”

Then one day in mid-2007, Lazo got a call from Edward Prochownik, director of oncology research at Children’s Hospital of Pittsburgh of UPMC. The two had been talking about a project they had been working on for a couple of years. Prochownik said that maybe there was something else they should talk about. It appeared he had created a stable cell line—of cancer stem cells. No one had ever said that to Lazo before. This is the kind of news that can get a drug researcher excited.

Lazo recalls, “Ed mentioned that he made this observation. Of course I’m interested in it!”

Prochownik had, Lazo says, “the missing piece of this big puzzle.”

The existence of stem cells was posited—and their name was coined—by Alexander Maksimov in 1908. More than 50 years after Maksimov advanced this theory, James Till and Ernest McCulloch were pursuing cancer research in Toronto with the help of irradiated mice. They found that bone-marrow cells injected into their subjects formed colonies of new cells within the mice, in fact replacing their entire decimated hematopoietic system—the organs and tissues (primarily the bone marrow, spleen, tonsils, and lymph nodes) that help make blood. What Till and McCulloch called “spleen colonies” are now known as adult stem cells.

Then, at the University of California, San Francisco in the early 1980s, Gail Martin and colleagues peeked into the mouse embryo and found what would be called an “embryonic stem cell,” the kind that can become anything and everything. For most of that century, scientists had thought these cells existed. Martin was the first to find, extract, and isolate them.

Since that time, teams of scientific research have been generated with the hope that these two basic kinds of stem cells might be employed to mend injured hearts and brains, generate new cartilage and ligaments and nerves and bone, and just about anything else that needs to be replaced.

That’s the positive stuff with stem cells.

Cancer stem cells, though, are not so helpful.

Although the debate is far from over, a growing population of investigators is sure that cancer stem cells are to blame for tumor regeneration and metastasis. The idea is this: Chemotherapy and radiation kill rapidly dividing cells, like the ones that make up the bulk of a tumor. Cancer stem cells do not divide rapidly, escaping the murderous intent of these therapies. Then, when it appears all is well—that the tumor has been eliminated—cancer stem cells kick into gear, and cancer begins afresh.

Prochownik, an MD/PhD, has spent decades treating children with cancer as, and an investigator, learning the ins and outs of what are known as myc oncproteins. When these proteins go berserk, they can cause diseases such as lymphoma, breast cancer, neuroblastoma, and lung cancer. Most of his research career has been spent quietly probing the basic science that governs how oncproteins work and finding important clues to stop them from doing harm.

Prochownik has also been interested in finding out how cancer stem cells work. Although not a sideline, this has not been the major thrust of his career.

About two years ago, his lab tried to figure out a way to follow cancer stem cells as they differentiated, using a certain breast cancer cell line—“It’s an established cell line, one that people had been working with for years.” Nothing unusual, he says.

Cancer stem cells, once removed from a body, don’t stay stem cells for long—they spin off millions of “conventional” cancer cells and become lost in the forest of rapid reproduction. It’s kind of like taking a tray of a few needles, turning around, and finding that the needles had generated a massive haystack.

Prochownik, the Paul C. Gaffney Professor of Pediatrics and a professor of microbiology and molecular genetics in Pitt’s School of Medicine, knew this and was trying to find a way to follow the needle-to-haystack development.

That’s when something odd—and potentially groundbreaking—happened.

Prochownik found something that may allow doctors to specifically target cancer stem cells with drugs. Being able to kill these stem cells while also applying conventional chemo and radiation therapies to treat the bulk of a tumor opens up the possibility that cancers could be eliminated. Cured.

But that’s not exactly what he was trying to do. Prochownik’s original plan was this: Genetically engineer a breast cancer cell line to express a gene only seen in cancer stem cells.

“We were looking for a way to be able to rapidly and easily follow these cells as they differentiated,” he says.

By tagging the stem cells with green fluorescent protein (GFP), Prochownik expected his cells to glow under UV light. As the cell population increased, a smaller and smaller percentage of them would fluoresce as the stem cells spawned their daughter cells.

“The prediction was that it’s only going to be a small population of cells that will express GFP; and the other prediction was that after you isolate this stem cell GFP-positive population and put it back into culture, within days or weeks it will lose the expression of GFP,” he says.

“Eventually you’ll end up with a population of cells that are 99 percent GFP-negative and 1...
percent GFP-positive—just like the starting population."

But something went wrong.

"Try as he might, Prochownik couldn’t make the cancer cells do what logic and every single scrap of research on the subject dictated they should do.

“What we saw was that all the stem cells remained GFP-positive. They never differentiated, and we still don’t know why," he says. “But we’ve done this multiple times in four cell lines, so it’s a real find—not a fluke.”

That’s what Prochownik says today. Two years ago, he was hoping this was a fluke.

“We didn’t really appreciate what we had. We were expecting to be able to show that these cells can differentiate and were frustrated that it didn’t happen. We said, ‘We’ve got to make these cells differentiate! How come they’re not differentiating?! There’s got to be something wrong with these cells. They can’t even possibly be stem cells.’”

So the cells weren’t differentiating like stem cells should. And nothing Prochownik tried altered this fact. But one thing nearly everyone suspects—and in some quarters, is certain of—is that if cancer stem cells are put into an animal, even in small populations, they’ll generate tumors.

Some investigators have shown that just a couple-hundred cancer stem cells can initiate a tumor in mice; yet it takes millions of conventional cancer cells to do the same.

So Prochownik took 100 of his maybe-stem cells and injected them into a mouse.

Tumors. Served up quickly and easily.

“When we grew these tumors up and isolated the cells, they were 100 percent GFP-positive and stained 100 percent for cancer stem cell markers,” Prochownik says. “Even after you put them into an animal and grew them up as a tumor, they never differentiated.” The cancer stem cells begot cancer stem cells.

Prochownik had grown tumors that were composed exclusively of stem cells. Usually, stem cells make up between 1 and 25 percent of a tumor. (The larger the population of stem cells inside a tumor, the more virulent it is and the more likely it is to metastasize.)

Now Prochownik had on his hands a stable cancer stem cell population that never changed. This, he thought, could be valuable.

“We got to thinking that perhaps we could actually use these cells to our benefit. Maybe there’s something we can do with these,” he says.

“And the obvious thing was, ‘Can we use these as a way to screen for drugs that selectively kill the stem cells?’”

Max Wicha, an MD, is a distinguished professor of oncology at the University of Michigan and founding director of its Comprehensive Cancer Center. Prochownik describes him as “one of the top two or three people in the breast cancer stem cell world.” As such, Wicha, who delivered the 2010 Bernard Fisher Lecture for Pitt’s School of Medicine in February, has become a confidant of Prochownik’s.

He considers Prochownik’s stem cell line a boon for cancer research and notes that many investigators might have just chuckled the whole thing as a bollixed-up experiment.

“Some of the best discoveries have been accidental,” he says. “Some people would have thought [the cells] were contaminated, thrown out, and started over. The best take what’s unexpected and go with it.”

Prochownik took his unexpected to Lazo.

“We went to him right after we made this discovery,” Prochownik says. “We said, ‘Can we use [high-throughput] screening to get an answer to [what might kill these cells]?’ He said, ‘Absolutely.’”

Prochownik and Lazo have been working together on various projects in recent years. In their early meetings on the cancer stem cell project, they decided that it would be better to throw selected “stuff” at the metaphorical wall rather than going through each and every one of Lazo’s organic compounds.

If you used every resource available to the Drug Discovery Institute, Prochownik says, you wouldn’t exactly be wasting time, but you’d be taking a longer, harder path. That’s why he and Lazo chose to use only compounds already recognized as drugs (some of which already have FDA approval for treating diseases besides cancer). This method could speed a new, safe, and efficacious stem cell–specific treatment for cancer to the clinic.

“There’s actually quite a history on this going back several years. You can find, for example, that drugs previously used to prevent seizures turn out to be pretty good antibiotics,” Prochownik says. “The advantage of using this approach is that [you are] screening for drugs that are already known to be active. You could conceivably find something that was FDA-approved and use it right away!”

