NEXT IS NOW
UNIVERSITY OF PITTSBURGH
SCHOOL OF MEDICINE
2013 ANNUAL REPORT

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and it marks the most disruptive convergence of events since the Flexner Report of 1910 initiated a revolution in medical education. Pittsburgh is poised to make the most of the current moment, in which a trio of rising forces promises to transform health care in this nation: the push for reform (by that, I mean improving quality and lowering cost), informatics (the ability to store and analyze huge troves of data), and an increasingly sophisticated understanding of biology (particularly at the cellular and molecular levels) that is giving us the ability to personalize medicine.

We should welcome these changes because the status quo is unacceptable. Consider how we treat metastatic cancer in adults. With the exception of testicular cancer and choriocarcinoma (a rare tumor of placental origin), chemotherapy isn’t likely to cure cancer at that runaway stage. (In contrast, both childhood cancers and children tend to respond better to chemotherapies.) What happens instead is heartbreaking: Adults with metastatic cancer are offered highly toxic, intensive chemotherapy cocktails. A small number of patients will have a remission, usually not a very durable one. Most will simply get sick from the drugs and spend their last days in the ICU. This is just one example of how modern medicine is off kilter. I could cite many more examples for many diseases.

Imagine if we could identify the genes or other molecular mechanisms that make people responsive to chemotherapy agents as opposed to resistant to them. We would save a great deal of money; more profoundly, we would avoid compromising the remaining quality of life that people have.
What physicians and other scientists intend to do at Pitt—and there are similar efforts at other academic medical centers—is to personalize care. That is, we want to give precisely the right treatment, at the right time, to the right patient. As of January 2013, Jeremy Berg, PhD—former director of the National Institute of General Medical Sciences and a thought leader in biomedicine—heads our new Institute for Personalized Medicine, which you will read more about in the pages of this report. Jeremy has been a member of our faculty since 2011; he serves as Pitt’s associate senior vice chancellor for science strategy and planning and as a professor of computational and systems biology. He takes the reins as the cost of sequencing a genome has trended down to almost $1,000. We expect that sequencing genomes of patients (likewise viruses, bacteria, and tumors) will be routine in the near future.

The University is taking part in a massive project to determine how to use patient data to foster personalized medicine. UPMC (University of Pittsburgh Medical Center) announced in 2012 that it is investing $100 million throughout the next five years in a data warehousing, integration, and analysis project that will bring together clinical, financial, administrative, genomic, and other information. This is a tall order—one of the most ambitious and comprehensive efforts of its kind in health care. (UPMC is partnering with Oracle, as well as IBM, Informatica, and dbMotion in this effort.)

When a patient walks in the door, we want to be ready to say, “You have mutation X, here is therapy Y.” To accomplish this goal, we need to link some crucial patient information—genotype and phenotype. Genotype is what we call the specific molecular signature that reveals peculiarities of a patient’s genome, or inheritable characteristics. A phenotype is the broader description of a person that ends up in clinical records (like diseases endured, medications taken, weight, and family history). This information, of course, may already exist for some patients and research participants. The difficulty lies in getting medical center and research data systems to talk to one other. We and our partners at Pitt and UPMC want to make that happen, but it’s messy work. And without an institutional foundation in place to facilitate the process, physicians and researchers who hope to merge clinical and research data for their studies have the odds stacked against them.

Think silos of data. Data sets that don’t match up. Absent fields. Data that never made it into the digital realm. “Data graveyards.”

Most researchers would just give up. But with Oracle, Pitt’s team of mathematicians, biostatisticians, programmers, informatics and IT experts, genomics whizzes, researchers, oncologists, and other physicians is doing the groundwork to make the linking of genotype and phenotype routine.

We have an extraordinary opportunity in Pittsburgh. Consider the research strength of this University (which shot up to No. 5 in National Institutes of Health research funding a few years ago), UPMC as the largest payer/provider linked to a research university, the technology powerhouse Carnegie Mellon University in the same neighborhood, and corporate technology partners like Oracle and IBM. Then add the secret ingredient: Pittsburghers. Pittsburghers love their town and are more likely to stick around than are folks who live in other biomedical meccas. “In the early days of genetic research, places with stable populations, like Salt Lake City, were the powerhouses,” reminds Jeremy. That stability, he notes, will be “good for a research tool and good for Western Pennsylvania.” And because this stable patient population is so large, we are in an excellent position to make advances in understanding and treating the diseases that arise within it.

Jonas Salk’s son, Peter, has said that the Salk polio vaccine could have been called the Pittsburgh, or Pitt, vaccine. And according to some, Dr. Salk would have wanted it that way. In the 1950s, Pittsburgh scientists, practitioners, and community members (including thousands of children) literally rolled up their sleeves to make history.

Welcome to the next Pittsburgh moment.

ARTHUR S. LEVINE, MD
Senior Vice Chancellor for the Health Sciences and John and Gertrude Petersen Dean of Medicine
When the steel industry collapsed decades ago, the outlook was bleak. Unemployment peaked at 18.3 percent in Pittsburgh in 1983 and reached as high as 25 percent elsewhere in the region. Thousands of people left, never to return.

Prospects are much brighter today for Pittsburgh, a city that hosted global decision makers during the G20 economic summit in 2009 and the next generation of international leaders during the One Young World Summit in 2012. Many of Pittsburgh’s newcomers are young, bolstered by 36,000 graduates from regional colleges and universities every year who contribute to one of the nation’s most educated workforces, according to the Pittsburgh Regional Alliance.

Among other recent accolades, The Economist rated Pittsburgh’s as the fifth best performing economy in the U.S., National Geographic Traveler named the city one of the world’s top 20 places to visit in 2012, and Departures included it as one of only two U.S. cities listed as an “Under the Radar Cultural Destination.” The Wall Street Journal, meanwhile, calls Pittsburgh “the standard-bearer for urban revitalization” and celebrates its arrival as “a city of cool.”

Augmenting the city’s winning strategy are three major professional sports franchises, more than 500 arts and cultural organizations, and the recent completion of the Great Allegheny Passage, a scenic 300-plus-mile rail-trail bike path that connects the city to Washington, D.C.

Another Pittsburgh Renaissance

Pittsburgh, known for its bridges, idiosyncratic speech, and sports fans, is gathering some fans of its own.

“Is Pittsburgh the New Portland?” blogger Jim Russell asks in Pacific Standard magazine, neatly upping the city’s coolness quotient in a few words. “Pittsburgh is thriving,” writes Russell, a geographer who maintains “Burgh Diaspora” and other blogs. “As the economy recovers, I argue that Pittsburgh is the place to be.”

Judging by a growing collection of national and international kudos, many people agree. Pittsburgh tops a list of 10 cities in Sperling’s Best Places to Relocate in America and comes in 11th in the latest analysis of America’s 50 Best Cities on Businessweek.com. MSN Money cites the region’s multifaceted economy, led in large part by Pitt, UPMC, other “eds and meds,” and an expanding energy sector. “Pittsburgh’s gross domestic product has increased by roughly $10 billion in the past five years,” MSN says, calling Pittsburgh a boom town in the making.

The Allegheny Conference on Community Development estimates that Pittsburgh’s health services sector employs more than 190,000 people and rests on a foundation of life sciences research, biomedical innovation, lifesaving technologies, and advances in medical devices, regenerative medicine, and pharmaceuticals.

“It’s all a result of a lot of hard work by a lot of people over the course of a generation,” says Bill Flanagan, Allegheny Conference executive vice president of corporate relations. “Our region’s been reimagined and remade.”
Two Elected to Institute of Medicine

Two faculty members of the School of Medicine have been elected to the Institute of Medicine (IOM), an honor that is considered among the highest in the field. They are Michael Boninger, MD, Professor and chair of Physical Medicine and Rehabilitation (PM&R); and Jennifer R. Grandis, MD, Distinguished Professor of Otolaryngology and UPMC Professor of Head and Neck Surgical Research.

Boninger, who is also director of the UPMC Rehabilitation Institute and a physician-scientist at the VA Pittsburgh Healthcare System, is known for his research on technologies to improve the lives of individuals with spinal cord injury and other disabilities. His work has been in the field of brain-computer interfaces; he is part of a Pitt-UPMC team that is enabling people with spinal cord injury to control devices through thought (see page 46).

Boninger earned his engineering and medical degrees from Ohio State University and completed a residency at the University of Michigan before joining the Pitt faculty in 1993 as an instructor in what was then the Division of PM&R — now a department that he chairs.

Grandis, who earned her MD at Pitt in 1987 and finished her fellowship, residency, and internship training at Pitt, also joined its faculty in 1993. She was elected to the American Society for Clinical Investigation in 2002 and the Association of American Physicians in 2010. In 2012, Grandis was appointed to a five-year term on the Board of Scientific Counselors for the National Institute of Dental and Craniofacial Disorders and received the Alton Ochsner Award Relating Smoking and Disease.

Her research efforts focus on understanding factors that contribute to the development and spread of squamous cell cancer of the...
head and neck and developing targeted therapies against the disease. Currently, her laboratory is investigating STAT3 (signal transducer and activator of transcription 3) as a potential therapeutic target, as well as other combined molecular approaches.

IOM was established in 1970 as the health branch of the National Academy of Sciences. Current IOM members select new ones from the health sciences, medicine, and public health in a rigorous process; and election requires a commitment to volunteer on boards and in other activities IOM carries out in its role as an independent, science-based advisor on health issues.

Scientists Get Satisfaction at Pitt

The University of Pittsburgh has been ranked as the top university in the United States—and fourth among all institutions nationwide—in The Scientist magazine’s 11th annual “Best Places to Work in Academia” survey. Assessment criteria included job satisfaction, peers, infrastructure and environment, research resources, pay, and tenure and promotions. Scientists were also asked to describe what they most value about their work, as well as to give suggestions for improvement. Among Pitt strengths noted in this year’s survey were institutional infrastructure and support. Survey results make clear that Pitt is gaining a global reputation as a preferred place to do pioneering research.

SIMULATION CENTER GETS RARE ACCREDITATION

The University of Pittsburgh Department of Anesthesiology’s Peter M. Winter Institute for Simulation, Education, and Research (WISER) has been accredited for teaching, assessment, and research and systems integration by the Society for Simulation in Healthcare (SSH) Council for Simulation Program Accreditation. WISER is the first civilian simulation program—and only the second program in the world—to achieve recognition that it meets the highest standards in all four accreditation focus areas offered by the SSH program.

“The leadership at Pitt and UPMC has long recognized the importance of simulation in the training and education of health care providers,” said Paul Phrampus, MD, WISER director. At WISER, students and seasoned health care professionals are able to work with computerized training mannequins programmed to replicate a vast array of medical situations. More than 100 different training programs, many of which focus on patient safety, are offered there.

Pitt Adds Two “Young Turks”

Among the School of Medicine’s 2013 inductees into the prestigious American Society for Clinical Investigation (ASCI) are Janet S. Lee, MD, associate professor of medicine (Division of Pulmonary, Allergy, and Critical Care Medicine [PACCM]) and Alison Morris, MD, MS, associate professor of medicine (PACCM), of immunology, and of clinical and translational science.

Members of ASCI, an organization of more than 2,800 physician-scientists who have achieved notable success relatively early in their careers, are known as Young Turks. Lee and Morris join 48 other Pitt colleagues on its membership rolls.

Founded in 1908, ASCI is a medical honor society with a clear preference for celebrating up-and-coming scholarly achievement in biomedical research. New members must be 45 or younger at the time of their election.
In Pursuit of Precision Medicine

A transformation is underway in biomedical science. Known as personalized or precision medicine, it is a revolution for which Jeremy Berg, PhD, associate senior vice chancellor for science strategy and planning, health sciences, believes the University of Pittsburgh is uniquely prepared.

“I think the attractive thing about personalized medicine in Pittsburgh is that it really can be approached soup to nuts,” says Berg, newly appointed director of the Institute for Personalized Medicine, a joint program of the University of Pittsburgh Schools of the Health Sciences and UPMC. “It spans from very basic research through to things on the UPMC side that are potentially very deep into implementation.”

For example, a unique drug combination could be the best bet for a few cancer patients, based on what’s in the DNA of their tumors. Historically, those few would get the treatment that seemed to do the most good for the majority of people, even if it might be less effective for them individually. Today, potential opportunities to customize care continue to arise from biomedical advances in proteomics, metabolomics, pharmacogenomics, and other emerging technologies.

“The issues are getting personalized medicine into the real world and taking advantage of the information to try to make people’s lives better,” says Berg, who came to Pitt in 2011. “It’s a whole new way of thinking in many cases; but from my perspective, that’s what’s exciting about it.”

The complete human genome was sequenced just 10 years ago, a limited time in terms of scientific investigation. Future research questions touching personalized medicine — scientific, medical, ethical, and those of public policy — continue to increase exponentially.
A virtual entity for now, the Institute for Personalized Medicine will find a permanent home in the Center for Innovative Science, a $300 million, 350,000-square-foot research center UPMC plans to develop on the site of the former Ford Motor Co. Building on Centre Avenue.

“For diseases like cancer, we will identify the genetic and environmental factors that determine the susceptibility of each individual and the best course and type of treatment,” says Steven D. Shapiro, MD, UPMC executive vice president and chief medical and scientific officer. “This major investment in good science will help us to develop the personalized treatments necessary to improve the effectiveness of health care.”

The institute also ties in with UPMC’s five-year, $100 million investment in a sophisticated data warehouse and enterprise analytics effort involving high-tech partners Oracle, IBM, Informatica, and dbMotion (see page 6). “This comprehensive analytics project will enable us to treat each patient in a personalized way,” says Shapiro.

“One of the poster children for personalized medicine is Gleevec, a drug that really transformed treatment for chronic myelogenous leukemia,” says Berg, explaining that the vast majority of these patients have essentially the same gene mutation. “Now, almost all respond to this relatively well tolerated drug, and many of them seem to be functionally cured.”

Determining appropriate personalized treatments for patients with most other cancers will be far more challenging because of heterogeneity — not only among patients with the same cancer diagnosis, but within the same patient, and even, in some cases, within the same tumor.

Big data, including electronic health records and DNA sequences, is meant to tackle these kinds of challenges — and the combined forces of Pitt and UPMC are ready, says Berg.

BERG SEES CATALYST ROLE FOR INSTITUTE FOR PERSONALIZED MEDICINE

These days, marshaling resources to advance personalized medicine research is a major objective for Jeremy Berg, PhD, associate senior vice chancellor for science strategy and planning, health sciences, and founding director of the Institute for Personalized Medicine. The institute will apply new knowledge in genetics, genomics, and other disciplines to promote and develop evidence-based medicine. Considerable talent and support are available now, not only at Pitt, but also through strategic alliances with academic institutions and industry within the region and around the world, Berg noted.

“There are some pilot projects already underway and more under discussion,” added Berg, former director of the National Institute of General Medical Sciences (NIGMS), part of the National Institutes of Health.

At NIGMS, he oversaw a $2 billion budget that primarily funded basic research in cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, bioinformatics, and computational biology, as well as clinical areas related to trauma and burn injury, sepsis, and wound healing.

“We are in the early stages of one of the most important journeys in modern medicine,” said Berg, who is also professor of computational and systems biology.

A world-renowned bioinorganic chemist, Berg investigates the processes by which biomolecules interact with one another inside cells using both experimental and computational methods.

Prior to his appointment at NIGMS, he directed the Institute for Basic Biomedical Sciences at Johns Hopkins University School of Medicine, where he also served as professor and director of the Department of Biophysics and Biophysical Chemistry. Berg received BS and MS degrees in chemistry from Stanford University and a PhD in chemistry from Harvard University. He is the author or coauthor of more than 150 research papers and seven textbooks.

Berg’s many professional honors include being named a fellow of the American Association for the Advancement of Science (2007); receiving the Distinguished Service Award from the Biophysical Society (2009) and the American Chemical Society’s Public Service Award (2011); and election to the Institute of Medicine of the National Academy of Sciences (2010). He currently serves as president of the American Society for Biochemistry and Molecular Biology.
Noted Lupus Researcher Named Immunology Chair

Mark J. Shlomchik, MD, PhD, a former Yale immunologist renowned for his contributions to the understanding of the autoimmune disease systemic lupus erythematosus and immune system antibody memory, has been recruited to lead the Department of Immunology in the University of Pittsburgh School of Medicine.

Shlomchik succeeds Olivera J. “Olja” Finn, PhD, Distinguished Professor and founding chair of immunology, who is continuing her research into peptide vaccines against pancreatic and colon cancers at Pitt. Shlomchik joined the faculty as professor of immunology and of pathology on July 1, 2013.

“Dr. Shlomchik has been very widely recognized for his research achievements,” said Arthur S. Levine, MD, senior vice chancellor for the health sciences and Petersen Dean of Medicine. “His research interests spanning basic to translational immunology mesh well with the institutional strengths of our immunology department and put him in a good position to further build them.”

While Shlomchik’s primary responsibility is departmental leadership, he also works closely with colleagues whose interests bridge various aspects of immunology, including those associated with the Thomas E. Starzl Transplantation Institute, the Center for Vaccine Research, and the University of Pittsburgh Cancer Institute.

With respect to lupus, a chronic autoimmune disorder that affects about 5 million people worldwide and causes inflammation and tissue damage to any organ system in the body, Shlomchik was among the first to elucidate the roles of B lymphocytes and toll-like receptors in promoting disease. Both are now targets of drugs that are either approved or in development to treat autoimmune disorders. In an October 2012 publication in Science Translational Medicine, Shlomchik and colleagues demonstrated that the enzyme complex NADPH oxidase (NOX), which plays an important role in the body’s resistance to bacteria and fungi, is also necessary to curb genetic predisposition to lupus. In addition to autoimmunity, B-cell immune responses, and how vaccines elicit protective antibodies, Shlomchik has worked on bone marrow transplantation, where some of his findings are currently being tested.

“Pitt has wonderful resources and people, and I look forward to working with faculty to broaden and deepen immunology research,” said Shlomchik, adding that his long-term goal is to positively affect disease therapy and prevention efforts.

In May, Shlomchik was selected as the first recipient of the Lupus Insight Prize, a $200,000 award given jointly by the Alliance for Lupus Research, Lupus Foundation of America, and Lupus Research Institute. The award will fund investigations into the connection between lupus and the death of neutrophils, the body’s most abundant white blood cells.

Shlomchik received his medical and doctoral degrees in 1989 from the University of Pennsylvania, where he also completed residency training in pathology and laboratory medicine. After postdoctoral work at Fox Chase Cancer Center in Philadelphia, he joined the faculty of Yale University, serving most recently as professor of laboratory medicine and of immunobiology.
Q & A with Olja Finn

After 12 years as founding chair of the Department of Immunology, Dr. Finn is stepping down but not slowing down.

Q: How have things changed for women in science over the course of your career?

FINN: It’s different from place to place. We had an amazing change in the School of Medicine when Art Levine came—he was actually the first dean who, while perhaps not setting out to make a statement, supported women in a gender-blind way. He was interested in quality and scientific integrity. When Art came, about 15 years ago, he wanted to start a Department of Immunology, and he appointed me as the founding chair. So I was the first female basic science chair in the history of the School of Medicine.

Almost simultaneously, he appointed Jeanette South-Paul to the Department of Family Medicine, and she was the first woman to chair a clinical department. He started a new Department of Computational and Systems Biology and appointed Ivet Bahar as chair. Art reaches out to get the best, and often if you throw that hook you’re more likely to catch a woman than a man. Angela Gronenborn was appointed chair of structural biology, and Susan Amara as chair of neurobiology. So, we went from having no women chairs, to four [of seven] basic science and two clinical departments chaired by women. You ask whether things have changed for women—it is still critical to have an advocate, preferably one like Art, who is gender-blind.

Q: How has immunology changed since the department was founded?

FINN: There’s a lot of immunology on campus. It’s central to a lot of things that we do, both in basic research and in the clinic. But before there was a department, researchers worked without any particular focus and without any special resources to add to the development of new ideas in immunology.

I took the chair position to organize things so that much more could be accomplished and immunology would be front and center in the School of Medicine. There has been so much growth in basic immunology that we had to make sure we had faculty representing new developments. The way you do that is to hire junior faculty who are at the cutting edge of immunology research. You need a department for this.

Q: Other medical schools don’t have departments of immunology?

FINN: Some do, but many don’t. Immunology tends to be spread out because it has so many applications. The minute we became a department (we started with five faculty but are now 14, with 56 secondary appointments), other chairs would say, “Maybe we could do this with Immunology.” Having a department has become a wonderful recruitment tool—every basic science or clinical department that hires faculty with an interest in immunology can offer a secondary appointment in our department. And, having a department has created a community. Once a year we get together for a retreat that more than 170 people attend, and both faculty and students enjoy belonging to a community.

Q: What will stepping down as chair allow you to do that you can’t do now?

FINN: Nothing [she laughs]. But it will allow my department to do a lot more. You need to stay on the cutting edge by having new ideas, new visions, and new blood. You need new leadership for that. Over the past 12 years, I have given this department everything I had in terms of my ideas, where I think we should go, and I think I’ve completed my mission. As a professor in the Department of Immunology, I’m going to do a lot better with a chair who has a new vision and new resources. As chair, I was a science cheerleader. I’m ready for another cheerleader from whom I can benefit.

Q: Is there anything you will miss when you step down?

FINN: Hmmmm… telling people what to do [she laughs again]. I don’t know, I will have to see. It was never my goal to chair a department. I was devoted to the community of immunologists here at Pitt. The community is very close, very collaborative, and very supportive of each other. If I were to leave, I would just miss the people.

Q: If you could have done anything differently in your own career, what would it be?

FINN: Knowing what I know now, I might have gone for an MD/PhD degree because I am so interested in translating the science to the clinic. I have to get a clinician to buy into my vision, and this takes a lot of time—the clinician has to be a special person. It was always my impression that somehow I could have short-circuited this aspect if I had prepared myself for the clinical arena as well.

I’ve been lucky, I’ve found incredible clinical collaborators who have bought into my vision and supported me, and given me the opportunity to influence what they did in the clinic. Early on these included Michael Lotze and Ramesh Ramanathan. My most recent wonderful collaborators are Rocky Schoen, Benny Weksler, and Randall Brand. I am deeply indebted to these colleagues.

Q: Any final thoughts you’d like to share?