Lazo is also screening Prochownik’s stem cell line against short interfering RNA (siRNA), segments of RNA that interfere with the expression of specific genes. Research related to siRNA won the 2006 Nobel Prize in Physiology or Medicine for Andrew Fire of Stanford University and Craig Mello of the University of Massachusetts. These RNA segments are not drugs; they are tools for finding genetic vulnerabilities within cancer stem cells.

“By virtue of them being specific for particular genes, they immediately give you a target,” Prochownik says. Let’s say that gene A is important for the survival of cancer stem cells. It might be possible to craft an inhibitor that will target the gene’s weak spot or, perhaps, there might be a molecule available to interrupt the gene’s signaling pathway, rendering it impotent.
Lazo adds, “By suppressing genes that are targets of or can be targeted by small molecules, you have an opportunity to relatively quickly identify future strategies for killing these cells.”

Their screening has produced a few hits. With siRNA, Lazo says, he has found more than a dozen genes that could play a role in the viability of cancer stem cells. Many of these, he adds, do not have drugs that target them. “It’s a fabulous opportunity to seek new compounds,” he says. “It certainly gives you a rationale for going after compounds, though that’s obviously a longer process [than using extant compounds already approved by the FDA].”

Prochownik says he and Lazo have found seven compounds that seem to kill cancer stem cells. “Of the seven drugs we’ve identified, four fall into the same class, and they inhibit a common target. … We know that, at least in our cell line, the stem cells express higher levels of this target.”

Prochownik had grown tumors that were composed exclusively of stem cells.

(Prochownik and Lazo are waiting to announce results in a peer-reviewed journal before they name these promising compounds to members of the news media.)

The next step, says Prochownik, is to demonstrate the same overexpression of the unnamed target in cancer stem cells taken directly from primary breast cancer tumors. He is working with Magee-Womens Hospital of UPMC to obtain the needed cell samples. If things work the same way in as Prochownik puts it, “the real world” as they do in vitro, a clinical trial is likely to come next.

“This is all kind of pie in the sky right now, but that’s what the potential is,” Prochownik says.

One compound has already been the subject of a clinical trial as a cancer treatment. It failed. Prochownik, however, thinks that a couple of flaws in the trial’s design could account for the undesirable result.

“Why did it fail?” he asks.

“One possible reason is that it was tried in advanced pancreatic cancer. You could hit those cells with a hammer and nothing would happen. But I think a more appealing reason it failed is the way they measured success.”

In the trial, Prochownik says, investigators were measuring tumor shrinkage. But if the drug compound targets cancer stem cells rather than run-of-the-mill cancer cells, as he believes it does, you’re not going to see shrinkage. “If a tumor is only 1 percent stem cells, and you kill that 1 percent, you’ll still have a tumor that hasn’t shrunk,” Prochownik says.

“The whole paradigm of how we assess drugs that are effective against cancer stem cells has to change.”

The potential created by work with Prochownik’s cancer stem cell line is huge, Lazo says. “These will knock out the stem cells, and other drugs that we have will take care of the rest of the cells.”

Prochownik’s cell line may have an impact far beyond Pitt, Lazo suggests.

“This system [the cancer stem cell line] could be widely exploited in academia and industry for many years to come,” Lazo says. “Remember that Ed is just using breast cancer cells. If you think about the 100-plus kinds of cancer out there, this could mean full employment for some people for a long time.”

Wicha agrees: “There will be a flood of multiple explanations, which could take a quarter-century to sort out. In the meantime, he would hate to see the use and study of his patented, arrested breast cancer stem cell lines “suffer because we don’t have a mechanism.”

As Prochownik hoped and expected, a prominent journal, Stem Cells, eventually did accept his lab’s paper on the cancer stem cell line for publication. The paper is slated to come out in the coming months.

And a postdoc working on the project, Fang Zhang, is in the running for a Susan B. Komen Foundation fellowship award to support further research.

The plus side of working in relatively unexplored territory is that you never know who will take the field another leap forward.

The pediatric oncology department of a children’s hospital, for example, “doesn’t seem like the traditional place this kind of stem cell work would come from,” says Prochownik.

In praising Prochownik’s discovery, Arthur S. Levine, dean of the School of Medicine and senior vice chancellor for the health sciences, said he found this aspect appealing. “Ed is a pediatrician, and this work comes out of Children’s Hospital. So this is another example of how really significant research can come from unexpected quarters,” he says. He points to Leland Hartwell’s work on cell division in yeast, which won the Nobel Prize for Physiology or Medicine for the University of Washington researcher in 2001.

“His is the most important work done in cancer biology in modern times,” Levine says of Hartwell, “Yet ... people looked on it as basic yeast biology.”

Levine considers Prochownik’s cell line to be “probably one of the most important pieces of research that’s unfolded here in recent years.”

Prochownik is confident that future work will reveal the mechanism that makes his stem cells durable and static. In the interim, he’s pushing forward with Lazo on the pragmatic and immediate aspects of his project.

“We’re going to try to use these things for practical purposes,” he says, “We’re going to take our limited resources and put them toward screening. We’re going to look for drugs.”

So says the pediatric oncologist from Pittsburgh.
Psychiatrist William Klunk no longer recruits patients to participate in his studies of Alzheimer’s disease. He’s not allowed. And like his collaborator, radiochemist Chester Mathis, if he wants to review raw research results, he must be attended by a colleague to vouch both for his integrity and that of the data. Each is also barred from serving as a principal investigator—or supervising anyone who does—of protocols involving human or animal studies related to research the pair has pursued since 1994.
Neither has run afoul of the law or even common decency. In fact, each is at the top of his career. Klunk is a professor of psychiatry in the University of Pittsburgh School of Medicine, codirector of the University of Pittsburgh Alzheimer Disease Research Center, and director of the Laboratory of Molecular Neuropharmacology at Western Psychiatric Institute and Clinic. Mathis is director of the UPMC Positron Emission Tomography Center and professor in the Department of Radiology in the School of Medicine.

The prohibitions that constrain how Klunk and Mathis conduct their quest for better tools in the fight against Alzheimer's owe, quite simply, to Pitt's commitment to integrity amidst the increasingly complex relations between academic medical centers and an array of business interests. Until 1980, research on college campuses rarely translated to commercial innovation, and there just wasn't much to worry about in the way of conflict of interest. Then Congress changed the laws governing the intellectual property that emerges from federally funded research.

“[Academic medical centers] can discover things from now to doomsday, but we don't know how to put them in bottles and market them.”

In the three decades since, the biotechnology sector has ballooned into a $55 billion-a-year industry. That cash infusion has fueled intensive research and innovation in an era of shrinking federal funding and simultaneously introduced a tangle of ethical concerns as academic researchers navigate the process that turns innovations at the bench into the drugs, devices, and health care services central to care at the bedside. It has also raised the stakes on marketing to clinicians, who were once relatively insulated from industry-funded promotions, blandishments, and lucrative consulting opportunities.

Klunk and Mathis developed Pittsburgh Compound B (PiB), the underpinning of a strategy now in Phase III trials to image amyloid plaque—the hallmark of Alzheimer's—in the brains of living patients. Previously, the only way to confirm the existence of plaque in a patient was at autopsy. PiB makes the plaque visible in a positron emission tomography scan, meaning a patient may be able to benefit from early-stage diagnosis and intervention. In 2004, GE Healthcare—which manufactures and sells PET scanners—acquired licensing rights to the multiple patents held by Klunk and Mathis with the University of Pittsburgh.

If GE's resulting product garners the requisite federal approvals—expected in 2011 at the earliest—it promises to transform detection and treatment of a debilitating condition that affects 5.3 million people in the United States. Already, research based on Klunk and Mathis' work has revealed new insights into the progression of the disease and has been used to test the effect of experimental therapies. Initial proceeds from the licensing agreement have also supplemented the scientists' salaries, augmented their research budgets, and provided Pitt with discretionary funds.

“The best thing that can happen is for the stuff you work on to be successful,” says Mathis, noting that the prospect of seeing research translated into new treatments can be a powerful motivator for basic scientists and clinicians alike. “Yet the more successful it is, potentially the more conflicts of interest it creates,” he says. “The University has to be very careful, demonstrating that we don't have a chance to misuse humans or animals or the data that derive from them for our own personal gain.”

Ultimately, says Mathis, he's happy to submit to the policies and regulations that manage conflict of interest and maintain transparency, if that's what it takes to see his work with Klunk improve the quality of care for people with Alzheimer's. “It's burdensome, but necessary,” he says. “It's the price we have to pay.”

Mathis was a newly minted PhD in chemistry in 1979 when an audit by the U.S. Comptroller General revealed that just 5 percent of some 28,000 federally funded discoveries were under commercial development. Unlike industry-funded research and development departments, academic researchers simply published their findings to further the collective research enterprise; patents for their work reverted to the government. Such scientists rarely accrued fame or fortune in the process, and neither did anyone else. If a business hoped to protect its investment with a license while developing intellectual property generated on campus, it had to sort through a tangle of more than two dozen federal agencies, each with its own unique policies. As a result, few bothered.

In 1980, the bipartisan University and Small Business Patent Procedures Act—known as the Bayh-Dole Act, in honor of senators Birch Bayh of Indiana and Robert Dole of Kansas, its cosponsors—turned the tables. Bayh-Dole mandated that colleges and universities patent and promote the commercialization of innovations sparked by federally funded research. In effect, the law assigned to federal grant recipients the same financial incentives for commercialization long enjoyed by industry-funded scientists—the 20-year head start afforded by patent protection that makes capital investments in the commercialization process more likely to pay off.

Between 1996 and 2007, university patent licensing had a $187 billion impact on the U.S. gross domestic product and created 279,000 new jobs through such ventures as Google, FluMist, and the hepatatis B vaccine. Closer to home, the Pittsburgh Life Sciences Greenhouse, a public-private partnership founded by Pitt, Carnegie Mellon University, UPMC, the Commonwealth of Pennsylvania, and a number of local foundations, has provided office and laboratory space...
The route from lab to market—where a device or drug can actually help patients—involves a tightrope walk to avoid conflicts of interest.
More recently, his investigations have expanded to include researchers at the National Institutes of Health (NIH) and many of the nation’s top academic medical centers.

Grassley sponsored the first version of the Physician Payments Sunshine Act to promote transparency and full disclosure of the relationships between clinicians and industry in 2007. This winter, U.S. Senator from Wisconsin Herb Kohl cosponsored a revised version of the act, which was appended to the health care reform bill. In 2009, the NIH began collecting comments on proposed rule changes related to federal conflict of interest management for its grantees. Even the Pharmaceutical Research and Marketing Association, which represents a segment of the biomedical industry that has faced particularly intense scrutiny, has developed new guidelines to address growing public concern.

Scrubbery of the relationships between academic medical centers and industry will only increase over time, says Barbara Barnes, the University of Pittsburgh’s associate vice chancellor for continuing education and industry relations, who is also UPMC’s vice president for sponsored programs, research support, and continuing medical education. “With the debate on health care reform and comparative effectiveness research, there will also be much more attention given to drugs and devices, looking for areas of overuse, misuse, and waste, and trying to understand where conflicts of interest might be playing a role.”

At the same time, says Barnes, medical schools committed to aggressive research agendas can’t afford to simply jettison their relationships with industry.

“There are a lot of questions as to what will happen to NIH funding after the [$1.1 trillion American Recovery and Reinvestment Act] goes away,” she says. “There will be more interest within academic medical centers seeking other sources of funds, and industry will be a prime target. We’ll want to work more closely with industry, but we need to be careful about maintaining those relationships and the highest level of research integrity.”

Pitt instituted its own comprehensive policy governing conflict of interest within the six health sciences schools, as well as UPMC, in early 2008, a few months ahead of a report from the Association of American Medical Colleges recommending that all medical schools implement such guidelines by 2010. (See our Spring 2008 story, “A New Diet for Docs.”)

Pitt’s policy bars pharmaceutical sales reps from patient-care areas, prohibits free meals and gifts from industry, imposes narrow limits on faculty consulting arrangements, and bars ghostwriting (specifically, the practice that conveys a faculty member’s credibility to industry-funded and authored publications). The policy also raised the bar for clinical researchers whose findings might have personally lucrative implications by imposing new checks and balances throughout the process of experiment design, data collection, and analysis.

“I’ve heard it said that Bill and I are the poster children for conflict of interest at Pitt,” says Mathis. “I think they mean it in a good way. We have conflicts; we’re required to manage those conflicts. Some things you can’t do; many things you can.”

In 2008, the American Medical Student Association awarded Pitt its Paul R. Wright Excellence in Medical Education Award in recognition of the new policy. The next year, Pitt was among nine of the nation’s 149 medical schools to receive an A on AMSA’s scorecard evaluating conflict of interest policies.

“The implementation went relatively smoothly, considering that we were changing our culture,” says Vice Chancellor for Research Conduct and Compliance Randy Juhl, who cochaired with Barnes the committee that wrote the policy. “That’s always a difficult thing to do.”

Early fears that industry might retaliate in the wake of the new policy by curtailing its involvements with Pitt haven’t been borne out, says Barnes. Although support for continuing medical education is likely to keep falling—because of mergers and consolidations that have cut the availability of funds, as well as concerns about the undue influence they leverage—faculty continue to consult and industry-sponsored trials persist. “I don’t see that we have really jeopardized any of the valid opportunities as a result of these policies,” she says. “What has gone away are the personal gifts, visits from representatives.”

The Kohl-Grassley Physician Payments Sunshine Act, as appended to the health care reform bill, requires industry to post online details of all direct physician payments with a value of more than $100. Already, Merck, Eli Lilly, Pfizer, and other pharmaceutical companies have signed corporate integrity agreements with the Department of Justice that mandate the creation of Web sites along the same lines. Device manufacturers Medtronic and Zimmer made similar disclosures in 2007 in the wake of a Justice Department inquiry, and many academic medical centers now also host similar Web sites. Pitt administrators have kept a close eye on such efforts but haven’t yet implemented policies to govern the public disclosure of relationships between faculty and industry. “We want to make available completely accurate information,” says Barnes. “If you look at the sites, they have a lot of disclaimers—we’re not so sure about the accuracy. From our perspective, it’s somewhat premature.”

Overall, says Barnes, Pitt’s approach to managing conflict of interest has been unique, both for its breadth and the administration’s sustained commitment to enacting the policy. Consequently, her current focus is on evaluating that process and publishing the findings to guide other academic medical centers.

“The fact that we could develop a policy and garner the support of the leadership and other key stakeholders is extremely important,” she says.

So what does the future of industry partnering look like for an American medical school?

That’s becoming increasingly difficult to predict. Yet, a nimble, entrepreneurial approach to funding research and navigating the commercialization process will be vital for universities as the intellectual-property landscape shifts in response to health care reform, the Kohl-Grassley Physician Payments Sunshine Act, and emerging case law.

Six months before Congress passed Bayh-Dole in December 1980, the U.S. Supreme Court ruled that living organisms could be patented, launching a new era in agribusiness and biotechnology. In late March of this year, a U.S. district court judge issued a landmark decision invalidating gene patents jointly held by the University of Utah and Myriad, a company launched by a former Utah faculty member who developed a screening test for a U.S. Supreme Court promises to further define the intellectual-property landscape.

Whatever the future holds, it shouldn’t hurt
Pitt that inventive partnering has become part of its culture. The collaborative spirit that yielded Pitt’s conflict of interest policy has infused the University and the medical school’s recent history. Administrators have inked partnerships with Intel, the nonprofit Rand Corporation think tank, Carnegie Mellon University, the Carnegie Museums of Pittsburgh, and even the Pittsburgh Zoo. UPMC, meanwhile, has built formal alliances with GE Healthcare, IBM, Alcatel-Lucent, and the Italian government, among others. Many of these partnerships focus on research, but they also are about delivering clinical care, updating operations, broadening graduate school offerings, and giving med students other class electives and opportunities for scholarship.