FINN: The School of Medicine is an incredibly caring place. There are very few places that are as well known and accomplished as the University of Pittsburgh School of Medicine. The morale has always been high because you feel that you are important to your community. I have tried to maintain this attitude in the department—a team goes farther than an individual. There is no room for prima donnas. As times get tougher, we need to maintain this morale rather than worry too much about funding because people are the strength of this institution.
Congratulations, Mr. President

David A. Lewis, MD, UPMC Professor of Translational Neuroscience and chair of the Department of Psychiatry, has been elected president of the American College of Neuropsychopharmacology (ACNP), an honor that acknowledges his contributions to mental health research and practice.

An internationally recognized expert in the fields of psychiatry and neuroscience, Lewis directs the University of Pittsburgh Translational Neuroscience Program and the National Institute of Mental Health–sponsored Conte Center for the Neuroscience of Mental Disorders. The Conte Center is focused on understanding the role of prefrontal cortical dysfunction in the pathophysiology of schizophrenia.

Lewis earned his MD at Ohio State University and completed additional training at the University of Iowa, where he was chief resident in internal medicine and psychiatry. Among his many honors, Lewis is a member of the Institute of Medicine.

Founded in 1961, ACNP promotes communication among researchers in a range of scientific disciplines of brain and behavior to increase the understanding of the causes of nervous system disorders.

Zeh Is New ACGT Investigator

The Alliance for Cancer Gene Therapy (ACGT) has named Herbert Zeh III, MD, associate professor of surgery, its 2012 ACGT Investigator. The $500,000 award allows him to continue his promising investigations into using genetic and immunotherapy approaches against pancreatic cancer.

“I am honored to receive this generous award from ACGT,” said Zeh, who is also principal investigator on four pancreatic cancer-focused trials and is chief of the Division of Gastrointestinal Surgical Oncology, UPMC CancerCenter. “It is my hope that my research will bring the medical community one step closer to beating pancreatic cancer.”

Zeh directs a translational research laboratory examining damage associated molecular pattern (DAMP) molecules in the setting of pancreatic cancer. New ACGT-funded studies will use a modified virus to produce hormones that attract tumor-fighting T cells that kill cancer and protect against potential recurrence.

Medical Alumni Association Honors Pollack

Ian F. Pollack, MD, A. Leland Albright Professor of Children’s Neurosurgery, has received the University of Pittsburgh Medical Alumni Association’s William S. McEllroy Award for 2013.

The McEllroy Award is presented annually to an outstanding non-alumnus who completed residency training at UPMC. The association also presents an award named for Pitt alumnus and Nobel Laureate Philip S. Hench, MD, ScD, to honor an outstanding graduate of the medical school. (To read about 2013 Hench awardee Johanna M. Seddon, MD, see page 76.)

Pollack, who completed a neurological surgery residency at the University of Pittsburgh in 1991, is an expert in pediatric neurosurgical care and noted researcher. He leads numerous National Institutes of Health–funded investigations to evaluate possible biomarkers for brain tumor prognosis and develop novel treatments. He codirects the University of Pittsburgh Cancer Institute’s Brain Tumor Program and is chief of pediatric neurosurgery at Children’s Hospital of Pittsburgh of UPMC.

The award honors the accomplishments of William S. McEllroy, MD, dean of the School of Medicine from 1938 to 1958, who vigorously pursued funding for research programs and recruited eminent scientists like Benjamin Spock, MD, and Jonas Salk, MD.

Under McEllroy’s guidance, the University established specialty residency programs, acquired Western State Psychiatric Hospital (now Thomas Detre Hall of Western Psychiatric Institute and Clinic of UPMC), and constructed Scaife Hall as a state-of-the-art home for the medical school.
could be as portable and easy to use as a standard ophthalmoscope,” said Schuman, who holds the Eye and Ear Foundation Chair in Ophthalmology.

In addition to Schuman, the prize-winning team includes engineers and researchers from the Massachusetts Institute of Technology and the Keck School of Medicine at the University of Southern California.

**Newest Pitt AAAS Fellows Named**

Pitt faculty members who were elected to fellowship in the American Association for the Advancement of Science (AAAS) for 2012 are Bruce A. Freeman, PhD, UPMC Irwin Fridovich Professor and chair of the Department of Pharmacology and Chemical Biology, and Valerian Kagan, PhD, DSc, professor and vice chair of the Department of Environmental and Occupational Health, Graduate School of Public Health.

Selected for their significant scientific contributions, Pitt's honorees are among 702 new AAAS fellows elected in 2012.

Freeman is known for his research on the biochemical links between oxygen radicals (like superoxide, hydrogen peroxide, and nitric oxide [NO]) and NO-dependent cell signaling, as well as how those interactions influence cell and organ function. He has authored more than 200 publications in peer-reviewed journals, 61 book chapters, and numerous invited reviews.

Kagan, who has secondary appointments as professor of pharmacology and chemical biology and of radiation oncology in the School of Medicine, has been honored for his distinguished contributions to the fields of free radical biology, medicine, and apoptosis.

His research is focused on molecular mechanisms of oxidative stress, antioxidants, tissue and cell acute and chronic injury, and nanotoxicology. Kagan’s team conducts novel investigations surrounding oxidative lipidomics—the study of lipids and their oxidation. He has published more than 500 peer-reviewed papers.

**SICKLE CELL DISEASE, RYAN CLARK’S CURE LEAGUE IS CALLING YOU OUT.**

In partnership with the University of Pittsburgh’s Heart, Lung, Blood, and Vascular Medicine Institute (VMI), UPMC, and the Institute for Transfusion Medicine, Pittsburgh Steelers safety Ryan Clark announced his namesake initiative in 2012. The Ryan Clark Cure League aims to raise awareness of and support for Pitt research to develop better treatments and, one day, perhaps a cure for the genetic disorder that distorts oxygen-carrying red blood cells into a sickle shape, with crippling, potentially fatal ramifications.

Clark, who forfeited his spleen, gall bladder, 35 pounds, and much of the 2007 football season to an altitude-related sickle cell crisis in Denver, knows the danger. One of Clark’s sisters-in-law died from complications of sickle cell disease.

“We have only one drug, one FDA-approved drug. We’re hoping we can be pioneers here.”

An estimated 2 million Americans carry one copy of the sickle cell gene. The disease results when two copies of the gene are inherited and can cause severe pain, anemia, stroke, organ damage, and death.
**Berg Hits a Double**

**Wendie Berg, MD, PhD,** professor of radiology, has been honored twice by the radiology Web site Aunt Minnie, a comprehensive Internet forum for radiologists and related professionals in the medical imaging industry.

For the second time since 2010, the organization has named Berg its “Most Influential Radiology Researcher.” A manuscript on which she was first author, “Detection of Breast Cancer with Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women with Elevated Breast Cancer Risk,” published in the *Journal of the American Medical Association* in April 2012, was also recognized as the site’s “Scientific Paper of the Year” for 2012.

The study found that, for women with increased risk of breast cancer and those who have dense breasts, adding ultrasound or MRI to annual mammography screening improved cancer detection rates but also led to an increase in false-positive findings.

Additionally, Berg has been named a 2012 Global Breast Cancer Medical Advancement Champion by the Avon Breast Cancer Crusade, a program of the Avon Foundation for Women, and an honorary fellow of the Austrian Roentgen Society.

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**Society Honors Whiteside**

**Theresa L. Whiteside, PhD,** has received the Society for Immunotherapy of Cancer’s 2012 Richard V. Smalley, MD, Memorial Award for outstanding research, work, and achievements in cancer therapy.

Whiteside is professor of pathology, of immunology, and of otolaryngology, as well as a member of the University of Pittsburgh Cancer Institute. Her research interests include tumor immunology and immuno-therapy, with special focus on mechanisms of tumor-induced immunosuppression, cytokine networks, development of anticancer vaccines, immunology of human head and neck cancer, and the role of natural immunity in the control of cancer progression.

Established in 1984, the society has an international membership that includes representatives of 17 medical specialties who are engaged in research and treatment of at least a dozen types of cancer.

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**Faculty Receive Carnegie Science Awards**

Among University of Pittsburgh faculty honored during 2012 with Carnegie Science Awards were **Nancy J. Minshew, MD, professor of psychiatry,** and **David A. Vorp, PhD,** William Kepler Whitford Professor of Bioengineering and associate dean for research, Swanson School of Engineering.

Minshew, who is also director of the Center of Excellence in Autism Research, received the Catalyst Award, which recognizes individuals whose work generates widespread public awareness and scientific influence. For more than 25 years, Minshew and her research team have focused on the cognitive, brain, and behavioral basis of autism and, more recently, on the condition’s underlying genetics and neurobiological mechanisms.

Vorp, who has secondary appointments in the Departments of Cardiothoracic Surgery and Surgery, School of Medicine, received the Life Sciences Award, which honors scientific advances in new and innovative biomedical and life sciences endeavors. His research on aortic aneurysm modeling has dramatically changed the way clinicians view the disorder, while his approach to tissue-engineered arteries may one day change surgical protocols for arterial bypass procedures.

Established in 1997 by the Carnegie Science Center, the Carnegie Science Awards recognize and promote innovation in science and technology across Western Pennsylvania.

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**Sports Medicine Society Taps Harner**

**Christopher D. Harner, MD, Blue Cross of Western Pennsylvania Professor of Orthopaedic Surgery,** has been installed as president of the American Orthopaedic Society of Sports Medicine (AOSSM) for 2012–13.

“He is a world leader in sports medicine, and being elected to this office proves it,” said Freddie Fu, MD, DSc (Hon), DPS (Hon), Distinguished Service Professor, David Silver Professor, and chair of the Department of Orthopaedic Surgery (himself an AOSSM president in 2008–09). “He has been instrumental in the rise of the sports medicine program here.”

Harner earned his MD from the University of Michigan in 1981 and joined the University of Pittsburgh faculty in 1987.

One of the first U.S. surgeons to perform meniscus transplants in the early 1990s, he has been recognized with several international awards and grants for clinical research. He served as a team physician at Pitt for 25 years and currently serves as head team physician for the Pittsburgh Penguins. In addition, he is medical director of the UPMC Center for Sports Medicine and director of the Sports Medicine Fellowship Program.

Formed in 1972, AOSSM promotes sports medicine research and education and works to improve the identification, prevention, treatment, and rehabilitation of sports injuries. Among the society’s 3,000 members are orthopaedic surgeons, physicians, athletic trainers, physical therapists, and other allied professionals.
WORKS IN PROGRESS

In the last few years, if you’ve read anything about the Diagnostic and Statistical Manual of Mental Disorders (DSM), the psychiatry manual (some would say “bible”), it probably hasn’t been good. The pharmaceutical industry isn’t making new drugs for psychiatric illness, say the blogs, because they can’t find targets, and that’s the DSM’s fault. The normal range of human emotion is getting all mushed up with disease and causing overprescription of potentially toxic treatments, say the editorials, and that’s the DSM’s fault. The response around the latest version, DSM-5, is even less popular.

“Did you see that one in The New York Times? They’re blaming [higher rates of ADHD diagnosis] already on DSM-5. It hasn’t even been published!” says David Kupfer, MD, sitting in his office on the second floor of Western Psychiatric Institute and Clinic of UPMC on a late afternoon in April 2013, just weeks before the culmination of the massive document-revision effort that he has tended to, around the clock, “like an emergency physician,” since 2006.

Kupfer, 72, Thomas Detre Professor of Academic Psychiatry, is tall and wiry with a warm smile, a welcoming presence, and, typically, a sharp suit. It’s fitting that, in a 2004 story about the process of applying for competitive federal research funding, The Wall Street Journal characterized him as a “salesman,” even though that’s not a word you’d expect to hear when the subject is a professor. But this particular academic’s claim to fame is building the once-minuscule research herd of the University of Pittsburgh’s Department of Psychiatry into one of the largest and most prominent in the country — a feat that took no small amount of combined persuasive power and business smarts.

Weighing heavily on Kupfer’s mind, and on the minds of the 160 members of the task force and work groups that he led through the DSM revision process, is the fact that the diagnostic criteria listed in the DSM are the bases for Medicare and Medicaid reimbursements. There are financial implications, treatment implications, and social implications. Hence, Kupfer made the revision process of the DSM-5 more transparent than any of its predecessors, putting the draft out to the public three times. Some 13,000 comments were posted online, and the task force and work groups read every one.

There has been tremendous outcry from patient advocacy groups, the pharmaceutical and insurance industries, the media, and the public. Members involved in drafting the previous DSM edition have written scathing commentaries and made the rounds of talk shows. At times, it’s gotten pretty ugly.

“He listens extremely well,” says James Scully Jr., MD, medical director of the American Psychiatric Association, which publishes the DSM. “He’s calm in the face of everybody lighting their hair on fire.”

Many of the concerns are well intentioned: What of the Asperger’s community? These people have fought hard for acceptance and understanding. Now Asperger’s is being stricken from the manual altogether. What of the bereaved, who are no longer explicitly excluded from the criteria for clinical depression? Will we be doling out antidepressants to everyone who loses a loved one, medicalizing a natural reaction to a horrible life event?

It’s complicated. But that should be no surprise. The brain is the most complicated organ in the body. It’s arguably the most complicated thing on earth. Psychiatry is still in an adolescent stage. For all the promising research — in genetics, imaging, and cognitive neuroscience — scientists are still grasping for biologically based diagnostic measures they can use with sensitivity and specificity.

Kupfer says that when he started this process, he honestly thought the DSM-5 would have a firmer foothold in science. Alas, the science isn’t there yet. But he’s confident that it’s coming. His hope is that the new DSM will help to nudge psychiatry, finally, into its rightful place — as a branch of medicine grounded in understanding, in evidence, and in measurable outcomes.

This has been an obsession of his for more than 40 years.

To read the full profile of and interview with David Kupfer and to learn more about the DSM-5, read the Summer 2013 issue of Pitt Med at http://pittmed.health.pitt.edu/Summer_2013/index.htm.
WANT TO SEE THE FUTURE?
LOOK TO PITTSBURGH.
PMC chief medical and scientific officer and professor of medicine Steven D. Shapiro, MD, was in Washington, D.C., to take part in a conference on the future of health care when one of the first speakers said, “Want to see the future? Look to Pittsburgh.” Shapiro jokingly looked around the room and wondered, “Well, what am I doing here, then?” He knew that a prime reason the speaker pointed to Pittsburgh was the combination of payer and provider in UPMC. With an insurance plan and the region’s top hospital system, UPMC has great incentive to address the primary objectives in American health care today: improved systems of health care delivery, reduced cost, and better outcomes—all of which happen to be in the best interests of the patient and the nation.

When Shapiro told this story, he was speaking to the future of health care in America, in a sense. The School of Medicine’s Class of 2013 was seated in the tiered rows of Lecture Room 6 of Scaife Hall on a late winter morning for a special, half-day course called, “Practicing Medicine—What Awaits You?” After four years of gaining clinical skills and core biomedical knowledge, these physicians-to-be were ready to think about where the rubber meets the road. The questions they would explore that day would challenge them to think systematically about where the health care system breaks down and to be creative to make it work for their patients. There was a sense of urgency and purpose in the room that day; in roughly six weeks’ time, each student would—with some combination of eagerness and trepidation—tear open an envelope containing a residency match letter to learn where he or she would spend the next few years of medical training.
Sitting and swinging his legs from the lip of the stage was one of the course directors—Loren Roth, MD, MPH, Distinguished Service Professor of Psychiatry and associate senior vice chancellor for clinical policy and planning, health sciences. He was clearly enjoying the lively give-and-take between Shapiro and this next crop of young physicians. As Roth pointed out the relevant facts of Shapiro’s background—a practicing pulmonologist in a health system’s leadership position—he explained to the students exactly why they were present today: “If you have no interest in these matters, you will practice medicine under policies shaped by others.”

Students rotated through three roundtable discussion groups in the morning. Each included around a half-dozen students and was led by a practicing faculty clinician. Exploring case studies with some of their clinical mentors, students were drawn into the sorts of scenarios they would navigate as new MDs. “This is the sort of nuts-and-bolts that not all med students get,” said one. “You can’t learn it in the first few years of med school, but it’s important for us to start thinking about it as we prepare for residency.”

In a discussion of cost control, Mark Roberts, MD, MPP, professor and chair of health policy and management, Graduate School of Public Health, and professor of medicine in the School of Medicine, asked the students how it can be that, in the United States, public health declines as costs escalate. “More specialists equals more referrals,” noted one student. “But is that always for the best?”

Roberts relayed a story about his patient who played on the Homestead Grays baseball team in the 1940s. “The guy knew Satchel Paige and Jackie Robinson! He got bronchitis when he was 99 years old, and an intern noted an elevated PSA [prostate specific antigen] level on his chart. Urology wanted to biopsy his prostate. I called them and said, ‘If you touch him, I will kill you.’” A lively discussion ensued exploring the benefits and risks of screening and the importance of understanding and respecting a patient’s wishes.
Down the hall, a cold rain tapped on the windows as Ateev Mehrotra, MD, MPH, MSc, associate professor of medicine, led an engaging discussion with seven med students. Mehrotra, a hospitalist and RAND Corporation health policy researcher (recently relocated to Harvard Medical School), shared details of a care and financing agreement between a health plan and a large primary care practice. The students explored how to improve health care delivery and patient compliance under the agreement. Would hiring a nutritionist and a communications director lead to healthier patients? Would it lead to savings through fewer hospitalizations and office visits?

“What would you do under this contract?” Mehrotra asked. “How are you going to stay in business?”

“It doesn’t seem fair. Physician pay is based on compliance,” a student said.

“Well, you’re not treating robots,” another replied. “If the outcome is poor, then you’re doing it wrong.”

Roth circulated through all of these sessions, offering context and war stories where he could and hauling two thick binders of course material under one arm. In one of the final sessions of the morning, Melissa McNeil, MD, MPH, professor of medicine and a perennial favorite of the students among their clinical instructors and mentors, offered some wisdom on the case of a 75-year-old man with hypertension, coronary artery disease, and congestive heart failure. Seven days after discharge, he was readmitted after neglecting his medications, eating bags of potato chips, and failing to monitor his fluid intake and weight.

“You have to get past, ‘The patient won’t comply,’” says McNeil. “Why did the patient do this? Did he know the cost in calories?” Then she raised related questions: “How do you bridge the hospital and home? What do you most want to monitor in a heart failure patient?”

“Weight,” ventured a student.

“Absolutely,” said McNeil. “What if the system paid for a scale in the home?”

As the morning sessions drew to a close before lunch, one student sat back from the table and said, “You know, the timing of this is just right. We still have some time in training because we’ll be residents for a few years. But this gives me a sense of the things I need to keep in mind and educate myself about.”
At the University of Pittsburgh, new medical students are still settling in when they first interact with real patients—an experience they frequently describe as moving, profound, and inspiring. It happens during the “Introduction to Being a Physician” course, which is also a powerful reminder—even to experienced faculty clinicians—of what it is to be a physician.

The course focuses on the patient experience of living with chronic disease. It begins with brief, educational overviews of specific disorders, followed by doctor-patient interviews conducted in front of the class. Students then disperse into small groups, where they engage in conversations with patients who volunteer to discuss their experiences living with chronic disease.

Patients with cystic fibrosis and HIV describe the lengths they go to in order to live normal lives, despite the obstacles they face. Another discusses how diabetes affects every aspect of her life. A mother holds her 15-month-old daughter and recalls what it’s like to have a doctor inform her that her newborn has Down syndrome.

Afterward, students report their surprise at how early in their medical training they are viewed as medical trainees who can be trusted with confidential and deeply personal information. They leave the course highly motivated and with a greater sense of purpose in becoming physicians.

The course is just one element of an important goal of the Pitt medical curriculum—an early introduction to the patient and the community. Other notable features include a scholarly research requirement, extensive opportunities to work with high-tech patient simulators, and regular encounters with standardized patients—actors specially trained to present realistic and consistent behavior, symptoms, and medical histories in simulated doctor-patient interactions.
Medical Education Awards
The Office of Medical Education (OMED) works to implement curricular refinements and innovations, as well as to provide instructional support to faculty and academic support to students. OMED also recognizes and rewards excellence in medical education. Awards given in 2012 included the Distinguished Service in Medical Education Award—a special recognition that, rather than being given annually, is given only as warranted. This award was presented to Kathleen D. Ryan, PhD, assistant dean for medical education and associate professor of cell biology. The award, the highest honor in medical education given by the School of Medicine, recognizes Ryan’s contributions over more than 10 years of service.

Other OMED awards given in 2012:

Kenneth E. Schuit Award, Recognizing the Dean’s Master Educators
Melissa A. McNeil, MD, MPH, Professor of Medicine
Christine Milcarek, PhD, Professor of Immunology

Sheldon Adler Award for Innovation in Medical Education
Larisa J. Geskin, MD, Associate Professor of Dermatology
Douglas W. Lienesch, MD, Clinical Assistant Professor of Medicine
Thomas A. Medsger, MD, Emeritus Professor of Medicine
Chester V. Oddis, MD, Professor of Medicine
Adam M. Yates, MD, Assistant Professor of Emergency Medicine

Donald S. Fraley Award for Medical Student Mentoring
Richard A. Steinman, MD, PhD, Associate Dean for the Medical Scientist Training Program, Associate Professor of Medicine and of Pharmacology and Chemical Biology

William I. Cohen Award for Excellence in Clinical Skills Instruction
Stephanie B. Dewar, MD, Associate Professor of Pediatrics
Margaret L. Watt-Morse, MD, Associate Professor of Obstetrics, Gynecology, and Reproductive Sciences

INNOVATION IN MEDICAL EDUCATION
Pitt Broadens the Inclusiveness of Training and Education in Cancer Research

In 2012, the Association of American Medical Colleges (AAMC) highlighted five exceptionally bright spots in biomedical research training and education in the nation. Winners of the AAMC Award for Innovations in Research Training and Education were recognized for advancing creative, collaborative partnerships that make an impact on institutional practices. Pitt’s award-winning program is the University of Pittsburgh Cancer Institute (UPCI)–Hampton University Education and Training Partnership, led by Richard Steinman, MD, PhD, associate professor of medicine and of pharmacology and chemical biology.

The program addresses the fact that, despite a greater burden of cancer in many minority communities, there is a paucity of minority biomedical and physician scientists actively involved in cancer research. Beginning in 2002, UPCI established a formal cross-institutional partnership to bolster faculty and student interactions with Hampton University, a historically black university in Virginia focused on didactic teaching.