For scientists, such collaborations have yielded new opportunities, which are perhaps even more important than access to funds. Cross-disciplinary teams have sparked new approaches to both basic investigation and the translation of associated intellectual property into clinical settings worldwide.

“Partnerships still lie at the heart of the innovation process, and they will continue to be essential,” says Margaret McDonald, associate vice chancellor for academic affairs, health sciences. She notes that universities must diversify their sources of research funds beyond the federal government and even conventional licensing ventures, especially in light of the uncertainties associated with patent law and commercialization.

Klunk thinks of licensing PiB to GE Healthcare as akin to sending a child off to boarding school or college. “[As clinician-scientists], we can’t take this technology to its full potential,” he says. “We don’t have the skills or funds.” That reality hasn’t stopped Klunk or Mathis from occasionally second-guessing the process.

To make PiB visible in a PET scan, the pair used a carbon-11 tracer, which has a half-life too brief for clinical applications. GE’s first task was to work with Klunk and Mathis to find an alternative tracer. A robust collaboration yielded a fluorine-18 tracer, and the company moved on to the next stage of commercialization. Klunk and Mathis weren’t convinced that the new tracer was ideal and persisted in the investigation using NIH funds. So far, they haven’t found anything better.

“They were right, and we were wrong,” says Klunk. “But that may change. We haven’t given up.”

The decision to proceed with a good-enough compound gained the company at least two or three years in the march to market, says Klunk. “It took us that long to realize maybe we’d never beat it.”

Klunk and Mathis have largely come to terms with the complexities and frustrations of the commercialization process. They realize that biomedicine is a risky and expensive business sector. (The Biotechnology Industry Organization estimates it costs about $1.2 billion to bring a biopharmaceutical to market; about 30 percent make it out of clinical trials.) Yet, it’s worth asking: What if someone in the original research group had brought PiB to market by launching a new company? Klunk says he wasn’t the man for the job.

“If I’d done that, I don’t know if it would have worked. There were times we thought we’d be better off if we were controlling everything, but not every decision we’d have made would have been right,” he says. “You control a bigger piece of the pie, but think of the headaches, all the other enterprises that have dried up and blown away.”

Perhaps the University of Pittsburgh’s highest-profile commercial venture to date is Stentor, a storage, management, and distribution system for digital radiology images. In fact, it was so successful, it inspired UPMC to commercialize some technologies on its own.

The Stentor system was created by Paul Chang, formerly a professor of radiology at Pitt and director of radiology informatics at UPMC. When Chang was recruited to Pitt in 1996, the management of digital radiology images depended on huge, centralized systems vastly more expensive and only marginally less cumbersome than the films they had replaced. “[Stentor] was a traditional research project to demonstrate that one could use more flexible mathematical algorithms to leverage less expensive PCs to use the Web,” says Chang, now professor and vice chair of radiology at the University of Chicago. To test his hypothesis, UPMC installed kiosks loaded with experimental software in emergency medicine, surgery, and a few clinics. “It worked so well, the clinicians preferred to use the prototype rather than the $70,000 commercial work stations.”

What happened next, says Chang, was a “support and management nightmare.” He and his team had the skills to test concepts; they weren’t equipped to sustain their system on the scale of an entire medical center. But it seemed like a great product.

Because Stentor relied only on software development, the project was free of the extraordinary costs and regulatory considerations associated with manufacturing clinical-grade biological materials. So instead of licensing a patent to an existing company with FDA-approved facilities and manufacturing expertise—prerequisites to the commercialization of a pharmaceutical or medical device—UPMC hired a management team and launched the company with help from venture capitalists. The approach preserved Chang’s involvement and an emphasis on the technology’s clinical requirements. The process was ideal, says the MD: “We academics tend to be very good at coming up with ideas, and because we’re physicians, we understand workflow and have the domain knowledge to know what’s required of tools to take care of patients. We’re not as good with marketing and all that stuff.”

The course Stentor took to commercialization was unique at the time, says Chang, and remains rare. UPMC has since taken a page from the playbook of the venture capitalists, whose early-stage investments had yielded rich profits by dedicating more of its own funds to the commercialization of homegrown ventures. (When Philips Electronics purchased the company for $280 million in the summer of 2005, Pitt earned $10.8 million, and UPMC, which had invested $9 million developing the technology, received $45.1 million. Much of the rest went to venture capitalists.) To date, UPMC’s International and Commercial Services Division has invested more than $200 million in 36 companies and committed additional funds to partnerships with firms like IBM, GE, and Alcatel-Lucent.

With Wall Street’s many surprises of late, a medical center’s choice to reinvest funds toward spin-off enterprises that further patient care and its own community’s growth starts to sound like a pretty good idea. —ST
What’s life like for husband-wife research teams? Anette and Stefan Duensing share their experiences of togetherness, 24/7.

Rolf and Magda Loeber stick to a morning routine. They plot their workday and hash out issues at their favorite coffee shop—a European-size espresso for him, decaf macchiato for her. (“Mostly milk foam,” she says, by way of explaining why her sturdy ceramic cup is about four times heftier than his.) Then the tall, trim couple stroll down Walnut Street to their exercise club.

“You work hard enough already!” Magda objects, with tenderness, when her husband’s voice betrays some ambivalence about how their research staffers show up at the office earlier than they do. In any event,
As he points out, Rolf starts at home by 5 a.m., tackling the monumental amount of work involved in their large-scale, longitudinal studies of delinquency. Likewise, Rolf is solicitous of her: After four decades of togetherness, he knows how his wife’s mind races and churns when she considers a problem or difficulty, so they try never to talk about work after 5:30 p.m., “or Magda would not sleep well.”

Not all husbands and wives who collaborate on research keep such a strict division between work and home life. Some take pleasure in animated work discussions over dinner and late into the night. Others—especially those with young children—have neither the time nor inclination to bring work home very often; they are just glad their partner knows exactly how hectic the day has been. The number of scientist couples continues to rise, and they all must figure out their own balance. (When they work in the same lab or research office, that may well include the question, “Are we both the boss?”)

Among the University of Pittsburgh’s most storied married biomedical couples early on were Thomas and Katherine Detre, who came to Pittsburgh in 1974. He was recruited from Yale University to chair the psychiatry department and eventually led all of the health sciences schools. She would become a Distinguished Professor of Epidemiology in the Graduate School of Public Health (GSPH). (See Last Call, p. 40.) David Kupfer, now Thomas Detre Professor of Psychiatry, followed and married Ellen Frank, Distinguished Professor of Psychiatry and Psychology.

Recruited to Pitt’s Department of Psychiatry in 1984, the Loebers have rewarded their employer with exceptional productivity: They have several books, more than 200 research articles, and a stellar grant record to their credit. “We were hired as a couple,” Rolf says—Loeber, R., and Stouthamer-Loeber, M., on research papers—“and both Detre and Kupfer told us to think big.”

They have thought big, but not always in the same way. “We are not Siamese twins,” Magda says, adding: “If I in a meeting say, ‘Well, I don’t agree with Rolf,’ it doesn’t mean that I’m talking about packing up my personal belongings and moving out.”

Some staffers can be startled, and then relieved, by the couple’s willingness to challenge each other openly, albeit graciously. Magda handles most personnel issues with the deftness of a psychologist, which, of course, she is. “This doesn’t happen often, but if people have a beef that involves Rolf, I won’t protect Rolf. They have to feel that I’ll listen, and there’s no penalty for saying this. Usually, I will say, ‘I hear you. You need to take this up with him.’ They know that Rolf will not eat them alive.”

Together for 43 years, the Loebers—both PhDs from Holland, and he a Distinguished Professor of Psychiatry, as well as psychology and epidemiology, and she an associate professor of psychiatry and psychology—may be unique among their contemporaries. Well into the early 1970s, antinepotism rules commonly kept married women from working in medical academia with their husbands. Maria Goeppert-Mayer won the 1963 Nobel Prize in Physics despite having been unable to secure official faculty positions at Johns Hopkins University, Columbia University, and the University of Chicago during the decades her husband was a professor at each of those institutions. Gertrude and Werner Henle, the husband-wife team who were first to link a virus (Epstein-Barr) to a cancer (Burkitt’s lymphoma) as well as mononucleosis, considered themselves equal partners when hired together at the University of Pennsylvania in 1937, but four years passed before Gertrude was promoted even to the level of instructor; she was not made full professor until 1965.

Likewise at Pitt, women sometimes struggled in the historically male-dominated medical-research arena, which Frances Finn (now Reichl) discovered after she married the famous peptide scientist Klaus Hofmann, who chaired Pitt’s biochemistry department. Finn had joined Hofmann’s lab as a graduate student in 1961, which, she says, only made her situation trickier. “I had a difficult time trying to define myself,” she recently wrote by e-mail from her home in Princeton, N.J. “I’m not sure I ever did. Even the Chancellor at the University could not place my face unless I was standing next to my husband;” however, the Chancellor’s wife always could, she adds.

But none of that diminished the sheer joy of collaborating with Hofmann, Reichl says. “People who are not in science don’t understand the thrill of solving a problem, putting all the evidence everyone has collected—including your latest results—together and suddenly seeing an answer no one knows about. It gives you a pretty heady feeling to think that you are the only people in the whole world to know something.”

She and Hofmann worked side by side for some 30 years, living and breathing science in the lab and at home. “Pulling out of the lab to go on vacation was like slowly removing adhesive tape from an open wound for me,” says Reichl, now retired from the Department of Medicine. “I always hated to leave.”

The sentiment is shared by Anette and Stefan Duensing, German MDs who for the last six years have shared lab space at the Hillman Cancer Center, where they run research programs that focus on genomic instability. He is associate professor of microbiology and molecular genetics; she is assistant professor of pathology. They usually drive to work together, rarely leave before 9 p.m., and tend to picnic in Stefan’s office, where the shelves are lined with antique books—"includ-
ing an 1867 edition of *Gray’s Anatomy of the Human Body*—which they find on the rare day off at used book stores like Caliban Book Shop on South Craig Street.

They have a complicated arrangement, supervising the same researchers in a shared lab yet maintaining their own separate projects. Still, they can easily oversee each other’s projects when one, say, leaves town for a meeting. For people in their lab, that means no letup. “You have two bosses,” Stefan says, “two people who criticize you.”

Both are intense and driven to make tenure on their own merits. “The advice we got,” early on, Stefan says, “was, ‘Do not put each other on papers, because it could look bad, like you’re not independent researchers.’” So on their first articles, they tried listing just one Duensing. But considering all the intellectual input they lent to each other’s work, that seemed “unnatural,” Stefan says. He and Anette add, at precisely the same moment: “It felt weird.” Most of their recent papers bear both names.

The medical school at Pitt appears to have been ahead of the curve in recognizing advantages to hiring husband-wife teams (and for at least the last two decades has made an effort to find spots for talented, so-called “trailing” spouses, when one in a couple is being recruited). Hard figures are difficult to come by, but anecdotal evidence suggests a steep rise in married couples in academic medicine. One local realtor, for instance, has shown homes to more than a dozen couples recruited by the School of Medicine in the last few years. Many double-hires are scientific standouts who publish together frequently: Notables include Kaposi’s sarcoma herpes virus discoverers Yuan Chang (professor of pathology) and Patrick Moore (professor with appointments in microbiology and molecular genetics in the medical school, as well as infectious diseases and microbiology in GSPH). New University of Pittsburgh Cancer Institute director Nancy Davidson, an MD, and Thomas Kensler, a PhD professor of pharmacology and chemical biology, also collaborate.

(Interestingly, all three Detre chairs are married to faculty members: neurobiology department chair Susan Amara, a PhD, to Geoffrey Murdoch, an MD/PhD and associate professor of pathology; geriatric medicine’s division chief Neil Resnick, an MD, to Susan Greenspan, an MD professor of medicine; and psychiatry’s Kupfer to Frank.)

In his 12th-floor office at UPMC Presbyterian, Matthew Rosengart is wearing running gear but probably won’t get outside before the sun sets. Behind him are large photos of his children, Anna Elaine and Maevis, and sitting across from him is their mother—his wife—Janet Lee. Rosengart, assistant professor of surgery and critical care medicine, is a trauma surgeon who runs a lab studying calcium in macrophage biology. Lee, assistant professor of medicine, treats critical care patients and investigates chemokine-mediated lung inflammation. They both have the gift, treasured by patients, of appearing attentive and calm, but clearly they live in overdrive.

“We have dinner as a family five nights a week,” Rosengart offers.

“I don’t know about that,” Lee says, “but we try.”

“We try,” Rosengart agrees.

They met at Johns Hopkins University as freshmen, couples-matched in Alabama for their residencies, and have found their research and clinical interests intersecting ever since. “I tend to do a lot of the statistical work [on our papers],” says Rosengart, who has an MPH. He also springs into action when Lee needs a quick surgical consult. “There’s warmth in her company,” he muses, “even if it is at a patient’s bedside.”

At home, they say, talk rarely turns to science. Instead, says Rosengart, “We’ll get a glass of red wine and just switch places on the psychiatric couch and talk.”

“He has a good sense of humor, which I need,” Lee adds. Sometimes, when both have had a particularly harrowing day, Rosengart says, “We just hope to God there’s a good comedian on Comedy Central, because we need a good laugh.”
Bradley Stephens seems satisfied with his residency match. He'll train in neurological surgery at Barnes-Jewish Hospital.

**ANESTHESIOLOGY**

Chen, Min-Shue  
UCLA Medical Center, Calif.  
Goff, Robert  
Stanford Hospital and Clinics, Calif.  
Kawaki, Joseph  
Stanford Hospital and Clinics, Calif.  
Lewis, Alexandra  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
McConnell, Matthew  
Ohio State University Medical Center  
Ta, Phuong  
SUNY Downstate Medical Center  
Talamo, Thomas  
UPMC Mercy/University of Pittsburgh, Pa.  
Wang, Dave  
Western Pennsylvania Hospital/Temple University

**DERMATOLOGY**

Yang, Xiao  
University of Michigan Hospitals and Health Centers

**EMERGENCY MEDICINE**

Beauchamp, Gillian  
University Hospital/University of Cincinnati, Ohio  
Chandra, Paaul  
Advocate Christ Medical Center/  
University of Illinois-Chicago  
Farkas, Andrew  
UPMC/University of Pittsburgh, Pa.  
Grosheider, Thomas  
University of Pennsylvania Health System  
Hormonein, Jeffrey  
Beth Israel Deaconess Medical Center/  
Harvard University, Mass.  
Kay, Joyce  
University of Maryland Medical Center  
Marchi, Mari  
UCLA Medical Center, Calif.  
Petersen, Shane  
New York–Presbyterian Hospital/  
Columbia & Cornell Universities  
Pham, Steve  
New York–Presbyterian Hospital/  
Columbia & Cornell Universities  
Ritter, Seth  
UPMC/University of Pittsburgh, Pa.  
Stephenson, Amanda  
New York Methodist Hospital/Cornell University  
Turnbull, Megan  
Hennepin County Medical Center/University of Minn.

**FAMILY MEDICINE**

Burke, Lorri Anne  
UPMC St. Margaret/University of Pittsburgh, Pa.  
Champlin, Nadine  
UPMC St. Margaret/University of Pittsburgh, Pa.  
Kuhle, Alberta  
Philadelphia College of Osteopathic Medicine/  
Temple University  
McKinney, Jamie Kaiser  
Permanente So. Calif./UCLA

**INTERNAL MEDICINE**

Arid, Tani  
University of California, San Francisco Family Medicine  
Chow, Jeremy  
University of California, San Francisco Family Medicine  
Emory University, Ga.  
DeCato, Thomas  
University of Washington Affiliated Hospitals  
Law, Joseph  
Strong Memorial Hospital/  
University of Rochester, N.Y.  
Lincoln, Anne  
Rhode Island Hospital/Brown University  
Liu, Jimmy  
UPMC/University of Pittsburgh, Pa.  
Madera, Charlie  
New York University Affiliated Hospitals  
Mendelson, David  
University of Toronto, Canada  
Nguyen, Quyen  
Cleveland Clinic/  
Case Western Reserve University, Ohio  
Oka, Chiko  
Loyola University Medical Center, Ill.  
Rapaka, Ritha  
Johns Hopkins Hospital, Md.  
Rhodes, Corinne  
Rhode Island Hospital/Brown University  
Rushlow, Michael  
University of Michigan Hospitals  
Shifrin, Meera  
Stanford University Affiliated Hospitals  
Sterin, Elissa  
McGraw Medical Center/Northeastern University, Mt.  
Tackett, Sean  
Johns Hopkins Bayview Medical Center, Md.  
Zator, Zachary  
Massachusetts General Hospital/Harvard University  
Zheng, Chie  
UPMC/University of Colorado at Denver Affiliated Hospitals

**INTERNAL MEDICINE—PEDIATRICS**

White, Anna Marie  
UPMC/University of Pittsburgh, Pa.