The collaboration has met with significant success. Goals achieved include the development of a cooperative curriculum, building of faculty competencies in teaching undergraduate cancer biology and undertaking cancer-related projects, and building student skills to enable later success in graduate and professional school. High-level institutional support and cross-institutional advisory committees enhanced the partnership process.

Key components of the partnership involved the establishment of a molecular biology laboratory at Hampton and four undergraduate cancer biology courses jointly taught by Hampton and Pittsburgh faculty. A subset of the Hampton undergraduates enrolled in a multi-year longitudinal “Cancer Fellow” curriculum undertook research rotations at UPCI and accrued teaching responsibilities in the curriculum. Of the 18 selected students who participated, 17 entered graduate or professional school. (Steinman points out that this is 94 percent, versus 15 percent of peers taking biology who did not participate in the program.) Currently, 10 are in medical school, residency, or fellowship; among the others, one is in private practice, two are conducting public health research, another is completing her PhD, and one is in postdoctoral training.
In addition to curing what ails us, the nation’s physicians advance our understanding of both basic and clinical science. For those medical students captivated by the prospect of being involved in biomedical research and other academic endeavors, there are numerous ways to get carried away at Pitt. Upon completing their first year of med school, more than 75 percent of students in the Class of 2015 engaged in various summer research programs. In addition, some students will take a year off at some point to earn a master’s degree in public health, biomedical ethics, or a related field; others will take a one-year leave of absence to conduct research through one of a handful of specialized programs available to Pitt med students.

**The Clinical Scientist Training Program**

Pitt’s Clinical Scientist Training Program (CSTP) offers a leg up for medical students who show an interest in and a talent for clinical research. Select students whose scholarly projects meet the NIH definition of clinical research are invited to delve deeper into their mentored scholarly projects during a fifth year of training. Interested students apply to the CSTP in January of the year they plan to commit to full-time research (typically between the third and fourth years of medical school). Selected students are appointed as research fellows for the research year, during which they receive a living stipend, research funds, travel funds, health insurance, and tuition toward the graduate certificate in clinical research. After successful completion of the fellowship year, they receive a CSTP scholarship toward the final year of medical school. By providing formal research training and partial tuition assistance, the CSTP seeks to increase the number of Pitt graduates who choose clinical research careers and contribute to the vital work of translating biomedical science into clinical care. Graduates from 2013 matched to the following residency programs:

**Ryan Li, MD**  
University Hospitals of Case Western Reserve University, Orthopaedic Surgery

**Benjamin Sprague, MD**  
UPMC Medical Education, Internal Medicine

**Lisa Tseng, MD**  
Washington University in St. Louis, Anesthesiology

**“SUPER-FELLOWSHIPS”**

Like most academic medical centers, Pitt has a large infrastructure dedicated to the care and feeding of medical residents and fellows. At any one time, the graduate medical education (GME) office is responsible for hundreds of physicians training in residency programs that range from anesthesiology to urology and everything between. Fellowship training is available for further specialization in areas like cardiothoracic surgery, pulmonology, or hematology/oncology.

But an interesting thing has happened as medical advances have made ever-increasing specialization possible — even desirable. Training programs are in demand for scores of specialty areas not officially recognized by the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties. What’s a GME office to do?

At Pitt, the answer has been to make the nonstandard programs as organized and rigorous as the accredited programs. Frank Kroboth, MD, George H. Taber Professor of Medicine and assistant dean for graduate medical education, and colleagues described their approach in a 2011 *Academic Medicine* article. They have another article under review right now, detailing measurable outcomes such as scientific publications, manuscripts, presentations, abstracts, and posters. (“The fellows have been amazingly prolific in academic accomplishments,” says Kroboth.)

“We believe this approach makes a better fellowship program,” Kroboth continues. “Each program has four elements — dedicated faculty who do the teaching and supervision; an established, written curriculum; an evaluation system that is implemented; and documented feedback given on the basis of the evaluation. We believe that, when you implement these elements, you have a better outcome.”

Nonstandard programs (sometimes called “super-fellowships”) at Pitt number approximately 100 right now. Most include a research component. There’s a program in multi-organ transplantation. Anesthesiology offers one in acute pain and regional anesthesia. Ophthalmology offers one each in cornea, glaucoma, retina, and oculoplastic surgery.

“These programs represent an opportunity for physicians to create a niche for themselves, above and beyond what is usual in patient care,” says Kroboth.
The Physician-Scientist Training Program (PSTP) is a five-year program for exceptionally talented students who, in addition to the regular curriculum, undertake two summers and a dedicated year of laboratory-based research training, as well as enrichment courses, to prepare them for careers in academic medicine. Those selected for the program receive partial tuition assistance for the four years of medical school plus a stipend during the two research summers and the research year. The Class of 2013 included six graduating PSTP students, all of whom matched to top residency programs, including obstetrics/gynecology at Johns Hopkins Hospital, neurology at Weill Cornell Medical Center, neurological surgery at Stanford University, radiation oncology at Memorial Sloan-Kettering in New York, diagnostic radiology at the University of Texas Southwestern Medical Center, and medicine/pediatrics at the University of Minnesota. Collectively, these six graduates have published 32 papers (12 as first authors), received 10 national or international awards (best poster, best talk, or travel awards), and received four research grants.

Top Students Win Prestigious Fellowships
Three of Pitt’s PSTP students were awarded highly coveted research training fellowships through the Howard Hughes Medical Institute Medical Research Fellows Program. The students will be supported through a one-year leave of absence, during which they can dedicate themselves to research projects and associated research training.

The award-winning students and their projects:

**Michael Burrow**
Mechanisms of Corneal Stroma Remodeling by Stem Cells

MENTOR:
James Funderburgh, PhD, Professor of Ophthalmology

**Erin Cummings**
Mitochondrial Dynamics in Parkinson’s Disease

MENTOR:
Gary Silverman, MD, PhD, Twenty-Five Club Professor of Pediatrics; Chief, Division of Newborn Medicine

**Bhavana Vangara**
The Role of MicroRNA-363 in Human Papillomavirus-Associated Head and Neck Squamous Cell Carcinoma

MENTOR:
Saleem A. Khan, PhD, Professor of Microbiology and Molecular Genetics

CO-MENTOR:
Jennifer R. Grandis, MD, UPMC Professor of Head and Neck Surgical Research, Distinguished Professor of Otolaryngology

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32 papers (12 as first authors)

10 (national/international) awards

4 research grants
William Markle, MD, clinical associate professor of family medicine, didn’t set out to work in global health, but he has a decades-long habit of directing his efforts wherever he sees a profound need. In 2013, the modest, unassuming physician-educator was honored with the Drs. Anvar and Pari Velji Award for Teaching Excellence in Global Health from the Consortium of Universities for Global Health (CUGH) in recognition of his work with Pitt med students and residents.

Markle has made an impact on a great many lives, including both patients and medical professionals. He is a sought-after teacher and consultant on issues concerning health care to the underserved, and he is known for his ability to tell an engaging story from his own experiences in global health to illustrate almost any point.

In the 1970s, Markle helped start the Mannboro Medical Center in an underserved rural area of central Virginia, where he remained in solo family practice for 11 years. The center continues today as a Federally Qualified Health Center. He later became medical coordinator for the Indonesia branch of the Wycliffe Bible Translators, providing primary care, teaching, and performing community health work in Irian Jaya (now Papua), Indonesia. He received a diploma in tropical medicine and hygiene from Mahidol University, Thailand, in 1993 and a certificate in clinical tropical medicine and travelers’ health in 1997.

In 1994, Markle joined the University of Pittsburgh School of Medicine Department of Family Medicine as a student preceptor. He served as clerkship director for medical students and helped start the global health interest group and area of concentration. In 2002, he became program director of the family medicine residency at UPMC McKeesport and continues there as the senior associate program director. Seeing a large number of people unable to get care in the McKeesport area due to lack of insurance, Markle was able to help start the 9th Street Clinic, a free clinic serving uninsured patients. He continues to direct this clinic, and many students and residents have rotated there. His interest in global health has resulted in an ongoing project to improve health care in remote areas of Honduras. With Pitt students, residents, faculty, and community physicians, Markle has performed extensive global health work in Honduras, Haiti, and countries affected by the Indian Ocean tsunami of 2004. He is the senior editor of the influential textbook *Understanding Global Health*. 

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In May, the *Pittsburgh Post-Gazette* published a lengthy profile of Meghan Wilson, who graduated from the School of Medicine with an MD and a PhD in neuroscience. Wilson was paralyzed at age 17 and afterward committed herself to her lifelong dream of becoming a doctor. Pitt was the only medical school to invite Wilson for a second interview, though her academic credentials were impressive. In an online interview, Arthur S. Levine, MD, senior vice chancellor for the health sciences and Petersen Dean of Medicine, recalled meeting Wilson, saying, “In a nanosecond I thought she should be admitted.” Wilson’s dissertation assessed a new way to predict how amyotrophic lateral sclerosis can progress. She will begin her residency in rehabilitation medicine at the University of California, Irvine.

**Uncommon Achievements**

**Education**

**Markle Recognized for Teaching**

**All Health Is Global**

**AN EXEMPLAR OF ACHIEVEMENT**

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**Markle (left) at the 9th Street Clinic**

**Markle Recognized for Teaching**

**All Health Is Global**
Coming less than a week after a highly successful Match Day, Scholars Day for the Class of 2013 had a relaxed and festive air in the elegant confines of the University Club. Following an informal breakfast and a poster session featuring student research, med school dean Arthur S. Levine, MD, kicked off the program with a brief history of the Scholarly Project, which has been a requirement for every MD student since 2004.

“When I first floated the idea that every medical student would conduct a scholarly research project during the four years of medical school, I was told that nobody would apply to medical school here,” Levine said. “However, the admissions office assures me that it keeps getting harder to get admitted to Pitt.”

Although many graduates will go on to conduct clinical and basic research, Levine pointed out that it was not only for them that scholarly research was added to the curriculum, saying, “We were convinced it would make all of you better physicians.”

Rather than avoiding Pitt because of stringent scientific requirements, applicants have flocked here for the benefits of being exposed to— and immersed in— scientific research. Medical schools at Harvard and Columbia have followed suit, adding very similar research requirements to their curricula. A whopping 70 percent of Pitt grads matched to one of the nation’s top 25 hospital systems in 2013. Students report that they are questioned extensively about their scholarly research during residency interviews, and many feel that their confidence in discussing research gives them a leg up on their peers from other universities. In Levine’s words, “Residency directors understand the value of the rigor to which you have been exposed.”

As evidence, the five students honored with a Bert and Sally O’Malley Award for Outstanding Medical Student Research matched to the University of California, San Francisco; Johns Hopkins; Pittsburgh’s own UPMC; Case Western Reserve University; and Harvard’s Brigham and Women’s Hospital, respectively. The awards are named for a pair of Pitt alumni (Bert O’Malley earned his MD from Pitt in 1963 and was awarded the 2007 National Medal of Science for his pivotal work on steroid hormone receptors), and they recognize the most outstanding scholarly projects in basic and clinical research.

### 2013 O’Malley Award Winners

**Colby Croft, MD**
Evaluation of the Representation of Lesbian, Gay, Bisexual, and Transgender Health Issues in the University of Pittsburgh School of Medicine Curriculum

**Jocelyn Fitzgerald, MD**
The Role of Mast Cells and PAR-2 Receptors in the Cross-Sensitization of Pelvic Afferent Nerves

**Kellie Middleton, MD**
Effects of Playing Nintendo Wii on Student Performance on a Virtual Reality (VR) Laparoscopic Simulator

**Thomas Phelps, MD**
The Potential Therapeutic Efficacy of the Atypical Antipsychotic Aripiprazole after Experimental Traumatic Brain Injury

**Rachel Orler Reid, MD**
Which Physicians Provide the Highest Quality Health Care? An Analysis of the Quality of Care Delivered by Massachusetts Physicians
When it was time for Matthew Hedberg to select a combined MD/PhD program, it came down to his top two choices. One option was to stay at his undergraduate institution, the University of Utah, where he could continue in the lab of 2007 Nobel laureate Mario Capecchi, PhD. Hedberg had done a six-week stint in a lab in Capecchi’s department (genetics) as a teenager, then was invited to stay on through high school. Later, he was hired as an undergraduate researcher; and around the time he graduated with a BA in chemistry, he was a coauthor with Capecchi and two others on a 2009 Cancer Research paper describing a new way of modeling sarcomas in mice.

Like most applicants who receive acceptance letters from Pitt’s MSTP (Medical Scientist Training Program), Hedberg ultimately chose Pittsburgh over other opportunities. He arrived here in June 2010 for a nine-week research rotation before the start of medical school— one of the hallmarks of Pitt’s program.

“Applicants often say this is the most supportively structured program in terms of keeping track of student progress, providing academic and career advisors, and building both clinical and research skills concurrently,” says Richard Steinman, MD, PhD, associate dean for the medical scientist training program.

Hedberg concurs, saying, “Pitt has developed a progressive program with integrated classes. It’s a cohesive unit instead of separate programs for the MD and PhD.”

The National Institutes of Health supports 43 MSTP programs around the country. With 81 students, Pitt’s program enables a lively student experience, both social and scientific. (Many programs support only a handful of students at a time.) NIH saw fit to increase support of Pitt’s MSTP by 25 percent since 2010, which is quite an endorsement in fiscally lean times.

Steinman, who is also associate professor of medicine and of pharmacology and chemical biology, says that the integrated nature and supportive structure of the program are vital, intentional elements. Though students begin with two years of medical school, they complete summer research rotations before, during, and after those years. Even during the intense years of PhD research, there are 40-some weeks in which they spend a half-day in clinic, never forgetting that they are becoming clinicians. Then, as they begin the final two years of medical school, MSTP students are offered a special elective with a master clinician to facilitate their reentry into clinical training. Throughout, there is a rigorous system of safeguards, evaluation points, and reviews to keep each student on track.

Current students have racked up significant accomplishments of late. Amin Afrazi, who completed his PhD in 2012 and is now working on his MD, is a coauthor on a slew of scientific papers, including two in Proceedings of the National Academy of Sciences, exploring inflammation and the molecular mechanisms behind necrotizing enterocolitis (see page 55). In 2012, Pitt MSTP students were coauthors on 79 scientific publications and first authors on 41. Jason Sanders’s work on the epidemiology of aging has been particularly productive, leading to eight first-author papers in journals like Epidemiology Reviews, Academic Medicine, and Journal of Gerontology: Biological Sciences. At the 2012 MSTP retreat, he received the Dr. S. Hamilton Sutton MSTP Scholar Award, the program’s top research honor.

The MSTP retreat is an annual highlight that is scientifically challenging, inspiring, and just plain fun. The experience builds community because artificial barriers between students and mentors tend to break down as everyone talks science, sings karaoke, plays volleyball, and hikes the woods of Western Pennsylvania together. The 2012 retreat featured a special keynote speaker—none other than the Nobel-winner Mario Capecchi, who accepted an invitation from his former student researcher Hedberg and enthusiastically participated from beginning to end.
When people think about medical school, they typically think about the MD program, which, at Pitt, has nearly 600 students. But many come to Pitt to earn a PhD or MS in one of many programs available to them. In addition to the 87 students in the combined MD/PhD program, there are more than 300 others pursuing a doctorate in programs like neuroscience, biomedical informatics, computational biology, molecular biophysics and structural biology, integrative molecular biology, and clinical and translational science. The biomedical informatics program is leading the way in online offerings, recently introducing a certificate program that can be completed entirely online.

In May 2013, the School of Medicine granted 51 PhD and 43 MS degrees. Recent graduates have fanned out and can currently be found serving as postdoctoral fellows at the National Institutes of Health, Fred Hutchinson Cancer Research Center, Emory, Yale, Harvard, Cincinnati Children’s Hospital Medical Center, Stanford, the Broad Institute, and many other academic institutions as well as in the biotech industry.

John Horn, PhD, professor of neurobiology and associate dean for graduate studies, directs the Interdisciplinary Biomedical Graduate Program, which features a core curriculum combined with specialized research and dissertation work in one of the following areas: molecular genetics and developmental biology, cell biology and molecular physiology, cellular and molecular pathology, immunology, molecular pharmacology, or molecular virology and microbiology.

“Every year, the program has become increasingly competitive,” says Horn. “Clearly, it’s now a national program, whereas that was not so obvious just 10 years ago.” Horn recently produced a map showing the home states of applicants to the interdisciplinary PhD program over two five-year periods. The first, ending in 2003, represents the period shortly after the founding of the program. Of 378 U.S. applicants during those years, 84 percent came from Pennsylvania and states that border it. Over the most recent five-year period, there were 1,275 U.S. applicants, with 55 percent coming from Pennsylvania and bordering states. Applications from the Pacific Coast states nearly quadrupled in that time; applicants from Minnesota and Wisconsin went from four to 54.

“The program continues to attract very accomplished students from around the country and the world,” says Horn.

Before coming to the School of Medicine, Zach Landis-Lewis earned his master’s degree in library and information science at Pitt. Now, as a PhD candidate in the biomedical informatics program, he is working with health care providers in HIV/AIDS clinics in Malawi, who use a national electronic medical record system. He is pursuing the research question, “What features of clinical performance feedback are most effective for improving health care provider performance?” Landis-Lewis is developing software that generates automated performance feedback to support clinical learning and implementation of national treatment guidelines.
Pitt Med & Tsinghua — getting to know you.
The second annual University of Pittsburgh and Tsinghua University Joint Symposium on Medical Sciences, which was held at the University of Pittsburgh in April 2013, was planned partly as a “getting to know you” event. After all, the first-of-its-kind collaboration between Pitt and Tsinghua is barely two years old. What’s more, the distance between Pittsburgh and Beijing is roughly 6,700 miles, so these partners don’t get together nearly as often as they’d like. The 2012 symposium had been hosted in Beijing by Tsinghua University, whose students were filled with questions about what life would be like in Pittsburgh. Since arriving in August 2012 to begin two years of intensive biomedical research training, 21 students have chosen scientific mentors, become part of laboratory teams, and delved into their own research projects to advance the work of their respective labs. The symposium was their first formal opportunity to demonstrate what they’ve accomplished for their peers and faculty members at Pitt. In addition to presenting their research during a lively student poster session, students were treated to scientific presentations by top faculty from both institutions. Session topics included current research in neuroscience; structural, computational, and systems biology; immunology; infectious diseases; epigenetics and cancer; reproductive and stem cell biology; and pharmacology and drug discovery.

Despite all the cutting-edge science on the agenda, the two-day symposium began with an exploration of what it feels like to experience nostalgia for those formative years of one’s life. Arthur S. Levine, MD, Pitt’s senior vice chancellor for the health sciences and Petersen Dean of Medicine, set the tone when he introduced his counterpart—Yigong Shi, PhD, dean of Tsinghua’s School of Life Sciences and executive vice dean of its School of Medicine. Levine described how Shi had declined to fly the last leg of his journey from Beijing to Pittsburgh. He deplaned in Chicago and, after visiting colleagues in Illinois, drove 500 miles to Pittsburgh by himself. It felt like coming home, said Shi, who first arrived in this country in 1990 to begin a PhD program in molecular biophysics at Johns Hopkins University School of Medicine and remained until 2008, when he gave up a prestigious endowed professorship at Princeton University to return to Tsinghua, his alma mater.

“Twenty-three years ago, I landed in Ames, Iowa, surrounded by cornfields, and drove 22 hours to Baltimore,” Shi recalled. “I’ll never forget the welcoming people of the Midwest or how fascinated I was by the landscape on that long drive.”

A large community at Pitt is working to give the Tsinghua students every opportunity for a similarly unforgettable experience. There’s evidence it’s working. Lijia Cui says that she has quickly fallen in love with the unfamiliar, hilly terrain of Pittsburgh, despite the fact that it exhausts her when she bicycles around the city. She was assigned to the lab of Elodie Ghedin, PhD, a MacArthur Fellow and associate professor of computational and systems biology. Cui was nervous at first about being in an American lab because she still has a lot to learn about conversational English. In Ghedin’s lab, however, she found herself on a team with Americans, Canadians, and an Indian, so the addition of a Chinese med student wasn’t unusual. “We are friends,” Cui says now.
Ghedin’s lab studies the genomics of infectious diseases. Working with her new colleagues, Cui developed an experiment using next-generation DNA sequencing to study the fungal microbiome in patients with both HIV and chronic obstructive pulmonary disease (COPD), which are commonly comorbid. Her studies yielded 19 fungal genera in these patients that did not show up in healthy controls. Only four of the 19 had previously been associated with HIV and COPD in the scientific literature, so Cui’s findings are novel. Next steps for Cui include further research to determine whether fungi are driving COPD symptoms in these patients and how.

Ghedin says that having Cui in the lab has been a boost to the team’s capabilities. Because Ghedin’s lab personnel are paid for by multiple grants, each has multiple areas of responsibility. But the Tsinghua students, paid for by the collaborative agreement between the partner universities and the Chinese government, are able to focus on one project at a time. “Because of limited resources, we weren’t even going to do this experiment,” says Ghedin. “But now she is finding really interesting stuff that is going to lead to further research.”

Another student, Luxi Sun, says that the Pitt-Tsinghua program is exactly what she hoped it would be. The daughter of two developmental biologists working at the Chinese Academy of Sciences, Sun arrived with a good sense of what she’s interested in. She was thrilled to find that Pitt has a strong and welcoming research program in DNA damage and repair mechanisms. The genome stability group, as it is called, includes multiple investigators from the medical school and the University of Pittsburgh Cancer Institute, including med school dean Levine. Working with mentor Li Lan, MD, assistant professor of microbiology and molecular genetics, Sun has become immersed in an exciting line of research in which Lan and others have devised a means of using the fluorescent protein KillerRed to induce damage in specific locations on the genome, then observe DNA repair proteins in action in live cells as they come to fix the damage. With the ability to target even something as small as the telomeres at the ends of chromosomes, the lab is observing and elucidating DNA damage response mechanisms that could have important implications for cancer and aging. Sun’s contributions to the lab’s work have already led to coauthorship on a forthcoming publication in the Journal of Cell Biology.

As for life in Pittsburgh, Sun is surprised and delighted by how easy it has been to explore American culture. She has taken in the Pittsburgh Symphony Orchestra performing Beethoven and the national tour of the musical Chicago, both just a short bus ride from campus. She finds Pittsburgh peaceful and says that the environment has allowed her to relax and commit completely to research.

As co-organizer of the symposium and a driving force behind the larger collaboration, Levine has always had high expectations of the Tsinghua students. But after spending much of two days with them at the symposium, he declared himself in awe of the students and their work. Both Levine and Shi expressed their hope that the Tsinghua students come to think of Pittsburgh as their alma mater and maintain this connection as they become independent investigators.

To further cement the bonds already formed between these two institutions, the final day of the symposium included a gift from one longtime friend and colleague to another, both of whom were pleased to be renewing collaborative efforts after many years. When he was a grad student at Johns Hopkins, Yigong Shi was mentored by Jeremy Berg, PhD, Pitt’s associate senior vice chancellor for science strategy and planning, health sciences, and director of the Institute for Personalized Medicine. Berg presented Shi with a 3-D model of a protein for which Shi had determined the crystal structure. Berg also announced that Shi had learned that very day that he was among 21 foreign associates elected to the U.S. National Academy of Sciences—a rare honor.

Shi raised the 3-D model that his mentor had given him and took the opportunity to speak to the gathered students and mentors about the personal connections they will make in their scientific careers. He pointed out that 23 years after they met at Johns Hopkins, Berg, who is scientific director of the Pitt-Tsinghua program, is still a valued mentor—but now for the Tsinghua students. “You are like the grandchildren of Jeremy,” he said. With those words, the second Pitt-Tsinghua symposium came to a close. However, as with all good family get-togethers, the moment left many participants looking forward to the next reunion, which will be in Beijing in 2014.
Family Photos
For fourth-year medical students across the country, March 15th was all about the envelope. On this Match Day at the University of Pittsburgh School of Medicine, students tried to pay polite attention while Donald DeFranco, PhD, professor of pharmacology and chemical biology, and other beloved Pitt educators Georgia Duker, PhD, and Melissa McNeil, MD, MPH, did their best warm-up acts.

Students were (not so) surreptitiously looking for Joan Harvey, MD, associate dean for student affairs. She had the envelopes stuffed with letters telling students where the next phase of their careers as new residents would take them.

Photos were snapped and toddlers fidgeted. The action was punctuated by occasional screeches, baby gurgles, high-fives, and hugs. A promotional video for the Scope and Scalpel musical revue offered scrubs-clad members of the Class of 2013 working the Harlem Shake. By the time Dr. Harvey made her way to the podium, toddlers weren’t the only ones squirming.

“This year, there were over 40,000 participants in the Match,” she announced, giving a special welcome to loved ones watching Pitt’s live Internet stream. “Along with many placements at our most prestigious institution — UPMC — your programs include virtually all the top programs in the country.”

In fact, she continued, nearly two-thirds of the Class of 2013 matched to a top-tier institution. Leading in numbers of incoming Pitt med grads were Harvard, Johns Hopkins, Northwestern, UPMC, and the Universities of Washington, Chicago, Pennsylvania, and California, San Francisco.

Ready, Set, Match!
In all, 142 Pitt med students matched to programs in 24 states and performed with distinction in some very competitive specialties. “I’m pleased to report that your class matched two-for-two in ENT, three-for-three in plastic surgery, eight-out-of-eight in general surgery, seven-for-seven in orthopaedic surgery, 13-for-13 in emergency medicine, and four-out-of-four in pediatrics,” Dr. Harvey declared to hoots and cheers.

Then Erin Nuzzo opened the first envelope. When she grabbed a microphone and reported her internal medicine residency match at Beth Israel Deaconess Medical Center, Scaife Hall’s largest auditorium erupted. The screaming — dancing, jumping, laughing, and LOTS of hugging — lasted for more than an hour.

The decibel level really shot up when MD/PhD student Meghan Wilson motored her wheelchair up to a microphone to announce she was off to the University of California, Irvine, for a residency in physical medicine and rehabilitation.

When all was said and done, Sergio Hickey, whose name was called last, collected a fat cash prize (traditionally, each student places $1 in the pot before learning his or her fate) and the joyful throng dispersed to continue individual celebrations.

“This is the happiest weekend of my life,” chimed Peter Asante, who is heading to a pediatrics residency at the University of Washington, while classmate Julie Steinbrink accepted congratulations on her internal medicine match to the University of Michigan Hospitals.

Ben Sprague, who entered Pitt med with the Class of 2012 but added a research year through the Clinical Scientist Training Program, is pleased to be staying at UPMC for his internal medicine residency.

“Pittsburgh has a very excellent program for training clinician researchers,” said Sprague, who is keen to conduct heart and lung disease-related investigations. “I would love to practice medicine in a teaching environment with residents and medical students.” Sounds like he’s in the right place.
The University of Pittsburgh continues to rank in the top 10 among academic institutions in terms of funding from the National Institutes of Health (NIH) — perhaps the most objective measure of research excellence available.

In fiscal year 2012, the faculty of the University of Pittsburgh ranked fifth in dollars awarded, with more than $460 million in total funding. The faculty of the medical and public health schools also rank fifth, with total funding of more than $400 million. In all, 1,069 individual awards and contracts were received in 2012.

Based on figures from fiscal year 2011, the National Science Foundation (NSF) ranks the University third among public institutions of higher education and fifth among all universities, public and private, in its federally financed research and development (R&D) expenditures, which include funding from agencies in addition to NIH. Pitt’s federally derived R&D expenditures for that period totaled $622.5 million; its total R&D expenditures for 2011 added up to $899.4 million.

A citation analysis ranks Pitt as the top public university in Pennsylvania in scientific output — and No. 9 among all U.S. public universities — demonstrating a rate of return any investor could respect. According to the 2012 Performance Ranking of Scientific Papers for World Universities, Pitt ranked at No. 18 among all U.S. universities (public and private) and No. 24 among all universities worldwide. The ranking, published yearly since 2007 by the Higher Education Evaluation and Accreditation Council of Taiwan and by National Taiwan University beginning in October 2012, evaluates academic journal publications from the top 500 universities worldwide in terms of research productivity, impact, and excellence.
QUEST FOR FUNDING

Student biomedical scientists have a lot to learn. Practical problems like finding the best reagents and the business end of a pipette might be a cinch, but the bottom line is this: The search for funding is perpetual.

Over the years, Pitt School of Medicine researchers have been extraordinarily successful in scoring financial support from many sources, including foundations, industry, and individual philanthropy. The National Institutes of Health (NIH) provides the lion’s share, however, with an alphanumeric soup of grants that correspond to scientific career advancement. Here are a few snapshots of active (fiscal years 2012–13) Pitt grants that range from training initiatives to independent investigations and multicenter collaborations.

PROGRAM PROJECT GRANTS

Program Project (P01) grants help independent investigators to mount large research efforts with a variety of projects and activities that share a defined focus. P01s support multidisciplinary collaborations among investigators and may include preclinical studies, clinical trials, or associated components like training programs. Results from P01-supported investigations can significantly advance scientific knowledge and influence standards of patient care.

VASCULAR SUBPHENOTYPES OF LUNG DISEASE — NHLBI — Mark T. Gladwin, MD, professor of medicine and chief, Division of Pulmonary, Allergy, and Critical Care Medicine, principal investigator ($2,437,987)

MITOCHONDRIAL PROTEINS IN PARKINSON’S DISEASE — NINDS — J. Timothy Greenamyre, MD, PhD, UPMC Professor of Movement Disorders, principal investigator ($1,223,987)

DIRECTING TUMOR-SPECIFIC T CELLS TO TUMORS — NCI — Pawel Kalinski, MD, PhD, professor of surgery and of immunology, principal investigator ($1,436,996)

IN VIVO PITTSBURGH COMPOUND B POSITRON EMISSION TOMOGRAPHY AMYLOID IMAGING: NORMALS, MILD COGNITIVE IMPAIRMENT, AND DEMENTIA — National Institute on Aging (NIA) — William E. Klunk, MD, PhD, Distinguished Professor of Psychiatry, principal investigator ($1,295,247)

AGING WELL; SLEEPING EFFICIENTLY — NIA — Timothy H. Monk, PhD, DSc, professor of psychiatry, principal investigator ($1,767,926)

NEW THERAPIES FOR LIVER FIBROSIS AND HYPERPROLIFERATION IN ALPHA 1-ANTITRYPSIN DEFICIENCY — NIDDK — David H. Perlmutter, MD, Vira I. Heinz Professor, Distinguished Professor, and chair of pediatrics, principal investigator ($1,894,047)

NOVEL STRATEGIES FOR BRAIN TUMOR THERAPY — NINDS — Ian F. Pollack, MD, A. Leland Albright Professor of Children’s Neurosurgery and chief, Division of Pediatric Neurosurgery, principal investigator ($1,237,376)

SPECIALIZED PROGRAM OF RESEARCH EXCELLENCE (SPORE)

Sponsored by the National Cancer Institute (NCI), SPORES are multidisciplinary team science awards that support translational research in specific cancers. At any one time there are about 60 active SPORES across all types of cancers in the United States.

“I believe that the SPORES have been catalytic forces for several of our disease-oriented research programs at UPCI,” says UPCI and UPMC CancerCenter director Nancy E. Davidson, MD, who is also the Hillman Professor of Oncology and Distinguished Professor of Medicine. “We have been highly successful in obtaining these awards because we have strong physician-scientist leaders immersed in the diseases under study, who assemble talented, dedicated teams and take advantage of our large patient base to investigate clinically relevant questions.”

Similar to program project grants, SPORES involve multiple projects within tightly focused themes and include mandated training programs. Results from SPORE-supported investigations have made major contributions to the advancement of cancer care.

SPORE IN HEAD AND NECK CANCER — Jennifer R. Grandis, MD, Distinguished Professor of Otolaryngology and assistant vice chancellor for research integration, health sciences, principal investigator ($2,300,000)

SPORE IN LUNG CANCER — Mark A. Socinski, MD, visiting professor of medicine, Division of Hematology/Oncology, principal investigator ($2,300,000)

SPORE IN SKIN CANCER — John M. Kirkwood, MD, Sandra and Thomas Usher Professor in Melanoma and vice chair for clinical research, Department of Medicine, principal investigator ($2,300,000)

TRAINING GRANTS

Among the grant mechanisms available to MD/PhD students and postdocs in the School of Medicine are Ruth L. Kirschstein National Research Service Awards. This family of grants includes institutional T32 and T35 awards to support short-term training. A handful of additional “T” grants fund other training programs. Among Pitt’s are:

RESEARCH TRAINING IN PEDIATRIC NEPHROLOGY — National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) — Carlton Bates, MD, associate professor of pediatrics, principal investigator ($228,165); two trainees

TRANSITIONAL RESEARCH TRAINING IN SLEEP MEDICINE — National Heart, Lung, and Blood Institute (NHLBI) — Daniel J. Buysse, MD, professor of psychiatry and of clinical and translational science, principal investigator ($297,750); six trainees

PREDOCTORAL TRAINING IN PHARMACOLOGICAL SCIENCES — National Institute of General Medical Sciences (NIGMS) — Donald B. DeFranco, PhD, professor and vice chair for education, Department of Pharmacology and Chemical Biology, principal investigator ($178,618); four trainees

TRAINING IN THE NEUROBIOLOGY OF NEURODEGENERATIVE DISEASE — National Institute of Neurological Disorders and Stroke (NINDS) — Michael J. Zigmond, PhD, professor of neurology, principal investigator ($221,193); three trainees

NIH Institutes: 18
Training Programs Supported: 46
Total Trainees: 121 predoctoral, 125 postdoctoral
Total Funding: $10.9 million

National Cancer Institute SPORES: 3
Total Funding: $6.9 million

Sources: NIH Research Portfolio Online Reporting Tools, University of Pittsburgh Office of Research, and Office of Academic Career Development, Health Sciences, and Office of the Senior Vice Chancellor, Health Sciences
Discoveries—no matter how revolutionary—change no lives when confined to the pages of scientific journals. Fortunately, the University of Pittsburgh “has an app for that” in the Office of Technology Management (OTM) and Office of Enterprise Development (OED).

Under the leadership of Marc S. Malandro, PhD, associate vice chancellor for technology management and commercialization and director of both OTM and OED, the two organizations serve as the hub of all the University’s innovation commercialization activities. OTM/OED specialists have expertise in business development; intellectual property protection; licensing; strategic planning; marketing; and financial analysis, reporting, and compliance. Currently, the offices also boast a pair of executives-in-residence with talents in software/information technology and medical devices.

“In terms of invention disclosures and innovation licensing, we’ve achieved record highs this past year—nearly a 21 percent increase over the previous year—thanks to Pitt innovators, our staff, and our commercial partners,” says Malandro, who picked up a Catalyst Award from the Carnegie Science Center in 2011.

“Vetting more than 300 innovations in a year can be a challenge,” Malandro notes. “OTM works closely with members of the University Technology Transfer Committee to evaluate each for technical merit, patentability, and market potential.”

Since 2001, the University and its innovators have been issued 382 U.S. patents. In all, 98 new start-ups based on Pitt innovations have been launched with guidance from OTM/OED.

Education in what OTM/OED calls “academic entrepreneurship” is a foundation of the organizations’ services. Among the newest offerings is an expanded, 15-week “Benchtop to Bedside” course. Sessions are designed to complement the Coulter Translational Research Partners II Program, a Wallace H. Coulter Foundation collaboration launched in 2011 to encourage partnerships among clinicians and bioengineers.

Recent Coulter program projects involving the School of Medicine include “Infection-Reducing Regenerative Treatment for Patients with Cardiac Device Implants,” led by David Schwartzman, MD, professor of medicine in the Division of Cardiology, and Yadong Wang, PhD, William Kepler Whiteford Professor of Bioengineering, Swanson School of Engineering, and associate professor of surgery. Their venture involves biocompatible, degradable spherical droplets designed to deliver fibroblast growth factor and antibiotics to promote healing after device placement.
A s director of the University of Pittsburgh Drug Discovery Institute (UPDDI), D. Lansing “Lans” Taylor, PhD, is convinced that academic institutions can — and should — contribute more than ever to the development of new therapeutics. Partnering with industry not only makes sense — it can be critical to mutual economic survival.

“The pharmaceutical industry is in a difficult position,” says Taylor, a cell biologist and Allegheny Foundation Professor of Computational and Systems Biology in the School of Medicine. “Academic centers could provide some of the innovation that’s been lacking in the industry for 20 years.”

Stakes have never been higher. Institutions like Pitt and UPMC face shrinking National Institutes of Health support for biomedical research and decreasing insurance reimbursements for health care. On the industry side, cost estimates range up to $1 billion to develop a single new drug at a time when patents are expiring for many top-selling pharmaceuticals, a coincidence pharma calls “the patent cliff.”

Some might run for the hills; UPDDI is chasing opportunities. We asked Taylor for an update.

Q. What makes UPDDI different?
TAYLOR: We are not a simple screening center, which is what a lot of academic drug discovery centers are. We’re implementing a relatively new paradigm called quantitative systems pharmacology. It’s a commitment to combining the best in computational and systems biology tools with the most sophisticated experimental approaches. This merger, especially of pharmacokinetics (PK) and pharmacodynamics (PD) with systems biology, could have a real payoff in the ability to understand drug interactions in individual patients.

Q. How does it work?
TAYLOR: Data derived from ’omics, patient samples, and disease models drive the experiments, which, in turn, drive data interpretation and the design of the next studies. Computational tools are used to define drug actions across multiple scales of biological complexity, from molecules to cells, tissues, organs, and organisms for a “systems-level perspective.” All of this is tied with clinical needs.

Q. Where is UPDDI focusing now?
TAYLOR: The first program is in metastatic breast cancer. Most people don’t die from primary cancer; it’s the metastatic disease, which has the most complicated biology. We’re just starting to peel the onion on that. In the continuum between Pitt, UPMC, and the complementary technologies that our collaborator Carnegie Mellon University has, we can field therapeutic scientists, computational and systems biologists, chemists, medicinal chemists, and PK/PD science and then move to clinical trials. We can design the program and the critical path — the steps to follow to get the information that leads to the next step. [Led by Nancy E. Davidson, MD, director of the University of Pittsburgh Cancer Institute and associate vice chancellor for cancer research, the team includes Adrian Lee, PhD, and Steffi Oesterreich, PhD, professors of pharmacology and chemical biology; UPDDI leaders Andrew Stern, PhD, Mark Schurdak, PhD, Lawrence Vernetti, PhD, and Andreas Vogt, PhD, who have faculty appointments in the Department of Computational and Systems Biology.]

We’re also planning a neurodegenerative diseases program and exploring some other possible therapeutic areas on which to focus.

Q. What’s happening with industry partnerships? Anything in the pipeline?
TAYLOR: We have four projects that were funded with Johnson & Johnson and we’re into our first year of that. Three of them are in cancer and one is in HIV/AIDS. [Faculty taking part include Edward Prochownik, MD, PhD, Paul C. Gaffney Professor of Pediatrics; Thomas E. Smithgall, PhD, William S. McEllroy Professor and chair of microbiology and molecular genetics; Flordeliza Villanueva, MD, professor of medicine; and Zhou Wang, PhD, UPMC Professor of Urological Research.]

We’re beginning a collaboration with GE Molecular Diagnostics in cancer. The idea is that, based on a diagnostic test, you can stratify patients and define the optimal treatment. We will be developing therapeutics for subsets of the patient population. The blockbuster drug model doesn’t really work. This is more complicated. We know enough about human heterogeneity that it now has to be done in segments.

Q. What lies ahead for UPDDI?
TAYLOR: We’re at a stage in many fields, including breast cancer science, where we believe that real, life-changing potential is around the corner. At the same time, funding is strained. Our philosophy is that if your vision is bold enough and good enough, you’ll get it funded. We’re being bold. I believe people are interested in investing in visions.
AWARDS OF NOTE

$11.5 MILLION

FOUR PITT HIV RESEARCH PROJECTS RECEIVE GATES FOUNDATION GRANTS

Researchers at the University of Pittsburgh Schools of the Health Sciences and Magee-Womens Research Institute were recently awarded four grants totaling nearly $11.5 million from the Bill & Melinda Gates Foundation.

More than 22 million new HIV infections will occur worldwide by 2015 despite the current decline in infection rates. A first-of-its-kind collaboration between the University of Pittsburgh’s Center for Vaccine Research, Drug Discovery Institute, and Graduate School of Public Health received a three-year, $1 million grant to develop a novel test to detect HIV in the earliest stages of the disease.

Instead of looking only at proteins made by the virus, this research will examine a novel class of HIV biomarkers in patient blood samples. This approach uses synthetic molecules that resemble proteins and can be produced in millions of different variations and would allow public health workers to better tailor anti-HIV regimens based on duration of infection.

In the two-year, $4.5 million Options Now project, researchers will assess the acceptability and safety of injecting rilpivirine, a long-acting HIV drug, into the muscles of HIV-negative people, with the aim of preventing infection.

“A system of regular injections has been shown to be acceptable, feasible, and effective for women worldwide as a method of pregnancy prevention,” said Ian McGowan, MD, PhD, professor of medicine and of obstetrics, gynecology, and reproductive sciences. “We want to see whether this kind of strategy will be effective at reducing the risk of HIV infection.”

A three-year, $5 million project led by Sharon Achilles, MD, PhD, assistant professor of obstetrics, gynecology, and reproductive sciences, will examine whether hormonal contraceptive methods cause changes in the genital tract that alter susceptibility to HIV. Of particular interest is the impact of contraceptive use on genital tract immune cells — the cells that HIV targets for infection.

“Some studies have indicated that the use of birth control shots, pills, or other hormone-based contraception is associated with a higher risk for HIV,” Achilles said. “This presents a challenge because HIV prevention strategies and contraception should work together, rather than in opposition, to maximize the public health benefit.”

Lisa Cencia Rohan, PhD, associate professor of pharmaceutical sciences in the School of Pharmacy, is leading a 15-month, $758,000 project that will assess the feasibility of thin film dosage forms for vaginal delivery of contraceptive or HIV prevention drugs.

Vaginal films that contain drugs targeted at preventing HIV infection have been developed in the lab through National Institute of Allergy and Infectious Diseases funding. But before further development and global implementation, said Rohan, “critical information to guide film product design and performance must be determined regarding whether such a product can be successfully manufactured and distributed to resource-poor locations and what traits it must have to be acceptable to large numbers of users in a variety of settings.”

$9.3 MILLION

NIH GRANT WILL ESTABLISH A BIOMEDICAL TECHNOLOGY RESEARCH CENTER FOR MULTI-SCALE MODELING OF BIOLOGICAL SYSTEMS

The University of Pittsburgh School of Medicine, Carnegie Mellon University, the Pittsburgh Supercomputing Center, and the Salk Institute for Biological Sciences in San Diego, Calif., have been awarded a five-year, $9.3 million grant from the National Institute of General Medical Sciences to establish a Biomedical Technology Research Center for Multiscale Modeling of Biological Systems (MMBioS).

The MMBioS team members will develop computational tools for modeling and simulating biological systems from the molecular level up to the tissue level.

“With these tools, our goal is to better understand and appreciate the impact of defective proteins and interactions at the cellular level and their effects on central nervous system behavior,” said Ivet Bahar, PhD, principal investigator of the center, Distinguished Professor, John K. Vries Professor, and chair of computational and systems biology in the School of Medicine. “We hope to bridge the gaps between molecular-, cellular-, and tissue-level studies conducted by computational biologists. Our goal is to synergistically integrate data to gain a better understanding of cell signaling and regulation mechanisms.”

The MMBioS Center will tailor computational models for five biomedical research projects — including neurotransmitter signaling, immune cell regulation, and neuronal circuit reconstruction — that are under way at Pitt, NIH, Caltech, the Allen Institute for Brain Science, and Bristol University in the UK.

“Until now, experimental scientists have been collecting data that are not testable by computational methods, while the computational scientists have been building models and making predictions that can’t be verified experimentally,” Bahar said. “We aim to bridge this communication gap, too, so that we can solve relevant problems computationally while generating new hypotheses that can be tested in the lab.”
Researchers from the University of Pittsburgh School of Medicine and the Statens Serum Institut in Copenhagen, Denmark, are collaborating to improve tuberculosis (TB) vaccines. The team is developing a new adjuvant to program T cells to respond more quickly against TB infection.

A five-year, $5 million grant from the National Institute of Allergy and Infectious Diseases will allow scientists in Copenhagen to devise several vaccine formulations, with input from principal investigator JoAnne L. Flynn, PhD, professor of microbiology and molecular genetics and a member of Pitt's Center for Vaccine Research.