**INTERNAL MEDICINE—PRELIMINARY**

Bray, Sarah  
UPMC/University of Pittsburgh, Pa.  
Garza, Christine  
Mehring Medical Center/SUNY Downstate  
Kong, Gerhardt  
Alleghe General Hospital/Drexel University, Pa.

**INTERNAL MEDICINE—PRIMARY**

Chung, Anita  
University of Washington Affiliated Hospitals  
Hansel, David  
University of California, San Francisco  
Patel, Amit  
Mount Sinai Medical Center/  
Albert Einstein College of Medicine, N.Y.  
Shoff, Swati  
Boston University Medical Center, Mass.  
Van Metre, Laura  
New York University Affiliated Hospitals

**INTERNAL MEDICINE—WOMEN’S HEALTH**

Lunardini, Jessica  
UPMC/University of Pittsburgh, Pa.  
Ross, Kelly  
UPMC/University of Pittsburgh, Pa.

**MAXilloFACIAL SURGERY**

Pizana, Raymond  
UPMC/University of Pittsburgh, Pa.

**NEUROLOGICAL SURGERY**

Deibert, Christopher  
UPMC/University of Pittsburgh, Pa.  
Stephens, Bradley  
Barnes-Jewish Hospital/  
Washington University in St. Louis, Mo.

**OBSTETRICS/GYNECOLOGY**

Bradley, Megan  
UPMC Magee-Womens/University of Pittsburgh, Pa.  
Danshevar, Candice  
Cedars-Sinai Medical Center/UCLA, Calif.  
Davila, Blum  
Stanford Hospital and Clinics, Calif.  
Gurubhagavaty, Priya  
University of Minnesota  
Horton, Christine  
Strong Memorial Hospital/  
University of Rochester, N.Y.  
Saunders, Alicia  
St Luke’s-Roosevelt Hospital Center/  
Columbia University  
Waltman-Towers, Rebecca  
NC Women’s Hospital & Wake Medical Center/  
University of North Carolina, Chapel Hill  
Wochet, Andrew  
Brigham & Women’s Hospital/  
Harvard University, Mass.  
Wilson, Leah  
University of Massachusetts Memorial Healthcare

**OPHTHALMOLOGY**

Bae, Ling  
Washington University Medical Center, Mo.  
Gonine, Ian  
University of California, San Francisco Affiliated Hospitals  
Klirkoeben, Jared  
UPMC/University of Pittsburgh, Pa.  
Ku, WanLun  
Northwestern University Affiliated Hospitals, Ill.  
Yang, Christopher  
Henry Ford Health System, Mich.

**ORTHOPAEDIC SURGERY**

Costanza, James  
Thomas Jefferson University Hospital, Pa.  
Laudermilck, Dann  
UPMC/University of Pittsburgh, Pa.  
McClosky, Michael  
UPMC/University of Pittsburgh, Pa.  
Oh, Nihil  
University of Michigan Hospitals Health System

**OTOLARYNGOLOGY**

Ahn, Sun  
Johns Hopkins Hospital, Md.  
Montag, David  
University of Minnesota  
Rafal, Ali  
UPMC Medical Center, Calif.

**PATHOLOGY**

Landau, Michael  
Cleveland Clinic Foundation/  
Case Western Reserve University, Ohio  
Leeman, Rebecca  
UPMC/University of Pittsburgh, Pa.

**NEUROLOGY**

Ambrose, Timothy  
Thomas Jefferson Hospital for Neurosciences/  
Thomas Jefferson University, Pa.

**OBSTETRICS/GYNECOLOGY**

Bradley, Megan  
UPMC Magee-Womens/University of Pittsburgh, Pa.  
Danshevar, Candice  
Cedars-Sinai Medical Center/UCLA, Calif.  
Davila, Blum  
Stanford Hospital and Clinics, Calif.  
Gurubhagavaty, Priya  
University of Minnesota  
Horton, Christine  
Strong Memorial Hospital/  
University of Rochester, N.Y.  
Saunders, Alicia  
St Luke’s-Roosevelt Hospital Center/  
Columbia University  
Waltman-Towers, Rebecca  
NC Women’s Hospital & Wake Medical Center/  
University of North Carolina, Chapel Hill  
Wochet, Andrew  
Brigham & Women’s Hospital/  
Harvard University, Mass.  
Wilson, Leah  
University of Massachusetts Memorial Healthcare

**PHYSICIAN/FAMILY MEDICINE**

Greenlee, Adam  
UPMC/University of Pittsburgh, Pa.

**RADIOLOGY—DIAGNOSTIC**

Yang, Adam  
Strong Memorial Hospital/  
University of Rochester, N.Y.  
Hawkins, Christopher  
UPMC/University of Pittsburgh, Pa.  
McDermott, Meredith  
NYU Langone Medical Center  
Misra, Sunit  
Barnes-Jewish Hospital/  
Washington University in St. Louis, Mo.  
Panagiotou, Nannina  
Detroit Medical Center/  
Wayne State University, Mich.  
Patel, Pranali  
Thomas Jefferson University Hospital, Pa.  
Rischall, Matthew  
University of Minnesota  
Shah, Rahul  
Northwestern Memorial Hospital/  
Northwestern University, Ill.

**SURGERY—GENERAL**

Chapman, Michael  
Medical College of Georgia Hospital and Clinics  
Downs-Cannon, Stephanie  
UPMC/University of Pittsburgh, Pa.  
Gross, Kristin  
Rush University Medical Center, Ill.  
Har, Seung  
Shands Hospital/University of Florida  
Lee, Lung-Yi  
University of Wisconsin Hospital and Clinics  
Lee, Wayne  
University of California, San Francisco  
Affiliated Hospitals

**SURGERY—PRELIMINARY**

Amundt, Reginald  
Alleghe General Hospital, Pa.  
Arffa, Rachel  
UPMC/University of Pittsburgh, Pa.  
Slater, Brian  
University of California, San Francisco  
Children’s Hospital, Pa.

**UROLOGY**

Rogers, Marc  
UPMC/University of Pittsburgh, Pa.  
Shin, Eunju  
LA County-USC General Hospital & UCS University Hospital/  
University of Southern California  
Walters, Daniel  
Brigham & Women’s Hospital/Harvard Univ., Mass.

**VASCULAR SURGERY**

Spaulding, Michael  
Dartmouth-Hitchcock Medical Center, N.H.

**PSYCHIATRY/FAMILY MEDICINE**

Greenlee, Adam  
UPMC/University of Pittsburgh, Pa.

**EQUIPMENT & ADVOCACY FELLOWSHIP, AMSA, Va.**

**SUMMER 2010**


**CLASS NOTES**

**‘40s** In October, Distinguished Service Professor of Surgery Bernard Fisher (MD ‘43) received the American College of Surgeons’ 15th Jacobson Innovation Award in Chicago. The following month, the American Philosophical Society presented Fisher with the John Scott Award, which recognizes innovators who have contributed to the comfort, welfare, and happiness of mankind. Fisher says he’s especially humbled by the latter honor, given that its previous recipients include Marie Curie, Thomas Edison, the Wright brothers, and Pitt’s own Jonas Salk.

Fisher overturned the Halsted anatomic and mechanistic paradigm, which had held radical mastectomy as the standard of care for breast cancer. In a landmark 1985 paper, he showed that lumpectomy was just as effective as mastectomy, because cancer did not spread from one area of the body to the next in an orderly sequence, as Halstedians believed. Rather, it was a systemic disease that traveled through the bloodstream and metastasized in no predictable pattern. These insights revolutionized cancer research and treatment.

**‘80s** On November 29, 2009, Ernesto Pretto (Critical Care Fellow ’85) settled in at the Hotel Montana in Port-au-Prince, Haiti. The next morning, he’d serve as head anesthesiologist in that nation’s first-ever whole-kidney transplant. Just weeks later, on Jan. 12, the Hotel Montana was reduced to rubble by an earthquake. Pretto, professor of clinical anesthesiology and chief of solid organ transplantation at the University of Miami, knew he had unfinished business. He’d worked at Pitt with Peter Safar, founder of the School of Medicine’s anesthesiology department and critical care medicine fellowship.

“We studied the needs of critically injured victims, particularly in major earthquakes,” says Pretto.

In response to the tragedy, Pretto’s Miami colleagues helped establish a 300-patient-capacity tent complex—one of the largest in Port-au-Prince—and Pretto, again in Haiti, was the anesthesia point man.

**‘90s** Simon Mears (Neurobiology PhD ’94, MD ’96) followed in his father’s footsteps—eventually. The assistant professor of orthopaedic surgery at the Johns Hopkins University is the son of former UPMC Shadyside chief of orthopaedic surgery Dana Mears (Orthopaedic Surgery Res ’75), who made a name for himself when the department was led by Albert Ferguson. The younger Mears says his journey into the family vocation of orthopaedics wasn’t preordained. He started off studying spinal-cord electrophysiology for his PhD, then slowly gravitated toward orthopaedic surgery. He completed a residency in orthopaedics at Johns Hopkins and a fellowship in orthopaedic traumatology at the University of Maryland. He then moved on to the Mayo Clinic to study knee and hip reconstruction—a field his father helped advance while at Pitt.

**‘00s** Brad Dicianno (MD ‘01) envisions a world where docs can say, “There’s an app for that.” Director of Pitt’s Adult Spina Bifida Clinic, Dicianno is principal investigator of a new telerehabilitation study funded by the National Institute on Disability and Rehabilitation Research (NIDRR) and the Verizon Foundation. He believes such technology will help patients manage their health, especially those in rural and underserved areas or those with cognitive problems.

Dicianno’s patients with spina bifida often end up in the ER with preventable health issues like urinary tract infections, he says. To help them head off these problems before they start, his team is providing study participants with smart phones, as well as several applications they’re designing to help patients manage their medications, bladder catheters, nutrition and exercise programs, and other important tools and therapies. The smart phones will send reminders to keep the patients on schedule, and the patients’ responses will go directly to a wellness coordinator, who will follow up if anything goes awry.

More than a year after publishing The Anti-Cancer Cookbook, Julia Greer (Cancer Epidemiology and Prevention Fellow ’05; Gastroenterology, Hepatology, and Nutrition Fellow ’07) says her parents still make the balsamic chicken with pears weekly. “It has a sweet and tangy blend of flavors,” she says. The cookbook, which includes

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**MEHDI GHAJARNIA**

**GLOBAL VISION**

Working at University Hospital, one of two hospitals in Kabul, Afghanistan, Mehdi Ghajarnia (MD ‘03, Res ‘07) did his best to put aside his own fears of a possible terrorist attack. Fortunately for him, corneal surgery and the simple act of communicating with a patient require one to be in the moment and attentive to detail.

For too long in countries like Afghanistan, war, poverty, political agendas, and violence have taken attention away from the basic medical care of its citizens, Ghajarnia says. He

Ghajarnia (center) at an outreach camp for cataract patients in Dhading, Nepal, in December 2008.
Emily Brown (MD ‘07) is certainly entitled to some bragging rights. This year, she’ll join Skolnik as a chief resident in emergency medicine at Brigham and Women’s and Massachusetts General Hospital; Brown is currently wrapping up her emergency medicine residency. In 2008, when the Steelers beat the New England Patriots 33–10, the Pitt grad was in vaunt mode, fashioning a Steelers shrine right in the middle of Massachusetts General Hospital’s emergency department. Brown’s creativity has traveled twice a year to poor and troubled nations as a volunteer, treating patients and sharing expertise with local physicians.

Ghajarnia, an ophthalmologist at the California Eye Institute in Fresno, started taking part in medical missions abroad when he was a Pitt resident. With others from UPMC Eye and Ear Institute, he traveled to Honduras, and he was gratified by how much he was able to help people with unmet medical needs and by how appreciative they were.

Since then, he has performed corneal and cataract surgery in Nepal, Madagascar, Tajikistan, and Afghanistan. On these trips, he has had the experience of restoring sight to patients who were legally blind. His expeditions have been supported by Surgical Eye Expeditions, Lions of Madagascar, and Pittsburgh-based Global Links.

On several of these trips, Ghajarnia has carried corneas on ice from the United States to his destination. Afghanistan and other countries do not have their own eye banks, but Ghajarnia is working to change that.

—Jamar Thrasher and Chuck Staresinic

THE WAY WE ARE
CLASS OF ’85

T he curtain rose, and clouds of smoke billowed from the stage, blinding the band and the audience. Fortunately, the Scope and Scalpel pyrotechnics fiasco of 1985 didn’t scare director Susan Dunmire (MD ‘85, Res ’88) and music director Sam Tisherman (MD ‘85, Res ’93, Fel ’94) away from the theater for good. Now associate professor of emergency medicine and associate professor of surgery and critical care medicine, respectively, Pitt’s Dunmire and Tisherman have been Scope and Scalpel faculty advisors since 1991. They’ve also been married since a few days after their class’s ill-fated performance. They’d met on the first day of class, at a cocktail party in Scaife Hall.

Dunmire recently developed a course called “Getting Ready for Residency,” one of several courses she teaches in Pitt’s Peter M. Winter Simulation Center. Dunmire and Tisherman have been married for 17 years, and both hold an MD and Res from the University of Pittsburgh.

M A N U F A C T U R E R S

Afshar in Patagonia.
burden off the heart will allow it to heal.

Cardiology dogma reserves mechanical devices for the last resort in class IV cases; and challenging that dogma has been, well, challenging, Dowling says. But he’s drawn inspiration from mentor Bernard Fisher, Distinguished Service Professor of Surgery, who revolutionized breast cancer research and treatment after years of resistance from his peers (see Class Notes, p. 36).

“Sometimes, when you’re doing the right thing, people tell you’re crazy,” says Dowling. “But you have to try anyway.”

Neal ElAttrache (MD ’85) can’t recall ever seeing Dowling wear anything but scrubs during their training. “I’d see him around Oakland, at the O, at the hospital, and he never wore a set of real clothes.” (Could it be he’s wearing scrubs in the rafting-trip photo to the left?) ElAttrache rubs shoulders with uniformed folks of all stripes these days. Based in Los Angeles, the orthopaedic surgeon consults for the Anaheim Ducks, the St. Louis Rams, the PGA tour, the L.A. Dodgers, and the L.A. Lakers. He’s also a clinical instructor of orthopaedic surgery at the University of Southern California, Los Angeles, and director of the sports medicine fellowship at Kerlan-Jobe Orthopedic Clinic.

ElAttrache has published widely on throwing-related injuries of the shoulder and elbow, including an arthroscopic technique he developed for rotator-cuff repair. Historically, most of these surgeries have failed. But ElAttrache’s patented SutureBridge had a healing rate of almost 90 percent in one 2008 study of 25 patients. The technique is now used widely throughout the world.

Since he started caring for the likes of Tom Brady, game day has taken on a different meaning for ElAttrache. “Instead of rooting for the team, you end up rooting for the guys you’ve taken care of,” he says. “[My athlete patients] have taught me a lot about the psychology of healing. I take those lessons to everyone in my practice.” —EV
When Bernd Groner arrived in Pittsburgh from Germany in 1970, he hadn’t yet gotten the hang of conversational English. You’d think that would have presented a problem for the young biochemist, but it turned out to be an asset of sorts.