Flynn studies host-pathogen interaction in TB, with special emphasis on the immune mechanisms that protect against or exacerbate disease.

Vaccines are primarily made of antigens, which are pieces of proteins from specific bacteria or viruses, and another component called the adjuvant, which stimulates the immune system’s production of antibodies against the antigens.

“Nearly all of the vaccines administered today use similar adjuvants derived from alum salts,” said Flynn. “That works well when an antibody response to an invading germ is needed, but it is not very effective against the bacteria that cause TB.”

In animal studies, the adjuvant developed by the Copenhagen scientists induced responses in two types of T cells (CD4 and CD8). Flynn’s team will test the new vaccine formulations.

“We can track whether vaccinated animals develop pockets of infection called granulomas in their lungs after they’ve been exposed to TB,” she said. “That could speed identification of a vaccine that could be tested in human trials.”

Antipsychotic drugs can help control the delusions and hallucinations that affect people with schizophrenia, but a combination of drug therapy and mental workouts to strengthen brain functions might be more successful than drug therapy alone in helping to improve the lives of people with schizophrenia.

A team from Pitt’s School of Social Work and the Department of Psychiatry, School of Medicine, has received $3.1 million from the National Institute of Mental Health to examine how cognitive enhancement therapy (CET) may help people with schizophrenia recover sufficiently to return to school or hold down a job.

“This project will be one of the first to study how much a nondrug intervention can help address core brain-based impairments in schizophrenia,” said principal investigator Shaun M. Eack, PhD, assistant professor of social work, of psychiatry, and of clinical and translational science.

CET was developed by Gerard E. Hogarty, MSW, a renowned schizophrenia researcher and a professor of psychiatry at Pitt from 1974 until his death in 2006. The treatment requires patients to complete cognitive exercises on computers, coupled with weekly social-cognitive group sessions, for 18 months.

Participants perform tasks to strengthen their working-memory and memory-coding abilities, two key cognitive functions that are disrupted in schizophrenia and that can keep patients from succeeding in the workplace and other aspects of their lives. They also participate in small groups to improve social cognition and help develop social wisdom.

The School of Medicine, said Eack, provides the institutional infrastructure that allows long-term research to be successful. “None of these treatments are going to help people unless there’s good psychiatry on board. This could not be done without close collaboration from our colleagues in medicine.”

In a collaboration involving Pitt’s Swanson School of Engineering, School of Medicine, and the Pitt-UPMC McGowan Institute for Regenerative Medicine, researchers are developing an artificial lung to serve as a bridge to transplant or recovery in patients with acute and chronic lung failure. Each year, nearly 350,000 Americans die of some form of lung disease, with another 150,000 needing hospital care. Current breathing-support technologies are cumbersome, often requiring patients to be bedridden and sedated.

A $3.4 million grant from the National Heart, Lung, and Blood Institute will allow the team, which includes William J. Federspiel, PhD, William Kepler Whiteford Professor of Bioengineering, professor of critical care medicine and of chemical engineering, and director of the Medical Devices Laboratory at the McGowan Institute; William R. Wagner, PhD, professor of surgery, of bioengineering, and of chemical engineering, and director of the McGowan Institute; and Christian Bermudez, MD, associate professor of cardiothoracic surgery and chief of the Division of Cardiothoracic Transplantation, to complement recent efforts by the University of Maryland to improve oxygen and carbon dioxide transfer and increase biocompatibility in wearable artificial lungs.

With the grant, Federspiel, Wagner, Bermudez, and colleagues from Carnegie Mellon University and Mississippi State University will develop a compact respiratory-assist device called the Paracorporeal Ambulatory Assist Lung, a wearable, fully integrated blood pump and lung designed to provide respiratory support for up to three months. One goal is to get patients up and moving in the hospital setting, a pretransplant transitional stage that is important to patient recovery.
$1 MILLION

TWO GRANTS TO IMPROVE CLINICAL OUTCOMES IN MELANOMA PATIENTS

Melanoma is responsible for more than 9,000 deaths each year in the United States. Nearly 80,000 Americans are diagnosed with melanoma annually.

Two researchers in the Division of Hematology/Oncology of the Department of Medicine have been awarded research grants by the Melanoma Research Alliance. Hussein Tawbi, MD, PhD, assistant professor of medicine, is one of three investigators sharing a $900,000 Team Science Award to continue a safety and efficacy study of the selective BRAF inhibitor drabafenib in melanoma patients with brain metastases. The BRAF protein helps transmit chemical signals from outside a cell to the cell’s nucleus. When mutated, BRAF has the potential to cause normal cells to become cancerous.

Understanding the effects of BRAF inhibitor treatment in brain metastases may identify specific strategies to improve clinical outcomes.

Hassane M. Zarour, MD, professor of medicine, of immunology, and of dermatology, received a three-year, $786,000 Academic Industry Award for his study of anti-PD-1 antibody and peginterferon alpha-2b therapies for melanoma. Metastatic melanoma patients generally have poor prognoses. A novel antibody targeting the inhibitory receptor PD-1 (expressed by T cells in the tumor microenvironment) has shown evidence of clinical efficacy in some patients with advanced melanoma. The trial will evaluate whether combination immunotherapy will strongly stimulate host immune responses to melanoma and further increase the clinical benefits provided by anti-PD-1 antibody alone.

Tawbi and Zarour are members of the NIH-funded Melanoma and Skin Cancer SPORE (Specialized Program of Research Excellence) at the University of Pittsburgh Cancer Institute.

$6.6 MILLION

MODEL SYSTEMS FOR TBI AND SCI

The School of Medicine’s Department of Physical Medicine and Rehabilitation has been awarded two grants aimed at improving the care and recovery of patients with traumatic brain injury (TBI) and spinal cord injury (SCI). A five-year, $2.15 million grant from the National Institute on Disability and Rehabilitation Research (NIDRR) distinguishes UPMC Rehabilitation Institute as a Model System of Care for TBI—joining its designation as a Model System of Care for SCI.

NIDRR initiated the Model Systems approach over 30 years ago, with the goal of promoting scientific research and enriching the lives of individuals with significant disability, including TBI, SCI, and burn injuries. “At Pitt,” said Amy Wagner, MD, associate professor of physical medicine and rehabilitation, “we have developed a program that we call ’rehabilomics.’ Our goal is to learn about the ’whole picture’ of how a person is affected by an injury, such as TBI, and to understand how we can help each individual return to the highest level of functioning possible.”

In addition, a five-year, $4.5 million project will involve more than 500 participants and use Internet-based training and group sessions to hone the skills of wheelchair use and prevent wheelchair failures. “This grant will start to tackle problems related to insurance cutbacks that have negatively affected individuals with spinal cord injuries,” said Michael Boninger, MD, Professor and chair of Physical Medicine and Rehabilitation. “Because they spend less time in the hospital after their injuries, they never learn how to effectively use and maintain their wheelchairs. We need an effective, low-cost way to provide people with training that maximizes their independence—this study tackles that problem.”

$5.4 MILLION

BETTER DIAGNOSTICS FOR WOUNDED WARRIORS AND OTHERS

Researchers at the University of Pittsburgh School of Medicine have received two U.S. Department of Defense grants totaling $5.4 million to evaluate whether a new imaging tool called high definition fiber tracking (HDFT) can accurately diagnose traumatic brain injuries (TBI) in wounded warriors.

Conventional CT and MRI scans often are unable to reveal damage to the brain’s network of neural cables, or fiber tracts, that could cause significant cognitive or physical impairments after TBI, explained principal investigator David Okonkwo, MD, PhD, associate professor of neurological surgery, clinical director of the Brain Trauma Research Center, and director of the neurotrauma program at the School of Medicine and UPMC.

“Our preliminary research indicates that HDFT can reveal breaks in brain wiring, just like X-rays show us broken bones,” Okonkwo said. “That’s a big step forward because knowing where the damage lies will allow us to better plan our treatments and give TBI patients more accurate predictions of the long-term prognosis.”

A team led by Okonkwo and Walter Schneider, PhD, professor of psychology, of neurological surgery, and of radiology, and senior scientist at Pitt’s Learning Research and Development Center, will perform HDFT scans at UPMC and multiple collaborating sites on 480 wounded warriors and civilians who have recently sustained a TBI and on 120 uninjured volunteers. The researchers hope to show that HDFT can identify brain injury through neuroimaging and correlate it with neurologic symptoms, including post-concussion syndrome.
Five years ago, the McGowan Institute for Regenerative Medicine joined a consortium of institutions including the University of Cincinnati and, as lead institution, the North Carolina Agricultural and Technical State University, in an $18.5 million effort—funded by the National Science Foundation (NSF)—to develop biodegradable metal implants for surgical use in orthopaedic, cardiac, and reconstructive procedures.

The NSF Engineering Research Center (ERC) for Revolutionizing Metallic Biomaterials also focuses on producing miniaturized sensing systems that monitor and control the safety and effectiveness of biodegradable metals inside the body, a technology that could provide physicians with control over the degradation process.

“We have several device prototypes that have been made,” said William R. Wagner, PhD, director of the McGowan Institute and professor of surgery, School of Medicine, and of bioengineering and chemical engineering, Swanson School of Engineering. “We’ve generated an array of new alloys; and we’re now beginning to use those new alloys in new device prototypes, as well as early-stage, preclinical testing.”

Most of the alloys contain magnesium—a metal used by industry to reduce the weight of various products from cars to computers. Designing biodegradable magnesium-based devices, however, is something altogether different.

“There’s a big regulatory challenge; the FDA has never approved a degradable metal device,” said Wagner. “We’re working with the FDA to better define it, but the nature of the regulatory pathway is still very unclear.”

Regulatory approval is far from the only challenge for faculty members working on the project, who represent the School of Medicine, Graduate School of Public Health (Pitt Public Health), Swanson School of Engineering, and School of Dental Medicine at Pitt, as well as dozens of engineers and doctors from other universities and private industry.

“We’ve begun to define the material properties we’d like to see,” said Wagner, who is deputy director of the NSF ERC. “For example, how long does that orthopaedic screw need to provide mechanical strength in fixing two pieces of tissue together?” Approaches to potential solutions depend on the answer to that question, as well as any specifications for the timing of complete degradation and absorption of the material.

“Generally, it falls between a 10-month to, maybe, a two-year time frame,” he said. “It’s hard to make things not corrode and then all-of-a-sudden start corroding. That’s where other technologies, like coatings, come into play—to buy early time before you get to the loss of mechanical properties.”

Aaron Barchowsky, PhD, professor of environmental and occupational health, Pitt Public Health, is providing toxicology support to characterize and measure degradation byproducts during preclinical testing. Barchowsky has a secondary appointment in pharmacology and chemical biology in the School of Medicine.

“Pure magnesium is a material that has mechanical properties somewhat similar to bone. It’s softer and lighter than a lot of the materials that are currently used,” said Wagner, a chemical engineer by training. “It can be flammable because it can oxidize
so readily. But it’s also amenable to alloying with other metals so that it degrades more slowly, is stronger, or has more ductility. That’s a lot of what we’re trying to do.”

Among devices being tested are a craniofacial plate, surgical screws, a fixation appliance designed to repair anterior cruciate ligament tears, a cardiovascular stent, and another stent for patients undergoing renal dialysis. Experiments involve polymer, ceramic, and even metal-on-metal coatings. Preliminary testing of steadily degrading prototype surgical screws is promising, said Wagner.

“Every metallic material that goes into the body today is designed to be there forever—even if it’s not needed,” he added. “We want to change that.”

Established in 2012, the University of Pittsburgh Center for Military Medicine Research, Health Sciences (CMMR), has been able to make several strategic advances toward its goal — developing new therapies for a wide range of battlefield injuries.

The center’s founding director, Rocky S. Tuan, PhD, has spent much of the past year building unit cohesion among academic and clinical faculty experts in regenerative medicine, reconstructive surgery, transplantation immunology, tissue engineering, and neuroscience — particularly among faculty members whose focus is traumatic brain injury, neurorehabilitation, and neuroprosthetics.

The biggest development, though, is the recent $75 million renewal of the Armed Forces Institute for Regenerative Medicine (AFIRM) grant. Through the McGowan Institute for Regenerative Medicine, Tuan is codirector for the grant, which was first awarded in 2008. With Anthony Atala, MD, at Wake Forest University, Tuan will manage some 60 AFIRM projects tackling craniofacial repair, wound healing, blast injuries, and composite tissue allografts for transplantation.

“In the past five years, Pitt and UPMC have received about $185 million in funding from the Department of Defense,” says Tuan, Arthur J. Rooney Sr. Professor of Sports Medicine.

Perhaps now more than ever, “team science” is imperative. In this respect, CMMR is on top of the trend, adds Tuan, who is also professor and executive vice chair for research, Department of Orthopaedic Surgery, and McGowan Institute associate director.

New to the team are executive director Ronald Poropatich, MD, MS, and managing director Ann Gleeson.

A retired colonel, Poropatich most recently served as deputy director of the U.S. Army’s Telemedicine and Advanced Technology Research Center at Fort Detrick, Md. Gleeson, a former deputy director of the Pittsburgh Tissue Engineering Initiative, has extensive experience in federal government, where she was a health care and technology policy analyst for former U.S. Rep. William J. Coyne.

Since joining CMMR, Poropatich and Gleeson have worked closely with key faculty like Peter L. Strick, PhD, Distinguished Professor and chair of neurobiology, Professor of Systems Neuroscience, and a CMMR leader; Andrew B. Schwartz, PhD, professor of neurobiology, who is prominently involved in Pitt’s groundbreaking brain-computer interface research (see page 46); J. Peter Rubin, MD, UPMC Professor and chair of plastic surgery; and Walter Schneider, PhD, professor of psychology (Dietrich School of Arts and Sciences) and of neurological surgery, of psychiatry, and of radiology (School of Medicine), who, with David Okonkwo, MD, PhD, associate professor of neurological surgery, continues to refine exceptional brain-mapping HDFT technology (see page 45).
Melatonin appears to do. Neural apoptosis underlies many brain disorders in addition to ALS—Huntington’s and Parkinson’s diseases, for example, as well as stroke and traumatic brain injury.

“Superficially, you can say therapy with melatonin inhibits degeneration—we’ve shown it in Huntington’s and ALS now, and in stroke—and that could be it,” said Friedlander. “But what’s really fascinating is that this has taken us to an important and fundamental mechanism of neurodegeneration.”

The mechanism is melatonin receptor 1 (MT1), a transmembrane receptor found mostly in brain cells. MT1 binds melatonin, a hormone involved in circadian rhythms that also is a powerful antioxidant. For the first time, the Friedlander team identified MT1 within the mitochondria, internal cellular structures that power critical functions.

“It’s only, apparently, the second G-protein [guanine nucleotide-binding protein] associated receptor ever identified in the mitochondria,” Friedlander said, explaining that pinpointing the role of MT1 in neurodegeneration has opened up “a whole new set of exciting investigations.”

In April 2013, President Barack Obama announced a $100 million enterprise to map the human brain in a concerted effort similar to that used to decode the human genome. The BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative aims to help researchers find new ways to treat, cure, and prevent brain disorders like Alzheimer’s disease, epilepsy, traumatic brain injury, and mental illness. If approved by Congress, the project will support research funded through the National Institutes of Health, the Defense Advanced Research Projects Agency, the National Science Foundation, and several private sector partners.

University of Pittsburgh faculty in neuroscience, neurosurgery, psychiatry, neurobiology, and many other disciplines are addressing these challenges daily through a robust program of research and clinical practice. Read on for a few highlights.

**RESEARCH INVESTIGATIONS & REVELATIONS**

**JOINING OBAMA’S MAPPING CHALLENGE**

**Pitt’s Year of the Brain**

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“**AT THE NEUROAPOPTOSIS LAB, WE’RE WORKING ON DEFINING THE RELEVANCE OF CELL DEATH PATHWAYS IN NEUROLOGIC DISEASES AND IDENTIFYING MANEUVERS TO STALL THAT PROCESS.”**

ROBERT M. FRIEDLANDER, MD

**A NEW APPROACH TO STOPPING NEURODEGENERATION**

For Robert M. Friedlander, MD, Walter E. Dandy Professor and chair of neurological surgery, finding that melatonin delayed disease progression in a mouse model of amyotrophic lateral sclerosis (ALS) was another step in a career-long march against neurodegenerative diseases (see page 59). About 5,000 people are diagnosed each year with ALS, which causes progressive muscle weakness and typically leads to death within five years.

Most recently, Friedlander, a neurosurgeon recruited from Harvard in 2010, and colleagues have been investigating inhibitors of the caspase-mediated cell death pathway. The goal is to interfere in the biochemical cascade of inflammation, oxidative damage, and apoptosis (programmed cell death)—something melatonin appears to do. Neural apoptosis underlies many brain disorders in addition to ALS—Huntington’s and Parkinson’s diseases, for example, as well as stroke and traumatic brain injury.

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“It’s only, apparently, the second G-protein [guanine nucleotide-binding protein] associated receptor ever identified in the mitochondria,” Friedlander said, explaining that pinpointing the role of MT1 in neurodegeneration has opened up “a whole new set of exciting investigations.”
PITT TO COMBINE MULTIPLE BREAKTHROUGHS IN BRAIN IMAGING

In recent years, University of Pittsburgh scientists have transformed brain research through landmark technological developments like Pittsburgh Compound B (PiB), an imaging agent that reveals the presence of amyloid-beta protein in the brains of living patients with Alzheimer’s disease, and high definition fiber tracking (HDFT), which provides three dimensional, color-coded images of internal brain structures in vivid detail. Now, with a pair of grants totaling nearly $5 million, funded by the U.S. Department of Defense, research teams led by David Okonkwo, MD, PhD, associate professor of neurological...
surgery; James Mountz, MD, PhD, professor of radiology; Walter Schneider, PhD, senior scientist at the Learning Research and Development Center; and Anthony Kontos, PhD, and Michael Collins, PhD, both associate professors of orthopaedic surgery, will use HDFT, PiB, positron emission tomography, and other tests to evaluate brain abnormalities in patients with chronic traumatic encephalopathy (CTE) and traumatic brain injury (TBI). The studies, which also target the accumulation of tau and beta amyloid proteins, will attempt to determine a definitive biological basis for diagnoses of, as well as test potential therapies for, CTE and TBI—two of the most critical public health issues in the U.S. and beyond.
MIND-CONTROLLED ROBOT ARM STUDY RECEIVES TOP 10 AWARD
A groundbreaking project underway at the University of Pittsburgh School of Medicine and UPMC — in which a woman with quadriplegia took a bite of chocolate using a robot arm she controlled with her thoughts — was selected for a Top 10 Clinical Research Achievement Award by the Clinical Research Forum. The awards come from an organization comprising the nation’s most prestigious and acclaimed academic medical centers, professional organizations, and industry and recognize research teams that, in 2012, published compelling examples of scientific innovation resulting from the nation’s investment in clinical research.

Andrew Schwartz, PhD, professor of neurobiology, was coauthor of the brain computer interface study published in the Lancet. Investigators used imaging technology in the operating room to guide placement of two quarter-inch square electrode grids in the regions of participant Jan Scheuermann’s brain that would normally control right arm and hand movement. The electrode points pick up signals from individual neurons, and computer algorithms are used to identify the firing patterns associated with particular observed or imagined movements, such as raising or lowering the arm. That intent to move is then translated into actual movement of the robot arm, which Scheuermann playfully nicknamed “Hector.”

“This breakthrough will provide opportunities for paralyzed individuals to interact in meaningful ways with their environments by using brain commands to control dexterous robotic prosthetic limbs,” said Steven Reis, MD, professor of medicine, of emergency medicine, and of clinical and translational science; associate vice chancellor for clinical research, health sciences; and director of the University of Pittsburgh Clinical and Translational Science Institute. “Also, it serves as a paradigm for high-impact translational research conducted by a multidisciplinary team.”

Using novel brain-computer interface technology developed at Pitt, Scheuermann can manipulate the arm. (She’s nicknamed it “Hector.”)
When the *New England Journal of Medicine* wanted a definitive medical review of severe sepsis, it was no surprise that they turned to the University of Pittsburgh, and, specifically, to Derek Angus, MD, MPH, Distinguished Professor, Mitchell P. Fink Professor, and chair of the Department of Critical Care Medicine. Pitt has a long track record in severe sepsis — a systemic inflammatory response to infection that is complicated by acute organ dysfunction. Many of the top clinical research papers in this area over the past few decades were written by Pitt investigators. The most cited paper on the epidemiology of sepsis is Angus’ 2001 analysis (with several Pitt coauthors) of incidence, outcomes, and associated costs of care. The *NEJM* review, coauthored with Tom van der Poll, MD, PhD, of the Netherlands and published in August 2013, will serve as an authoritative resource for physicians from the intensive care unit to the emergency department.

Severe sepsis is common, frequently fatal, and expensive. As recently as 30 years ago, it was typically lethal. Even today, mortality rates of 20 to 30 percent for in-hospital severe sepsis are not unusual. It is recorded in 10 percent of all ICU admissions; as a pioneering center for critical care medicine, Pitt has contributed to numerous aspects of improving intensive care. The roots of this work can be traced all the way back to the late Peter Safar, a Pitt Distinguished Service Professor of Resuscitation Medicine who established the second intensive care unit in the country at then–Presbyterian University Hospital. (He was also responsible for the first, which was at Baltimore City Hospital.)

“Sepsis has always been a big problem for intensive care specialists,” says Angus. “And running such a huge ICU service here at the University of Pittsburgh—I mean it’s a massive program—you can’t escape the overwhelming clinical problem of trying to manage sepsis and multisystem organ failure. In wanting to make the lives of our patients better, we can’t help but try to treat sepsis better.”

Perhaps the most influential severe sepsis study to date was conducted by Emanuel Rivers, MD, MPH, of Henri Ford Hospital and Wayne State University in Michigan, who completed fellowship training in critical care medicine at Pitt. Combining the work of several Pitt intensive care specialists, Rivers introduced the idea that, as with stroke, early recognition and prompt treatment are critical to improving patient outcomes. In practical terms, that means diagnosing sepsis in places like the emergency department.

“It’s basically bringing the intensive care to the patient,” says Angus. “The kind of care we deliver in the ICU has to be moved up front and started even before the patient gets to the ICU.”