“I really relied on Nancy and four or five other graduate students for help translating and explaining things,” says Groner (PhD ’75), laughing. “It was so kind of them, especially because graduate school was expected to be so competitive.”

Nancy is Nancy Hynes (PhD ’75), who entered the biochemistry PhD program in the University of Pittsburgh School of Medicine at the same time as Groner. Amid numerous and frequent requests for help understanding English, the two became fast friends. By the time they were selected to work in the lab of former Pitt professor Steven Phillips, they were a couple. After graduation, they married in Berlin, where each had secured a postdoctoral fellowship at the Max Planck Institute. Nearly 40 years after meeting in Pittsburgh, they are still crossing borders, often just to get together.

Groner is the director of the Georg-Speyer-Haus Institute for Biomedical Research in Frankfurt, Germany. Hynes is a senior staff scientist at the Friedrich Miescher Institute for Biomedical Research in Basel, Switzerland. On the weekends, Groner typically drives the three hours to the family home in Basel.

The living arrangement works well, says Hynes—except when there are major home renovations, like a recent five-week project. “He managed to avoid the dust, while I was with it every day,” she says, chiding him with a laugh.

At the Miescher Institute, a basic research center funded by Novartis and linked to the University of Basel, Hynes runs a lab that is focused on breast cancer.

“We want to sort out the different types of breast cancer and see whether we can come up with new therapeutic targets,” she says, adding that some of their work has led to new therapies that are in the clinic today. It’s a long process. For example, Hynes’ lab began investigating a gene for RTK (receptor tyrosine kinase) in 1986. They demonstrated that it was overexpressed in 20 to 25 percent of breast cancers.

“We were the first to show at the level of the protein that it is overexpressed and that this would correlate with other signs of poor prognosis in the clinic,” says Hynes.

The lab did a lot of the early work to learn what the gene did and how it worked. The researchers later experimented with creating antibodies as therapy. Eventually, the biotechnology giant Genentech ran a series of large clinical trials of antibodies, resulting in the 1998 approval of the synthetic antibody trastuzumab (marketed as Herceptin) for breast cancer. It has been highly successful.

As director of Georg-Speyer-Haus, Groner leads a cancer research institute of approximately 100 people. The institute is closely aligned with the Johann Wolfgang Goethe University of Frankfurt, where Groner is a professor of tumor biology and infectious diseases, as well as a researcher with Frankfurt University Hospital. He has been a leader in cancer research for more than 25 years. Groner’s lab is focused on a protein called Stat3, a well-known contributor to cancer. Breast and brain tumor cells appear to be dependent upon Stat3, which helps to regulate such key cancer-cell activities as proliferation, survival, angiogenesis, and migration. In animal models, Groner and his colleagues integrate a peptide into a recombinant protein, which then is able to enter tumor cells, inhibit the function of Stat3, and thereby kill the tumor cell. The group is investigating this therapeutic approach for cancer and for other disease processes, such as chronic inflammation.

Hynes, who grew up in Syracuse, N.Y., says that her family appears to be continuing the traditions of scientific investigation and pond jumping that she and Groner began. Their daughter, Anna, is wrapping up a PhD in biological sciences in Lausanne, Switzerland. She is planning to do a postdoctoral fellowship in the United States.
In her new book, *Beyond the Bounds, A History of UPMC*, Mary Brignano tells how a certain academic medical center came to be, beginning with psychiatrist Thomas Detre’s enlistment of a few key people: [After confirming that he would leave Yale University for the University of Pittsburgh, Detre] began recruiting talented managers to staff WPIC [Western Psychiatric Institute and Clinic]. One of his first picks was Vivian Goodman Romoff, his chief psychiatric nurse at Yale-New Haven. Both he and she ... demanded a strong, collaborative partnership between physicians and nurses. ... “I wanted her to come to Pittsburgh. She said she had a husband, and I thought that was unfortunate,” Detre deadpans. “But I wanted to chat with him.”

This “chat” would change Pittsburgh. The 27-year-old who appeared for an interview in Dr. Detre’s New Haven office was Jeffrey A. Romoff—brilliant, brash, hard-driving, idealistic. ... In 1972, he worked in “a very small mental health counseling planning group in Waterbury, Conn.”

Under Jeffrey Romoff’s eventual leadership, UPMC would become one of the nation’s largest nonprofit global health enterprises. Before that, Vivian Romoff would build one of the largest psychiatric nursing services in the country here. Detre himself held a number of positions in Pittsburgh, including president of UPMC and Pitt’s senior vice chancellor for the health sciences. Also joining Detre in Pittsburgh way back when, of course, was his wife, Katherine Detre, an MD and DrPH. That “trailing spouse” became a Distinguished Professor of Epidemiology at Pitt, regarded as one of the foremost experts in her field. Sadly, both Vivian Romoff and Katherine Detre died of cancer—Katherine in 2006, and Vivian in 1983 (at the age of 37, as Thomas Detre and her husband were beginning to plan a new cancer center for Pittsburgh). —Erica Lloyd
CALENDAR
OF SPECIAL INTEREST TO ALUMNI AND FRIENDS

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

ANNUAL SIMMONS RESEARCH DAY
MAY 12
8 a.m.–1 p.m.
University Club
Ballrooms A & B
For information:
www.surgery.upmc.edu

MEDICAL ALUMNI WEEKEND 2010
MAY 21–24
Reunion Classes:
2000 1995
1990 1985
1980 1975
1970 1965
1960 1955
1950

SENIOR CLASS LUNCHEON
MAY 21
11 a.m.
Alumni Hall, Connolly Ballroom

ALUMNI WEEKEND WELCOMING RECEPTION AND COCKTAILS
MAY 21
5:30 p.m.
Alumni Hall, Connolly Ballroom

SCOPE AND SCALPEL'S “CIALIS'S WONDERGLANDS”
MAY 21
7 p.m.
May 23
2 p.m.
Hillman Center for Performing Arts
Shady Side Academy
For information:
www.scopeandscalpel.org

ALUMNI BREAKFAST & MEDICAL SCHOOL TOUR
MAY 22
9 a.m.
Scaife Hall

TOURS OF THE NEW CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC
MAY 22
Noon

REUNION GALA
MAY 22
6 p.m.
LeMont, Pittsburgh

CLASS OF 2010 COMMEMORATION
MAY 24
10 a.m.
Carnegie Music Hall

DEPARTMENT OF SURGERY GRAND ROUNDS
MAY 26
“Gut Origin Sepsis—Evolution and Thought”
Edwin Deitch, MD, Speaker
Scaife Hall, Lecture Room 5
www.surgery.upmc.edu

AAMC PITT RECEPTION
NOVEMBER 7
5:30–6:30 p.m.
Washington, D.C.
For information:
412-648-9000
vicedeanstaff@medschool.pitt.edu

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TO FIND OUT WHAT ELSE IS HAPPENING AT THE MEDICAL SCHOOL, GO TO www.health.pitt.edu
Mildred Danch is not one to let the engine idle. Crowned queen of her Youngstown nursing class, she then embarked on a 50-plus-year career as a commercial flight attendant. Lest her jet-setting life lack excitement, Millie kept her scrubs at the ready so she could hop off a plane and into a delivery room for her other job as a maternity nurse. These days, life on the family farm isn’t as hectic, but Millie keeps it lively, zipping around town in her red Corvette. When orthopaedic problems threatened to slow her down recently, she sought out care from Drs. Lawrence Crossett and William F. Donaldson in Pitt’s Department of Orthopaedic Surgery.

Millie doesn’t intend to hit the brakes anytime soon. And she has continued her lifelong commitment to quality health care. With the substantial donations she has pledged in support of the research of Drs. Crossett and Donaldson, she’s helping others keep their prized independence, too.

Consider making a planned gift to the school yourself. It can be directed toward research, scholarships, or other meaningful projects.

For information, please contact:
Clare Flanagan
Forbes Tower, Suite 8084
3600 Forbes Avenue
Pittsburgh, PA 15213
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fclare@pmhsf.org

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