Rivers’ study of “early goal-directed therapy,” published in 2001, looked at fewer than 300 patients in a single hospital. To rigorously test different treatment protocols, Angus is leading a large, multicenter clinical trial involving nearly 1,350 patients who arrive in the emergency department in septic shock. Funded by a grant from the National Institutes of General Medical Sciences, the five-year trial completed enrollment in August 2013, and the eagerly anticipated results are expected in early 2014.

As that investigation nears completion, Angus and other Pitt colleagues are launching another NIH-funded clinical trial exploring the use of biomarkers to guide antibiotic decisions in patients who come to the hospital with suspected sepsis and infection.

“Normally when you start the trial you hope to only determine whether the drug works,” says Angus. “Here we are going to ask questions about whether the drug works and in whom in the same trial.”

The study is part of a larger effort to bring personalized medicine to the treatment of severe sepsis, which is in turn an example of the University’s extensive work with UPMC making personalized medicine a part of everyday care.
When it comes to the search for 21st-century cures for disease, developmental biology is rapidly emerging as one of the most exciting and promising areas of research. With a focus on the mechanisms of development, differentiation, and growth in organisms at the molecular, cellular, and genetic levels, the field has historically been considered basic science, meaning most researchers tried to answer basic biological questions rather than solve clinical problems like heart disease.

Cecilia Lo, PhD, has always held a broader vision. She found her opportunity to act on it when she arrived at the University of Pittsburgh in 2009 as founding chair of the Department of Developmental Biology—one of a very few such academic departments to have a home in an American medical school.

“My vision was to build a department that is very strong in basic science relating to developmental biology, but to do so with investigators who have research interests that provide a natural bridge to clinical science in the School of Medicine,” says Lo, who is the F. Sargent Cheever Professor of Developmental Biology.

Four years later, research programs are investigating heart, lung, kidney, and liver organogenesis using zebrafish and rodent animal models, as well as through the study of embryonic stem cells and their differentiation into organs. These studies promise to yield new insights into the developmental origins of human disease.

The zebrafish (a vertebrate that shares a great deal of genetic code with humans) has become a powerful tool in biomedical research. Small and easy to maintain, zebrafish have embryos that are transparent, allowing for visualization of every cell during their rapid development. (Just 48 hours after fertilization, zebrafish larvae are free swimming and have formed major organs, including the brain, visual system, heart, and kidneys.) The University of Pittsburgh houses one of the largest zebrafish facilities in the world, with more than 11,000 tanks supporting as many as 500,000 adult zebrafish. The facility provides ample space for multiple independent large-scale research projects to run simultaneously.

Research programs in the department utilize a wide range of cutting-edge technologies. Examples include deployment of whole genome, exome, and transcriptome analysis with next-generation sequencing technology, automation in high-throughput chemical screens for drug discovery, and the pursuit of genetic analysis with large-scale mutagenesis screens.

**A FEW HIGHLIGHTS OF TRANSLATIONAL RESEARCH FROM THE DEPARTMENT OF DEVELOPMENTAL BIOLOGY:**

- While studying precursor cells involved in the formation of kidneys, Neil Hukriede, PhD, associate professor and vice chair of developmental biology, discovered compounds that modulate kidney fibrosis, an important step in the progression of kidney disease. He and colleagues are screening compounds for those that modulate the fibrotic response in zebrafish embryos and other preclinical models.

- Zebrafish hearts are different from human hearts in that, after an injury like a myocardial infarction, the cardiomyocytes can regenerate, whereas humans are frequently saddled with dead heart tissue after such an event. Michael Tsang, PhD, associate professor of developmental biology, has screened zebrafish embryos to find the mechanisms or pathways responsible for modulating...
cardiac regeneration. Using small molecules that modulate this pathway, Tsang’s lab is trying to help regenerate lost myocardial tissues to improve recovery of function after heart attack.

- Donghun Shin, PhD, assistant professor of developmental biology, is working on liver development and regeneration, trying to understand the signaling pathway involved in setting aside precursors that form the liver and pancreas. While his research aims to advance fundamental understanding of biology by figuring out how to use zebrafish to understand what pathways are important in organogenesis, he is acutely aware that physicians might one day use this knowledge to modulate organ regeneration in humans.

- Lo’s lab is interested in congenital heart disease. Using large-scale chemical mutagenesis screens and next-generation sequencing, the group has identified nearly 100 genes involved in structural heart defects. In parallel with these animal studies, her lab is recruiting patients with congenital heart disease for clinical studies that involve large-scale sequencing to try to identify mutations relevant to structural heart disease.

It’s a big step, but the path ahead is long. Asked when he expected that scientists would be able to build a whole human heart for implantation, 38-year-old Yang quipped, “Hopefully before I die.” That said, the results of this study (published in *Nature Communications* in August 2013) may find significant application sooner—perhaps to regenerate heart-tissue patches for implantation or as a model to test cardiac drug therapies.

The group’s new approach starts with decellularized mouse hearts. And how do you get one of those? Researchers “wash out” the cellular content of a mouse heart using detergents and enzymes, removing virtually all of the cellular innards. What’s left is the so-called ECM, or extra cellular matrix. ECM is basically the stuff that holds us together. It is secreted by fibroblasts, specialized cells that occur in connective tissue, and it retains its architecture after the cellular contents have been removed—providing a foundation upon which to build a new heart.

Researchers then seed what’s left of the mouse heart with human pluripotent stem cells, which have the potential to differentiate into organ-specific cells. The stem cells were coaxed into producing multipotential cardiac progenitor (MCP) cells. MCPs are precursors to three types of heart cells: cardiomyocytes, smooth muscle cells, and endothelial cells.

Once introduced to their new home and subjected to a complex diet of growth factors and other cellular delights, MCPs colonized the mouse heart scaffold and began to differentiate into the aforementioned three cell types. Even more significant: Specific cell types appeared right where they belonged. After 20 days of proliferation, the brand new heart construct started to beat spontaneously—though it was a little weak and slow by human heart standards.

Yang and his colleagues will next try to seed hearts so they produce a faster and more forceful beat. Success could send a lot of hearts racing.
You are a scientist. A certain peptide keeps showing up in your experiments. It could be important, but you don’t know much about it, and that bothers you. What are its properties? How many valuable hours will it take to get up to speed on this compound?

Enter the “molecular librarian”—a specialist from the Molecular Biology Information Service at Pitt’s Health Sciences Library System (HSLS). Before you even finish formulating your questions, here’s what you can find out: the full-length protein sequence that includes the peptide, its three-dimensional structure, the matching gene sequence that codes the peptide and its precise location in the genome, and the peptide’s possible implication in a genetic malfunction.

At Pitt, molecular biology information specialists stand ready to facilitate your access to, and understanding of, all of this information. Thanks to a unique program at the HSLS, Ansuman Chattopadhyay, PhD, and Carrie Iwema, PhD, MLS, do it all: They teach workshops on the use of available bioinformatics tools, provide users access to the tools through a Web portal (that they designed), consult with investigators when software questions arise, and work with other HSLS librarians to negotiate software licenses for the Pitt community.

It wasn’t always this way. Prior to 2002, each Pitt lab using DNA sequencing software licensed a single copy and trained a bench scientist in its use. Each lab bore the costs of the license, not only in dollar terms, but in human capital terms—staying current with the latest versions as well as migrating to new products and keeping up with advancing technology. Barbara Epstein, MLS, current HSLS director, and her predecessor Patricia Mickelson realized that the explosion of information in molecular biology could lead to a new role for the library.

They persuaded the medical school to fund a position for a librarian with specialized skills in molecular biology, plus access for all investigators.

Since Chattopadhyay, head of the Molecular Biology Information Service, was hired in 2002, there has been steady growth in the program (leading to a second hire, Iwema, in 2007), and exponential savings in licensing fees. Overall, HSLS spends less than $200,000 for licenses having a market price of more than $6 million per year, says Epstein. Thirteen bioinformatics tools are licensed by the University; the most popular, Ingenuity Pathway Analysis, has more than 380 registered users.

Like all good librarians, Chattopadhyay and Iwema work tirelessly to facilitate knowledge transfer to the research community. They offer weekly workshops on a wide range of bioinformatics topics, including “Cancer Informatics,” “DNA Analysis Tools,” “Pathway Analysis Tools,” “SNPs and Genetic Variation,” and “Microarray Data Analysis,” which, in 2012, were attended by more than 470 investigators. They also teach segments in graduate and undergraduate bioinformatics courses. Overall, 844 Pitt researchers received hands-on bioinformatics training in 2012.

Last, but not least, HSLS offers a Web portal to provide access to the licensed software as well as publicly available software and databases. At the portal you can find information on upcoming workshops, send a question to a molecular librarian, access available software and tools, search public gene and protein databases, and search video libraries of laboratory protocols and other visual instructional tools. And be sure not to miss the blog “What’s New @ HSLS MolBio,” which has announcements on new software, workshops, and much, much more.
When Jeffrey Walch, an MD/PhD candidate in Fadi Lakkis’s laboratory (Lakkis, MD, is the Frank and Athena Sarris Professor of Transplantation Biology; professor of surgery, of medicine, and of immunology; and scientific director of the Thomas E. Starzl Transplantation Institute), started his PhD work, the prevailing view of the organ rejection process was that chemokines, molecules known to effect cell movement, directed immune cells into the transplanted tissue. Blockade of chemokines was a major focus of drug development efforts to overcome transplant rejection, but blockade was not 100 percent effective. Walch and Lakkis wanted to find out why. To answer this and other questions, the team undertook a series of experiments. Their findings, reported in the *Journal of Clinical Investigation*, are considered a breakthrough in the understanding of host-transplant rejection.

Some initial work by Walch and another member of the Lakkis lab, Martin H. Oberbarnscheidt, MD, PhD, research assistant professor of surgery, found that chemokine signaling was not required in the migration of immune cells to transplanted tissue; primed T cells still showed up in the transplant.

What was directing the T cells into the new organ? Although the antigen–T cell relationship has been well-studied, at the time it was not thought that cognate antigen (antigen from the transplant, considered foreign to the host) directed T cells into transplanted tissues. The Lakkis team asked whether cognate antigen could be responsible. They found that if the antigen was not expressed in the graft or if the T cells injected into the mouse did not recognize the antigen, then the T cells did not migrate to the transplanted organ, confirming that cognate antigen was necessary and responsible.

Next, Walch wanted to find out which cells were presenting antigen to the T cells. Prior to this research, it was thought that donor endothelial cells that line the lumen of the blood vessels in the donor kidney were solely responsible for presentation of antigen to T cells migrating into the transplanted organ. Walch designed experiments to differentiate between antigen-presenting cells and found that dendritic cells were much more effective in retaining T cells within the transplant than endothelial cells. Finally, Walch found that nonprimed (nonspecific) T cells, although not able to migrate into the organ alone, were able to infiltrate the transplant when transferred along with donor-reactive T cells.

This work has major implications for transplantation. While the chemokine paradigm has been upended, the experiments elucidate the initial stages of rejection and point to activation of T cells as a new target for intervention.
Our DNA is continuously exposed to agents that cause damage, like ultraviolet light, air pollution, and cigarette smoke. Imagine — in the time that it takes you to read this sentence, every cell in your body has suffered at least one type of DNA damage. How is it that we manage to keep our DNA healthy in the face of this perpetual onslaught? Bennett Van Houten, PhD, Richard M. Cyert Professor of Molecular Oncology in the Department of Pharmacology and Chemical Biology, has a favorite analogy: Visualize a helicopter with a blind pilot trying to locate and repair potholes on more than 6,000 miles of street in Los Angeles. There are more than 6 billion DNA bases in each human cell, but far fewer repair proteins. It is thought that repair proteins recognize damage-induced distortions in the DNA helical structure through a highly dynamic process. Somehow, the helicopter finds the potholes.
Van Houten and the members of the Genome Stability Group at the University of Pittsburgh Cancer Institute are dedicated to elucidating how DNA repair mechanisms work. Van Houten studies the intricacies of nucleotide excision repair (NER), which involves removal of defective base pairs. In humans, NER is thought to involve more than 30 proteins, with separate proteins for recognition, excision, and other steps in the process. Van Houten’s lab conducts structure-function studies of repair proteins using atomic force and fluorescence microscopy of quantum dot-labeled molecules, tools that permit visualization of repair proteins as they bind to DNA.

Other scientists in the group focus on different pieces of the puzzle and are refining methods to enable visualization of the repair process at the molecular level in living cells. Li Lan, MD, assistant professor of microbiology and molecular genetics, developed a method for visualizing DNA damage and using the fluorescent protein KillerRed to induce damage at defined genomic locations. Repair proteins, lit up by fluorescent markers of different colors, can be seen congregating at sites of damage. This technique has helped to elucidate whether repair mechanisms activated during transcription, when the DNA is relatively open, differ from those that repair condensed (unexpressed) DNA — and it appears that they do.

Defects in repair proteins (or their absence) can lead to many diseases, including cancer. Kara A. Bernstein, PhD, assistant professor of microbiology and molecular genetics, studies Sgs1, a repair protein that repairs double-strand breaks in DNA. Defects in Sgs1 lead to devastating diseases like Rothmund-Thomson syndrome, a skin disease associated with osteosarcoma. Bernstein hopes that knowledge of double-strand break repair mechanisms will lead to a deeper understanding of tumorigenesis and cancer progression.

The multiplicity of DNA repair pathways in normal cells is often incomplete in cancer cells, a difference that can be exploited for the selective killing of cancer cells. Christopher J. Bakkenist, PhD, associate professor of radiation oncology, studies a group of repair proteins that are defective in some pancreatic and lung cancers. Bakkenist is testing the hypothesis that another repair protein functions in parallel to this group and is essential for the viability of the cancer cells. Inhibition of the second repair pathway might selectively kill the pancreatic or lung cancer cells while leaving normal cells intact.

Robert W. Sobol, PhD, associate professor of pharmacology and chemical biology, is also focused on the role of DNA repair proteins in cancer. Glioblastoma, the most commonly diagnosed brain malignancy, is treated with an alkylating agent, temozolomide, but with limited success due to the development of resistance. Sobol’s group is studying whether certain steps in the base excision repair pathway can be selectively targeted to reduce resistance and lead to better outcomes in patients with the disease.

What makes the Genome Stability Group at Pitt stand out? “The size of the group, the quality and quantity of publications, and the methods we are using to explore specific questions—we can now observe DNA repair in living cells as it happens. And our applications range from bench science to bedside problems in cancer. Very few labs in the world can do this,” says Van Houten.

And he notes with excitement, “The group is still growing!”
The Richard King Mellon Foundation Institute for Pediatric Research at Children’s Hospital of Pittsburgh of UPMC has named Stephen Maricich, MD, PhD, and Timothy Sanders, MD, PhD, as the first two physician-scientists in its Mellon Scholars Program, which enables promising physician-scientists in the early stages of their careers to pursue potential breakthrough research projects. Both Maricich and Sanders are visiting assistant professors of pediatrics in the School of Medicine.

Maricich is a neurologist whose research focuses on understanding sensory system development. He studies Merkel cells, touch receptors that detect curvature, shape, and size. Maricich and his colleagues identified the first gene necessary for Merkel cell creation and showed that deletion of Merkel cells abolished a particular type of sensory nerve response, answering a 130-year-old question in sensory system biology. Deranged growth of Merkel cells is also thought to cause a type of cancer that is resistant to chemotherapy. Maricich also studies how disruptions of neuronal development lead to reorganization of connectivity and function of the auditory system.

Sanders is a neonatologist who conducts research on the control of neural and limb development in the embryo. He uses high-end cell imaging with real-time video microscopy that permits visualization of organ development as it happens. Recent work from his research fellowship published in *Nature* characterized the role of contact-mediated signaling in the development of the vertebrate limb.

Established through a gift from the Richard King Mellon Foundation, the institute, led by Jay K. Kolls, MD, is an incubator for research that challenges conventional wisdom and can lead to paradigm shifts in pediatric medicine. This kind of high-risk, high-impact investigation is not typically funded through government or conventional sources, placing the Department of Pediatrics and Children’s Hospital in a unique realm of pediatric research centers.

The focal point for basic laboratory research is the John G. Rangos Sr. Research Center, which houses one of the nation’s fastest growing pediatric research programs. The center supports nearly 390 active protocols pursued by more than 125 principal investigators in 63 separate laboratories. (See sidebar for a few examples.)

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**PEDIATRIC RESEARCH HIGHLIGHTS**

**The Mellon Scholars Program**

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**390 protocols 125 principal investigators 63 separate laboratories**

**JAY K. KOLLS: Harnessing the Lung’s Mucosal Immune System To Fight Lung Infections**

Lung infection is the leading reason children visit doctors and is a major cause of death and illness among children throughout the world. The laboratory of Jay K. Kolls, MD, investigates the complexities of the mucosal immune system in the lung and develops immunological tools or vaccines to help doctors win the battle against viral and bacterial infections of the lungs. Kolls is vice chair for translational research, director of the Richard King Mellon Foundation Institute for Pediatric Research, and professor of pediatrics. A major focus of Kolls’ research is investigation of lung immune defenses in healthy and immunocompromised patients and the development of new treatments for pneumonia, asthma, and allergic bronchopulmonary disease in children with cystic fibrosis.

**ALEJANDRO HOBERMAN: Perfecting Diagnosis of Acute Otitis Media**

The Department of Pediatrics is also a leader in clinical research. Alejandro Hoberman, MD, chief, Division of General Academic Pediatrics, Jack L. Paradise Professor of Pediatric Research, and professor of pediatrics, focuses his research on the prevention, diagnosis, and treatment of two of the most frequently occurring pediatric conditions, acute otitis media (AOM) and urinary tract infections. In 2011, he was the lead author of a landmark paper in the *New England Journal of Medicine* providing strong evidence that treatment with antibiotics was the best course of action in children diagnosed with AOM. Hoberman has also been involved in the development of a multimedia series of educational programs aimed at improving diagnostic accuracy in children with AOM. These resources have been used to train medical residents across the country and audiences worldwide in diagnosis of AOM.

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**GARY A. SILVERMAN: Studying Cell Death as a First Step in Preventing or Treating Diseases in Newborns**

Gary A. Silverman, MD, PhD, Twenty-Five Club Professor of Pediatrics and chief, Division of Newborn Medicine, studies processes that lead to cell death. Silverman and his colleague Clifford J. Luke, PhD, discovered a new subset of a group of proteins, the serpins (short for “serine protease inhibitor”), that blocks destructive proteases, a class of proteins that kills cells if uncontrolled and protects cells from injury. Surprisingly, the new subset resides within cells, rather than circulating throughout the body. With further investigation, it may be possible to harness serpins to direct some cells, such as tumor cells, to die (by depriving them of serpins), while boosting serpins in others, such as degenerating neural cells in Alzheimer’s and Parkinson’s diseases.
Very year in this country, more than half a million babies arrive prematurely (before 37 weeks of gestation). That’s around 12 percent of babies who are, to some extent, small, underdeveloped, and/or facing challenges; this is especially true of those born as early as 24 to 25 weeks, at the outer edge of viability. Capitalizing on scientific discoveries, new drugs, and greater understanding of the needs of these smallest of humans, specialists in neonatal intensive care units have become increasingly skilled at negotiating these challenges. However, that is not the case with necrotizing enterocolitis (NEC), a life-threatening inflammation of the intestine. In the worst cases, the dead and dying sections of intestine. In the worst cases, the toxic stew in the abdomen sets off a cascade of inflammatory reactions from which the child cannot recover. Between 20 and 30 percent of infants with NEC do not survive, with sepsis and multisystem organ failure often contributing to death.

“NEC is challenging because, early on, it’s hard to diagnose. And there’s no specific treatment. It’s frustrating, because our success hasn’t improved in the last 30 years,” says David Hackam, MD, PhD, the Watson Family Professor of Surgery and associate dean for medical student research.

Hackam, who has a secondary appointment in the Department of Cell Biology, operates on babies with NEC to remove dead and dying sections of intestine. In the worst cases, the toxic stew in the abdomen sets off a cascade of inflammatory reactions from which the child cannot recover. Between 20 and 30 percent of infants with NEC do not survive, with sepsis and multisystem organ failure often contributing to death.

In June 2012, Hackam and colleagues published groundbreaking research in *Proceedings of the National Academy of Sciences (PNAS)* describing how amniotic fluid stops NEC from developing in mice. The work not only provided an explanation for why preemies suffer from NEC while full-term babies do not, it opened up tantalizing avenues for stopping NEC in its tracks.

Making yet another big splash in a June 2013 edition of *PNAS*, Hackam and several Pitt colleagues have recently shown that breast milk might also prevent NEC.

This line of research began with the theory that the death of intestinal tissue was related to inadequate circulation of blood. Collaborating with Mark Gladwin, MD, professor of medicine, chief of the Division of Pulmonary, Allergy, and Critical Care Medicine, and director of Pitt’s Heart, Lung, Blood, and Vascular Medicine Institute, the Hackam lab demonstrated that activation of a receptor (TLR4) in blood vessels led to impaired blood flow to the gut, causing or contributing to NEC in mice. Trying to determine why breast milk prevented NEC, the team discovered that breast milk was high in sodium nitrate, which gets converted to the vasodilator nitric oxide and improves blood flow. To test whether sodium nitrate was breast milk’s active ingredient to prevent NEC, they added sodium nitrate to infant formula fed to mice predisposed to NEC. The supplemented formula was protective; the researchers were able to measure improved blood flow and show that NEC did not develop in these mice. Hackam and Gladwin are now planning a clinical trial to administer a similar therapy in infants at risk for NEC.

In some NEC survivors, not enough intestine remains to support normal digestion. These children, who have short bowel syndrome, require intravenous nutrition, which comes with significant risks. Hackam has long envisioned an artificial intestine that would enable these patients to eat a normal diet. To this end, he and John March, PhD, a Cornell University biophysicist, formed a collaboration, which won support from the Hartwell Foundation in 2012. Hackam provided the expertise in growing intestinal stem cells, while March contributed techniques for making bioscaffolds that mimic the complex shape of the human intestine. Most bioscaffolds are made with a process called laser etching, which works well for detailing very small features but cannot reproduce the folds and tiny fingerlike projections that line every inch of the intestine’s interior. March’s secret to overcoming this challenge is to form the scaffold using a sacrificial mold that dissolves and leaves only the scaffold.

The team’s scaffolds are made from modified FDA-approved materials—compounds similar to elastin and collagen, which are naturally found in intestinal tissue. Their first experiments with it involved implanting it into the fatty abdominal tissue of mice. As they had hoped, the presence of their implant stimulated the growth of blood vessels, which are needed to feed and sustain the implant. Since then, they have been able to implant and sustain artificial intestines in mice. As of yet, this work is still unpublished, but Hackam is optimistic.

“If you had asked me six months ago how long it would take to do this—to take these cells and culture them on a scaffold and then have success in animals—I would have said maybe a year, and maybe more,” Hackam said in early 2013. “But we’ve made great progress in the last six months.”
Patients entering Magee-Womens Hospital of UPMC may not realize how they benefit from Magee-Womens Research Institute (MWRI), the first and largest independent research institute to focus exclusively on the health of women and infants. Established in 1992 and led by Yoel Sadovsky, MD, the Elsie Hilliard Hillman Professor of Women’s and Infants’ Health Research, professor of obstetrics, gynecology, and reproductive sciences, and of microbiology and molecular genetics, the institute fosters a wealth of collaborations among basic scientists and clinicians. While the institute is closely aligned with the Department of Obstetrics, Gynecology, and Reproductive Sciences in the School of Medicine, its scientists also represent numerous other basic science and clinical disciplines, and of microbiology and molecular genetics, the institute fosters a wealth of collaborations among basic scientists and clinicians. While the institute is closely aligned with the Department of Obstetrics, Gynecology, and Reproductive Sciences in the School of Medicine, its scientists also represent numerous other basic science and clinical disciplines, bringing a wide range of expertise to bear on issues in the health of women and infants. Just across Craft Avenue is Magee-Womens Hospital, which presents clinical research opportunities that are otherwise hard to come by, benefitting both patients and researchers. Two examples of current investigations at the institute are highlighted here.

**PLACENTAL ROLE IN IMMUNOLOGICAL PROTECTION OF FETUS**

In a remarkable study (published in an early online edition of the Proceedings of the National Academy of Sciences in July 2013), Elizabeth Delorme-Axford, PhD, a graduate student in the lab of Carolyn B. Coyne, PhD, associate professor of microbiology and molecular genetics, and members of Yoel Sadovsky’s lab at MWRI, found that trophoblasts—specialized cells in the placenta—grown in cell culture are highly resistant to infection by diverse viruses. Additionally, when the culture medium was taken from the trophoblasts after 24 hours and transferred to nonplacental cells, the medium conferred resistance to viral infections in the nonplacental cells. The trophoblast-conditioned culture medium had vesicles called exosomes containing a unique group of microRNAs, indicating that the trophoblasts released specific components that conferred viral resistance to nonplacental recipient cells. MicroRNAs are small segments of RNA involved in regulation of gene expression, usually gene silencing, by preventing translation of targeted messenger RNAs and/or by accelerating their degradation.

The Coyne and Sadovsky labs also found that trophoblast-derived exosomes and microRNAs induced autophagy—a process the cell employs to degrade and consume unwanted material and invading pathogens—in the recipient cells and thereby enhanced antiviral defenses. These findings illuminate a pathway used by trophoblasts to suppress viral infections systemically by conferring viral resistance to nonplacental cells, suggesting a novel mechanism for shielding placental and maternal cells against viral infections during pregnancy.

**UNLOCKING THE MYSTERY OF PREECLAMPSIA**

Preeclampsia is a pregnancy-specific syndrome and a leading cause of maternal and fetal morbidity and mortality. While several preexisting conditions are associated with an increased risk of preeclampsia, such as diabetes, hypertension, renal dysfunction, and obesity, the underlying cause of preeclampsia is unknown. Robert W. Powers, PhD, associate professor of obstetrics, gynecology, and reproductive sciences, in collaboration with Carl A. Hubel, PhD, James M. Roberts, MD, and Robin E. Gandley, PhD, studies obesity-related risk factors in preeclampsia, including the role of asymmetric dimethylarginine (ADMA), a naturally occurring chemical found in blood plasma. ADMA interferes with production of nitric oxide, a key chemical used by blood vessels to signal the surrounding smooth muscle to relax, thus increasing blood flow and vasodilation. Powers uses biochemical and molecular biology techniques to investigate ADMA as one possible mechanism by which obesity-mediated vascular dysfunction in pregnancy increases the risk of preeclampsia. The role of ADMA on vascular function in pregnant women and obese animal models is also being studied.
Wanna see my picture on the cover
Wanna buy five copies for my mother
Wanna see my smilin' face
On the cover of the Rollin' Stone
SHEL SILVERSTEIN
Scientists are rightly pleased — maybe even giddy — when their research paper is selected for the cover of a peer-reviewed journal, especially when the journal is considered prominent in the field. And when it’s a transcendent journal like *Nature*, which selects the best science from all fields, watch out!

For the first time, researchers have described the 4-million-atom structure of the HIV capsid, or protein shell. “The capsid is critically important for HIV replication, so knowing its structure in detail could lead us to new drugs that can treat or prevent the infection,” said senior author Peijun Zhang, PhD, associate professor of structural biology. “This approach has the potential to be a powerful alternative to our current HIV therapies, which work by targeting certain enzymes, but drug resistance is an enormous challenge due to the virus’s high mutation rate.” The team used cryo-electron microscopy and cryo-electron tomography combined with all-atom large-scale molecular dynamics simulations to reveal a three-helix bundle with critical molecular interactions at the seams of the capsid — areas that are necessary for the shell’s assembly and stability and which also represent vulnerabilities in the protective coat of the viral genome. “The capsid has to remain intact to protect the HIV genome and get it into the human cell, but once inside it has to come apart to release its contents so that the virus can replicate,” said Zhang. “Developing drugs that cause capsid dysfunction by preventing its assembly or disassembly might stop the virus from reproducing.”

A new study reports that some cancer cells are unable to divide properly when deprived of a key protein. All cells have a network of mitochondria — tiny structures essential for energy production and metabolism — and dynamin-related protein 1 (Drp1) helps mitochondria undergo fission, a process by which they split themselves into two new mitochondria. In breast or lung cancer cells made to be deficient in Drp1, a team of
Researchers observed a huge network of highly fused mitochondria. These cancer cells appear to have stalled during a stage in cell division called G2/M. Unable to divide into new cells, the cancer growth stops. Those cells that do try to divide literally tear their chromosomes apart, causing more stress for the cell. “Once we revealed this process for halting cancer cell growth by knocking out Drp1, we began looking into existing compounds that might utilize a similar mechanism,” said senior author Bennett Van Houten, PhD, Richard M. Cyert Professor of Molecular Oncology in the Department of Pharmacology and Chemical Biology. “Now that we know affecting mitochondria in this manner inhibits cell growth, we could target drugs to this biological process to treat cancer.”

MOLECULAR CANCER RESEARCH

More than 125 genetic components in a chemotherapy-resistant, brain tumor-derived cell line have been identified by researchers, which could offer new hope for drug treatment to destroy the cancer cells. The potential drug targets were identified after testing more than 5,000 genes derived from glioblastoma multiforme, an aggressive brain tumor. The genes were evaluated for their role in responding to the chemotherapy drug temozolomide, which works by modifying the cancer’s DNA in a way that triggers cell death. “Unfortunately, some cancers—particularly glioblastoma multiforme—are able to repair the DNA damage done to the tumor by temozolomide before the cancer cells are destroyed,” said senior author Robert W. Sobol, PhD, associate professor of pharmacology and chemical biology, School of Medicine, and of human genetics, Graduate School of Public Health. Sobol and colleagues, including MSTP student David Svilar, PhD, identified multiple “druggable” targets that could make the cancer more sensitive to temozolomide and elucidated the processes that allow the tumor to survive the onslaught of surgery, radiation, and chemotherapy.

CANCER RESEARCH

The administration of high-dose interleukin-2 (HDIL-2), which promotes an immune response to cancer and has durable antitumor effects in 5 to 10 percent of patients with melanoma and renal cell carcinoma, is often limited by side effects due to the drug’s toxicity. Autophagy is the self-consumption by a cell of internal components, and Pitt researchers suggest that the autophagy inhibitor hydroxychloroquine, an oral medication, could reduce HDIL-2’s toxicity. According to Michael T. Lotze, MD, professor of surgery, School of Medicine, and of bioengineering, Swanson School of Engineering, the drug combination in mice with cancer was dramatically more effective than HDIL-2 alone. Traditional chemotherapy and radiation therapy often promote autophagy; the findings provide a novel clinical strategy to enhance the efficacy of HDIL-2 immunotherapy for patients with cancer while protecting healthy tissue that could be used in other cancer therapies as well.

DIABETES

Researchers from Pitt recently concluded that dendritic cells (DC), which are involved in the tissue recruitment and activation of macrophages, promote macrophage infiltration and make up a substantial proportion of obesity-associated increases in CD11c+ cells in adipose tissue (AT) and the liver. Robert M. O’Doherty, PhD, associate professor of medicine and of microbiology and molecular genetics, and colleagues used flow cytometry, electron microscopy, and loss-and-gain of function approaches to assess the contribution of DC to the pattern of immune cell alterations and recruitment in obesity. They found that mice lacking DC had reduced AT and liver macrophages, that DC replacement in DC-null mice and delivery of bone marrow-derived DC to lean wild-type mice increased liver and AT macrophage populations, and that mice lacking DC were resistant to the weight gain and metabolic abnormalities of a high-fat diet. Together, the data demonstrated that DC are elevated in obesity, contribute to the determination of tissue immunophenotype, and play a role in systemic metabolic responses to a high-fat diet.

NEUROBIOLOGY OF DISEASE

Melatonin injections delayed symptom onset and reduced mortality in a mouse model of amyotrophic lateral sclerosis (ALS), according to a study led by Robert M. Friedlander, MD, Walter E. Dandy Professor and chair of Neurological Surgery, and head of that department’s Cerebrovascular Surgery Program. The causes of ALS are not well understood, thwarting development of a cure or even effective treatments. Friedlander’s team found that receptors for melatonin, a naturally occurring hormone known for its role in sleep regulation, are found in nerve cells, and that melatonin acts as a powerful antioxidant to block apoptosis, or programmed cell death. “Our experiments show for the first time that a lack of melatonin and melatonin receptor 1, or MT1, is associated with the progression of ALS,” Friedlander said.

BIOLOGY OF REPRODUCTION

Male fertility depends on maintenance, controlled disruption, and reformation of the blood-testis barrier (BTB), a large junctional complex between adjacent Sertoli cells in the seminiferous tubules of the testis. William H. Walker, PhD, associate professor of obstetrics, gynecology, and reproductive sciences, along with postdoctoral fellow Pawan Puri, PhD, recently found that SHP2, a nonreceptor protein tyrosine phosphatase, is a key regulator of BTB integrity and Sertoli cell support of spermatogenesis and fertility.
The presence of certain T cells allows the immune system to effectively police tuberculosis (TB) and prevent it from turning into an active infection, according to a study led by Shabaana A. Khader, PhD, assistant professor of pediatrics, and published in the Journal of Clinical Investigation.

A hallmark of TB is the granuloma, a collection of immune cells that surround infected lung cells. Khader studied the differences between protective granulomas, as in latent TB, and the nonprotective granulomas seen in active TB patients. She found that, in latent TB, the granulomas contained lymphoid structures resembling lymph nodes and CXCR5+ T cells within the lymphoid structures. Granulomas that did not contain lymphoid structures and CXCR5+ T cells were associated with active TB. When CXCR5+ T cells were transferred from donor animals to TB-infected mice that lacked CXCR5, T cell localization and lymphoid structure formation were restored, leading to decreased susceptibility to active TB. The protective power of CXCR5 points to a new direction for management of TB, with implications for the development of vaccines to prevent infection.

Pitt scientists, in conjunction with researchers from Sanofi-Aventis and Regeneron, discovered that a monoclonal antibody was able to inhibit chemicals involved in inflammation and reduce breathing problems, improve lung capacity, and decrease inflammation among people with a common type of moderate-to-severe asthma. Their findings were published in the New England Journal of Medicine. Recent estimates suggest that 10 to 20 percent of asthma patients don’t have optimal control of their symptoms despite currently available medications, said senior author Sally E. Wenzel, MD, professor of medicine and director of the Asthma Institute at UPMC.

“We suspect that there are different underlying causes that lead to these different types of asthma, so different treatment approaches are likely needed,” she said. In a Phase IIa clinical trial, patients who received weekly injections of the antibody dupilumab had an 87 percent reduction in asthma attacks compared to patients in the placebo group and also had lower levels of biomarkers of inflammation. The findings suggest that dupilumab holds promise for the treatment of moderate-to-severe asthma, although further studies are needed to better define the patients who will do the best with this new approach.
A Pitt study revealed for the first time a mechanism that causes tinnitus, a chronic and sometimes debilitating perception of phantom sound, and suggested that an epilepsy drug might prevent tinnitus from developing after exposure to loud noise. The team focused on an area of the brain that is home to an important auditory center called the dorsal cochlear nucleus (DCN). After taking a close look at the biophysical properties of tiny channels — called KCNQ channels — through which potassium ions travel in and out of the cell, researchers found that mice with tinnitus have hyperactive DCN cells because of a reduction in KCNQ potassium channel activity. Treatment of mice with an FDA-approved epilepsy drug called retigabine, which increases KCNQ channel activity, immediately after noise exposure prevented the development of tinnitus. “Such a medication could be a very helpful preventive strategy for soldiers and other people who work in situations where exposure to very loud noise is likely,” said senior investigator Thanos Tzounopoulos, PhD, associate professor of otolaryngology.

Each year an estimated 1.7 million Americans sustain a traumatic brain injury due to traffic accidents, falls, assaults, and sports participation. A multidisciplinary Pitt research team developed an agent that can cross the blood-brain barrier in an animal model and prevent oxidation of cardiolipin, a phospholipid found in mitochondrial membranes. Treatment prevented the secondary damage of severe traumatic brain injury and preserved function that would otherwise have been impaired, as reported by Hülya Bayır, MD, associate professor of critical care medicine and senior author of the study, published in Nature Neuroscience. Such a targeted oxidation blocker might also be beneficial in the treatment of other neurological disorders, like Parkinson’s disease, amyotrophic lateral sclerosis, and stroke.

Allergens and biologic molecules that suppress the immune system are transferred from mothers to infants via breast milk and block the development of allergic diseases like asthma later in life. This protective immune function is a form of immune tolerance. A common childhood virus, respiratory syncytial virus (RSV), disrupts immune tolerance, leading to increased susceptibility for allergic asthma later in life, as reported in Nature Medicine by senior authors Prabir Ray, PhD, and Anuradha Ray, PhD, professors of medicine and of immunology, and lead author Nandini Krishnamoorthy, an MD/PhD student in the Ray lab. Infant mice tolerized to the allergen ovalbumin via mother’s milk, when infected with RSV and subsequently challenged with ovalbumin, developed asthma-like symptoms, with increased immune cell infiltration in their airways and increased mucus production. However, an uninfected control group did not mount an allergic immune response upon allergen challenge. RSV infection control may be a promising approach to reducing the current asthma and allergy epidemic.

Eric Lagasse, PhD, PharmD, associate professor of pathology, and his team tested the possibility of using lymph nodes as a new home for cells from other organs in what is called an “ectopic” transplant. Healthy liver cells were injected into lymph nodes of mice at various locations. The result, reported in Nature Biotechnology, was an enlarged, liver-like organ that functioned akin to the liver; a single hepatized lymph node rescued mice with a lethal liver disease. Likewise, thymus tissue transplanted into the lymph nodes of mice that lacked the organ generated functional immune systems, and pancreatic islet cell transplants restored normal blood sugar control in diabetic animals. “Our goal is not necessarily to replace the entire liver but to provide sufficient cell mass to stabilize liver function and sustain the patient’s life,” Lagasse said. “That could buy time until a donor organ can be transplanted or permit the diseased organ to recover.”

In a study of prepubertal male macaque monkeys published in Cell Stem Cell, previously frozen spermatogonial stem cells restored production of sperm that successfully fertilized eggs to produce early embryos, according to senior investigator Kyle E. Orwig, PhD, associate professor of obstetrics, gynecology, and reproductive sciences and investigator at Magee-Womens Research Institute. The findings are encouraging because several centers in the U.S. and abroad are already banking testicular tissue for boys in anticipation that new stem cell-based therapies will be available in the future to help them father their own biological children. Orwig directs the Fertility Preservation Program in Pittsburgh, which offers education and treatment options for children, as well as adult men and women who are at risk of becoming infertile due to medical problems, including cancer.
In one of the largest genetic studies ever conducted, an international team of researchers including Richard Duerr, MD, Professor of Inflammatory Bowel Disease Genetic Research and one of 12 co-investigators who conceived, designed, and managed the study, analyzed data from 15 large studies on the genetics of inflammatory bowel disease (IBD), which includes Crohn’s disease and ulcerative colitis. They identified more than 25,000 single nucleotide polymorphisms (SNPs), or genetic variations, that had at least suggestive evidence for association with Crohn’s disease, ulcerative colitis, or both. These association signals were followed in more than 41,000 IBD and control samples at 11 centers around the world, including the University of Pittsburgh, to verify that 163 genomic regions, including 71 newly identified ones, are associated with IBD. The study, published in Nature, uncovered pathways shared between responses to mycobacterial infections, such as tuberculosis and leprosy, and those predisposing people to IBD.

More than 100,000 Americans suffer from chronic pancreatitis, a progressive inflammatory disease characterized by abdominal pain and permanent pancreatic damage; excessive alcohol consumption is a major risk factor. Researchers from the School of Medicine and more than 25 other health centers across the United States found a genetic variant on chromosome X near the claudin-2 gene (CLDN2) that predicts which men who are heavy drinkers are at high risk of developing chronic pancreatitis. The discovery of a genetic basis for the disease, reported in Nature Genetics, solves a major mystery about why some people develop it and others do not and also explains why some men have a higher risk of developing pancreatitis with alcohol consumption, according to lead author David C. Whitcomb, MD, PhD, Giant Eagle Foundation Professor of Cancer Genetics, professor of medicine, and of cell biology, and co-investigator Dhiraj Yadav, MD, MPH, associate professor of medicine.

Human cytomegalovirus (HCMV) is one of the leading prenatal causes of congenital intellectual disability, deafness, and deformities worldwide. According to the U.S. Centers for Disease Control and Prevention, one of every 150 children is born with HCMV infection. One in five of those infected goes on to develop permanent problems, such as intellectual disability, vision and hearing loss, and seizures. A study by Pitt researchers, including Vishwajit Nimgaonkar, MD, PhD, professor of psychiatry, and published in PLoS ONE, revealed that primitive human stem cells are resistant to HCMV infection. However, as stem cells and other primitive cells mature into neurons, they become more susceptible to HCMV. This knowledge could allow investigators to find effective treatments for the virus and prevent its potentially devastating consequences.

In a study published in Current Biology, lead author Karen L. Bunday, PhD, postdoctoral associate, and senior author Monica A. Perez, PhD, assistant professor of physical medicine and rehabilitation, found that when impulses from the motor cortex were precisely timed to arrive at the spinal cord 1-2 milliseconds before impulses from a peripheral nerve in the wrist reached it, there were improvements in hand muscle activity, strength, and manual dexterity in a precision grip task in spinal cord injured patients. They also observed an increase in corticospinal transmission in both injured and uninjured individuals that lasted for up to 80 minutes. “We are using noninvasive electrophysiological measures to understand the mechanisms of recovery and to determine how we can best enhance transmission of remaining descending pathways to muscles in patients with incomplete spinal cord injuries,” said Bunday. “The ultimate aim is to improve the patient’s ability to execute daily functions, like eating and grasping, as independently as possible.”

An increased risk of autism spectrum disorders (ASD) could result from an accumulation of many small, common genetic variations rather than large-effect, rare changes in the genetic code, according to a multicenter study published in Molecular Autism and led by researchers in the School of Medicine. The investigators used sophisticated quantitative genetic techniques to examine thousands of DNA samples from families in which one child but no parent or sibling had an ASD; families in which more than one child had an ASD; and unaffected subjects. “In families where only one child has an ASD, 40 percent of the risk is inherited, while in families with more than one affected child, the risk rises to 60 percent. These small gene changes can add up, even though individually they do little harm,” said senior author Bernard J. Devlin, PhD, professor of psychiatry. “This might explain why parents who do not have autism traits can have children who do.”
Genes that have roles in the same biological pathways change their rate of evolution in parallel, a finding that could be used to discover their functions, as reported in *Genetics* by lead author Nathan Clark, PhD, assistant professor of computational and systems biology. Clark’s group studied the evolving genomes of 18 yeast species and 22 mammalian species, looking at genes that are involved in meiosis, a cell division process, and in DNA repair. They found parallel changes in evolutionary rates not only among genes encoding proteins that physically interact with each other but also among those that had no direct contact but still participated in meiosis or DNA repair pathways. “In the future, a researcher studying a particular disease process might be able to plug a couple of known genes into a database of evolutionary rate changes to find others that have a parallel history,” Clark said. “That could provide new insight into the workings of the biological pathway of interest.”

An international, multicenter study led by Pitt researchers found biomarkers that indicate whether a patient is at risk for acute kidney injury (AKI), a condition that often affects those in intensive care and can occur after serious infections, surgery, or taking certain medications. The results, published in *Critical Care*, provide insight into the potentially deadly condition that affects up to 7 percent of all hospitalized patients. Existing methods of determining kidney function may not indicate changes for several days, allowing time for significant kidney damage to occur. Biomarkers, which are naturally occurring proteins or other molecules in the blood, urine, or other body fluids or tissues, may help physicians more accurately determine the risk of AKI in critically ill patients so that early treatment can minimize progression and save lives, according to senior investigator John Kellum, MD, professor of critical care medicine.

A small HIV protein called Nef interacts with many other proteins in infected cells to help the virus multiply and hide from the immune system. In findings published in *Chemistry and Biology*, Pitt researchers developed a way to track Nef activity in high-throughput drug screening protocols by linking it to an enzyme called Hck, which is activated by Nef in HIV-infected cells, explained senior author Thomas E. Smithgall, PhD, William S. McEllroy Professor and chair of microbiology and molecular genetics. Smithgall’s group showed that targeting this vulnerable spot could stop the virus from replicating, potentially thwarting HIV infection from progressing to full-blown AIDS. One of the compounds they discovered, called B9, seemed particularly potent at blocking Nef. The team is working with medicinal chemists at the University of Pittsburgh Drug Discovery Institute to find analogs of B9 that have therapeutic potential and plans to assess them in animal models of HIV/AIDS.

Smartphone applications that claim to evaluate a user’s photographs of skin lesions for the likelihood of cancer returned highly variable and often inaccurate feedback, according to a study led by researchers at the University of Pittsburgh School of Medicine. In fact, the study found that three out of the four smartphone applications tested incorrectly diagnosed 30 percent or more melanomas as “unconcerning” based on their evaluation of user images. The findings, published in *JAMA Dermatology*, suggest that relying on these “apps” instead of consulting a physician may delay the diagnosis of melanoma and timely, life-saving treatment. “These tools may help patients be more mindful about their health care and improve communication between themselves and their physicians, but it’s important that users don’t allow their ‘apps’ to take the place of medical advice and physician diagnosis,” said lead researcher Laura Ferris, MD, PhD, assistant professor of dermatology.

Colorectal cancer is the third leading cause of cancer death in the United States. A first-of-its-kind vaccine developed by University of Pittsburgh Cancer Institute researchers successfully prompted the immune system to respond to early indications of colon cancer in people at high risk for the disease. The results of the preventive colon cancer vaccine were reported in *Cancer Prevention Research* and involved people with a previous history of an advanced adenoma, which places them at higher risk for subsequent colorectal cancer. “This prophylactic colon cancer vaccine boosts the patient’s natural immune surveillance, which potentially could lead to the elimination of premalignant lesions before their progression to cancer,” said Olivera Finn, PhD, Distinguished Professor of Immunology, who developed the vaccine. “The vaccine might spare patients the risk and inconvenience of repeated invasive surveillance tests, such as colonoscopy, that are currently used to spot and remove precancerous polyps.”
Liver transplantation for hepatoblastoma, the most common liver malignancy in children, is on the rise because more tumors are detected earlier, according to a study published in *Surgery* and led by Rakesh K. Sindhi, MD, professor of surgery and codirector of pediatric transplantation at Children’s Hospital of Pittsburgh of UPMC. “Advances in the care of premature babies, and their increased survival as a result, are important reasons for the increased incidence of this tumor,” said Sindhi. His group reviewed data from a variety of sources and found that hepatoblastoma cases in the United States increased four-fold between 1975 and 2007. Estimates suggest that more than six in 10 children with hepatoblastoma can be cured with surgical removal of the mass after chemotherapy. When surgical removal is inappropriate due to the size of the mass, children can be treated with transplantation, and 75 percent of these can be cured.

Almost one in seven new mothers experienced depression during or after pregnancy, with the largest portion having it postpartum, according to a recent study by Pitt scientists published in *JAMA Psychiatry*. About 22 percent of mothers in the depressive group had bipolar disorder, and roughly 20 percent of the depressive group had suicidal thoughts. The study confirmed findings of prior studies: New mothers were more likely to test positive for depression if they were younger, single, publicly insured, less educated, and African-American. Dorothy K.Y. Sit, MD, assistant professor of psychiatry and an investigator on the study, said one good outcome of the study was that investigators could offer follow-up services for new mothers who tested positive for depression — including immediate assistance to the nearly 20 percent who said they’d had suicidal thoughts.

Puerto Rican children who have asthma are more likely to have been exposed to violence and have changes in a gene associated with stress, according to a study led by Pitt researchers and published in the *American Journal of Respiratory and Critical Care Medicine*. The study is the first to examine the links among asthma, stress, and gene variation. Asthma rates are known to be higher among Puerto Rican children, said senior investigator Juan C. Celedón, MD, DrPH, the UPMC Niels K. Jerne Professor of Pediatrics and chief of the Division of Pediatric Pulmonology, Allergy, and Immunology at Children’s Hospital of Pittsburgh of UPMC. Celedón and colleagues found that increased methylation of the promoter (the “on-off” switch) of a gene called ADCYAP1R1, which a previous study linked to the largest portion having it postpartum, according to a recent study by Pitt scientists published in *JAMA Psychiatry*. About 22 percent of mothers in the depressive group had bipolar disorder, and roughly 20 percent of the depressive group had suicidal thoughts. The study confirmed findings of prior studies: New mothers were more likely to test positive for depression if they were younger, single, publicly insured, less educated, and African-American. Dorothy K.Y. Sit, MD, assistant professor of psychiatry and an investigator on the study, said one good outcome of the study was that investigators could offer follow-up services for new mothers who tested positive for depression — including immediate assistance to the nearly 20 percent who said they’d had suicidal thoughts.

A Pitt–Mount Sinai Medical Center team discovered a novel mechanism that regulates replication of insulin-producing beta cells in the pancreas, as reported in *Diabetes*, a journal of the American Diabetes Association. Scientists had previously assumed that cell-cycle replication proteins resided in the cell’s nucleus. The team’s experiments showed that proteins that promote replication were actually in the cell’s cytoplasm, while the proteins in the nucleus were inhibitors of replication. Understanding how these proteins block replication could lead to methods for blocking their activity, providing an approach for reviving beta cell regeneration, said lead author Nathalie Fiaschi-Taesch, PhD, assistant professor of medicine in the Division of Endocrinology and Metabolism. In a second *Diabetes* paper, the team described the intracellular localization of all cell cycle proteins in the beta cell, a biochemical atlas to guide other researchers.

Pitt scientists discovered a new pathway of innate immunity that increases inflammation and identified agents that can block it, leading to increased survival and improved lung function in animal models of pneumonia. Pneumonia and other infections sometimes provoke an inflammatory response that is more detrimental than the disease-causing bacteria, according to senior author Rama K. Mallampalli, MD, professor and vice chair for research, Department of Medicine, and director of the Acute Lung Injury Center of Excellence at Pitt. “Bacteria activate a protein called Fbxo3 that degrades another protein, Fbxl2, which is needed to suppress the inflammatory response,” said Mallampalli, who is also chief of the pulmonary division of the VA Pittsburgh Healthcare System. “The result is an exaggerated inflammatory response that can lead to further damage of the lung tissue, multiorgan failure, and shock.” In the study, reported in *Nature Immunology*, the researchers developed a small molecule, called BC-1215, that inhibited Fbxo3, leading to reduced inflammation and improved lung mechanics in mouse models of pneumonia and sepsis. The team will study the effects of BC-1215 on other inflammatory conditions like colitis and arthritis.
Stem cells and tissue-specific cells can be grown in abundance from mature cells by blocking a certain membrane protein, according to a Pitt–National Cancer Institute (NCI) collaborative study published in Scientific Reports. Jeffrey S. Isenberg, MD, MPH, associate professor of medicine and coauthor on the study, noticed that in the absence of the cell membrane receptor CD47, or when CD47 function was blocked, lung endothelial cells maintained their growth and function for months, unlike untreated cells. The team also discovered that four genes considered essential for induction of pluripotent stem cells had increased expression in cells and organs from animals lacking membrane CD47. In normal mice and human cells (that have CD47), therapeutically blocking CD47 activation or pharmacologically suppressing its expression upregulated the panel of necessary stem cell genes. When placed in a certain growth medium, cells lacking CD47 spontaneously formed clusters characteristic of induced pluripotent stem (iPS) cells. By introducing various growth factors into the medium, the cells could be directed to become cells of other tissue types. Despite their vigorous growth, they did not form tumors when injected into mice, thus avoiding a major disadvantage encountered when using existing iPS cells and other cell-transforming technologies. Scientists hope lab-grown stem cells can one day be used to treat diseases and repair damaged tissues.

A multicenter study led by scientists in the School of Medicine, reported in the Journal of Neurotrauma, shows that mild traumatic brain injury (TBI) after blast exposure produces inflammation, oxidative stress, and gene activation patterns similar to disorders of memory processing. Blast-induced TBI has become an important issue in combat casualty care, said senior investigator Patrick M. Kochanek, MD, professor and vice chair of critical care medicine and director of the Safar Center for Resuscitation Research. In many cases of mild TBI, conventional imaging technology may not show overt damage to the brain. The scientists examined brain tissue of rats exposed to blasts and found that gene activity patterns resembled patterns seen in neurodegenerative diseases, particularly Alzheimer’s. “Our research reveals that, despite the lack of neuronal death, there are marked molecular and genomic derangements in the brain early after a single blast exposure,” Kochanek said. “Even subtle injuries resulted in significant alterations of brain chemistry.”

In a study by Pitt scientists, published in the Journal of Urology, a common obstruction in infants between the kidney and the ureter can be successfully repaired with minimally invasive surgery. The problem is usually repaired with pyeloplasty, a procedure that uses an incision in the infant’s side to remove scar tissue where the kidney meets the ureter, said senior investigator Michael C. Ost, MD, associate professor and vice chair, Department of Urology, and chief, Division of Pediatric Urology. A minimally invasive approach called transperitoneal laparoscopic pyeloplasty has emerged as a safe, effective alternative to the standard procedure and is commonly used in pediatric patients, but its role in infants was less well defined. “This population can be challenging to treat laparoscopically because of the small size of the abdomen and ureter,” Ost said. In a group of children under 1 year old who were followed, 92 percent had successful repairs with the minimally invasive approach.

Pitt researchers serendipitously discovered a new antibiotic for drug-resistant bacterial infections that uses the same approach that HIV uses to infect cells. “This discovery was an unexpected result of basic research on HIV proteins,” said senior author Ronald C. Montelaro, PhD, professor of microbiology and molecular genetics and codirector of Pitt’s Center for Vaccine Research. Montelaro and colleagues found that a particular sequence of amino acids on the tail end of an HIV envelope protein allows the virus to “punch into” and infect cells. The team manufactured synthetic and more efficient versions of this sequence — called engineered cationic antimicrobial peptides, or “eCAPs” — that, in laboratory tests, have rapidly destroyed bacteria that are otherwise resistant to most antibiotics. eCAPs are attracted to the surface of bacteria, where they disrupt the bacterial membrane, causing death within seconds or minutes. Laboratory tests indicate that eCAPs work well against biofilms, bacterial communities that develop high levels of resistance to antibiotics by protecting the films’ inner bacteria from traditional treatments. eCAPs appear to push through outer layers of a biofilm to destroy the entire bacterial community. The discovery, reported in Antimicrobial Agents and Chemotherapy, was featured in April at the University Research and Entrepreneurship Symposium in Boston as one of the year’s 10 breakthroughs in life sciences.
Researchers have found that Medicare beneficiaries with diabetes are two to three times more likely to use expensive name-brand drugs than a comparable group of patients treated within the Veterans Affairs (VA) Healthcare System. The report is the first large-scale comparison of prescription drug use between Medicare Part D and the VA. “Our study shows that we can make a big dent in Medicare spending simply by changing the kinds of medications people are using — and physicians are prescribing — without worrying about whether the government should or should not negotiate drug prices,” said lead author Walid Gellad, MD, MPH, assistant professor of medicine and of health policy and management, Graduate School of Public Health. “The levels of generic use found in the VA are attainable, and they are compatible with high quality care.”

Youth football players ages 8-12 get fewer concussions in practice than in games but are similar to high school and college football players in their incidence rate of concussions, according to research conducted on 468 players on 18 youth football teams from suburban Pittsburgh and Central Pennsylvania. “This finding suggests that reducing contact-practice exposures in youth football, which some leagues have done recently, will likely have little effect on reducing concussion risk, as few concussions actually occur in practice,” said principal investigator Anthony Kontos, PhD, associate professor of orthopaedic surgery. “Instead of reducing contact-practice time, youth-football leagues should focus on awareness and education about concussion. We believe that practice is when tackling technique can be taught and reinforced in a much safer environment than in games.” The study is the first in-depth statistical analysis of medically diagnosed concussions in youth football.

Researchers have discovered that depleted numbers of a specific type of white blood cell in the immune systems of people infected with HIV/AIDS appear to be associated with increased levels of unchecked and often damaging inflammation in the body. “People with well-controlled HIV have been shown to have higher rates of chronic, non-AIDS-related diseases, such as cardiovascular disease. This is believed to be related to the persistent immune activation and inflammation associated with chronic HIV infection,” said corresponding author Bernard J.C. Macatangay, MD, assistant professor of medicine. The study found that low numbers of white blood cells, known as CD4+CD73+ T cells, persist, even when HIV is well controlled with medications. The team hopes to look for ways to repair the damage to the natural pathways by which these cells act.

Researchers have found that certain asthma sufferers improve with drug regimens that suppress the immune system in ways that corticosteroids do not. In a study of severe asthma, reported in the American Journal of Respiratory and Critical Care Medicine, 10 of 19 patients undergoing surgical biopsies had lesions called granulomas, which are nodules of inflammation sometimes seen with certain infections or autoimmune diseases. “The unexpected finding of granulomas in a subset of patients with severe asthma warrants approaching it as a newly described disease, seen with certain infections or autoimmune diseases. ‘The unexpected finding of granulomas in a subset of patients with severe asthma warrants approaching it as a newly described disease,’ said lead author Sally E. Wenzel, MD, professor of medicine and director of the Asthma Institute at UPMC. Because granulomas can be produced by an overactive immune system, the team treated the 10 cases with drugs that suppress it. Nine of them reduced their steroid doses and had improvements in standard lung-function tests while one experienced difficulty tolerating the powerful immune suppressants. More research is needed to determine the immunological pathways that contribute to the disease and to develop biomarkers that will simplify its diagnosis.
According to a recent viewpoint paper, doctors should screen their patients to determine whether they are consistently taking prescribed medications for long-term ailments and treat patients’ non-adherence behaviors as they would other medical problems. “We propose medication non-adherence be viewed as a diagnosable and treatable medical condition,” said corresponding author Zachary A. Marcum, PharmD, MS, research assistant professor of medicine. Researchers have found that between 30 and 50 percent of adults in the United States do not adhere to long-term medication regimens, leading to an estimated $100 billion in preventable costs annually. While there are reliable screening tests to “diagnose” medication non-adherence, the study noted that most clinicians are not formally trained to do this or on how best to treat the problem if detected. “Each medication non-adherence behavior requires different diagnostic tools and treatments, in the same way that specific medical conditions require specific treatments,” said Marcum.

Researchers have found that a physician’s choice of words when talking with family members about whether or not to try cardiopulmonary resuscitation (CPR) if a critically ill patient’s heart stops may influence the decision. When asked in a hypothetical situation to choose between having their loved ones receive CPR if their hearts should stop — a treatment with a 10 percent chance of successfully reviving them — or the alternative, a “do not resuscitate” (DNR) order, 60 percent of participants in a recent study chose CPR. When the alternative was described as “allow natural death,” the number choosing CPR dropped to 49 percent. “This study suggests that the change isn’t just window dressing — it makes a real difference in the choices that people make,” said lead author Amber E. Barnato, MD, MPH, MS, associate professor of medicine and of clinical and translational science. “We expect that it also may reduce feelings of guilt for choosing against CPR by making family members feel like they are doing something positive to honor their loved ones’ wishes at the end of life, rather than taking something away from them.”

A retrospective study confirmed that mitral valve repair is not only safe but also is a well-tolerated and lasting solution for the treatment of elderly people with severe heart disease. “This information will improve medical guidelines to emphasize the importance of timely referral of older patients for mitral valve surgery,” said Vinay Badhwar, MD, visiting associate professor of cardiothoracic surgery, director of the UPMC Center for Mitral Valve Disease, and author of the study, published in Annals of Thoracic Surgery. “This may lead to an improved quality of life, less need for re-operation, and improved long-term survival. It can also lead to a lower likelihood of readmission for heart failure.”

Although medical emergencies during commercial airline travel can be a frightening experience, researchers found that passengers and flight attendants, in collaboration with consulting physicians on the ground, were able to treat sick fellow passengers in 75 percent of emergencies studied. The study, which examined records of in-flight medical calls from five domestic and international airlines to a 24-hour, physician-directed medical command center, found that most medical emergencies could be effectively managed by flight attendants, who are trained in emergency procedures and have access to an FAA-required emergency medical kit, along with medical volunteers. “We hope to look more closely at the most common conditions and which ones require follow-up care so we can better tailor treatment recommendations for passengers,” said Christian Martin-Gill, MD, MPH, assistant professor of emergency medicine.

The STAT3 (signal transducer and activator of transcription 3) protein has been identified in many cancers and is associated with poor prognosis. Jennifer R. Grandis, MD, Distinguished Professor of Otolaryngology and of pharmacology and chemical biology and director of the Head and Neck Program at the University of Pittsburgh Cancer Institute, and her research team fooled the protein into binding to a harmless decoy molecule, rather than the gene sequence that would have initiated the production of cancer-promoting proteins. As reported in Cancer Discovery, the researchers developed a version of the decoy that could be injected into the bloodstream and that inhibited tumor growth in a mouse model of head and neck cancer. “We found reduced expression of the STAT3 target genes in tumors that had been treated with the decoy compared to those that got a placebo,” Grandis said. “This finding indicates that we were able to selectively inhibit STAT3, which is a significant step forward.” In a phase 0 clinical trial, the decoy blocked the genes associated with growth downstream of STAT3.
Parents have plenty to worry about when their children begin dating. Relationship abuse should be part of that concern, especially since a Centers for Disease Control and Prevention (CDC) survey noted that one in 10 adolescents report being hit or physically hurt on purpose by a boyfriend or girlfriend at least once in the previous year. Elizabeth Miller, MD, PhD, associate professor of pediatrics and chief, Division of Adolescent Medicine at Children’s Hospital of Pittsburgh of UPMC, is working to curb adolescent relationship abuse. She collaborated with the national nonprofit Futures Without Violence to create Coaching Boys into Men (CBIM), a program that trains coaches to talk to their athletes about the importance of nonviolent behaviors toward women and girls. The program combines discussions of personal responsibility, being a positive bystander (stopping disrespectful behaviors among peers), respectful relationships, and preventing technology-based bullying, and leverages the influence of athletic coaches as powerful messengers for violence prevention and male athletes as leaders in their communities.

In a CDC-funded study, Miller evaluated the long-term effectiveness of CBIM in 16 high schools and with the more than 2,000 athletes who participated in the study. Athletic coaches from eight of the 16 schools received training and delivered the program. The remaining eight schools did not participate in the CBIM program until after the evaluation was complete. Miller’s findings will help some parents worry less.

“At the end of the sports season, boys who participated in the program were significantly more likely to stop abusive behaviors among their peers. Now, one year later, we find that the rates of abuse perpetration actually increased among youths who didn’t participate, whereas perpetration did not increase among the male athletes whose coaches delivered the program,” she reports.
debola Giwa, MD, realized he wanted to become a physician one day in seventh grade. In science class, he was learning about the heart and quickly grasped its basic functioning, correctly answering every question his teacher posed to the class. Then, he had his “aha moment.”

“I remember thinking to myself, ‘I pretty much know everything to become a cardiologist, so I should be a doctor,’” he says, laughing. “I thought, ‘I’m set! What else is there to know?’”

Giwu’s road to becoming a physician was more arduous than he imagined as a seventh grader, but he worked diligently to get there. He attended the University of Notre Dame on an academic scholarship and earned his medical degree from the University of Pittsburgh in 2013, matching in pediatrics at one of his top choices, the University of Chicago.

But as people from different minority groups are gaining representation in medical school, African Americans are losing ground, with the number of African American men lagging the most, according to a recent Association of American Medical Colleges report on medical school diversity.

Pitt medical school’s 8 percent average for African American enrollment is higher than the national average of 7 percent, and Pitt administrators, med students, faculty members like Dwight E. Heron, MD, professor of radiation oncology and of otolaryngology, alumni, and community physicians are working to lead more African Americans into the medical field.
Guiding that mission is Chenits Pettigrew Jr., EdD, assistant dean for student affairs, assistant dean for faculty diversity, and director of diversity programs. He says one of the reasons there are fewer African American physicians is because, until well into the early decades of the 20th century, organized medicine accepted the exclusion of African Americans from medical school and residency. This exclusion resulted in fewer African American physicians to mentor and guide prospective students into careers in medicine. And many students are underprepared and unable to pursue careers in medicine.

“If students don’t engage in rigorous math and science courses in high school, they will not be able to enter the pipeline to get into medical school,” Pettigrew says. “Our goal is to support our students so they’re successful in getting through medical school; and we provide programs, initiatives, information, and services for that to occur.”

In addition to numerous academic support and peer mentoring programs at the undergraduate and medical-school levels, Pitt offers programs to the local community. The Level I Summer Premedical Academic Enrichment Program helps underrepresented high school seniors and first-year college students strengthen academic skills and focus on medical careers. Students receive academic and personal support and the opportunity to interact regularly with physicians and medical students with similar backgrounds. Pittsburgh-area high school students can also find mentoring in Pitt’s Medical Explorer program, which includes meeting weekly for lectures, science discussion, job shadowing, mentoring from Pitt medical students, and laboratory experiences. The Gateway Medical Society Inc., affiliated with the National Medical Association, offers the Journey to Medicine program with in-kind support from UPMC and Pitt. African American men and their parents are interviewed and selected to be involved in an academic mentoring and nurturing program, which includes mathematical and research tutorials, hands-on medical exposure using Pitt’s WISER human simulation lab, CPR training and certification, a science experiment camp in the summer, vocabulary training, educational field trips, mentoring by physicians, and learning to create and deliver presentations.

“One of the program’s goals is to give students hands-on exposure to different fields of medicine. Many of these young boys don’t have members of their families who are involved in medicine,” says William Simmons, MD, visiting clinical associate professor of anesthesiology and president of Gateway Medical Society.

“I didn’t grow up in an affluent neighborhood,” says Giwa. “My parents always pushed me to do my best, to strive for excellence, but I didn’t see a lot of people who looked like me or who offered an example of what I could do with my life. What pushed me into mentorship was to give kids what I didn’t have. I go back to my neighborhood, and people say, ‘Look at him. This guy was on 29th Street, right there in the projects, and look at him now. He’s at one of the top medical schools. You can do that too.’”

Giwa admits, “There were times in college when I got discouraged or questioned getting into medicine, and then I would think about going home and telling people I wasn’t going to be a doctor. I have to do as well as I can to show people back there they can do it too. Because there are people watching — it’s not hypothetical. They’re going to ask what I’m doing.”

One of those people watching Giwa might be another sharp-witted seventh-grader, poised to have his or her own “aha moment.”
Take a city, a university, a community organization, and a newspaper: Each has needs that can be served by the other. City residents want reliable information about health care issues that affect them. The University of Pittsburgh’s Clinical and Translational Science Institute (CTSI) needs to effectively communicate what health research is being conducted here and how participating in that research can benefit local residents. The Urban League of Greater Pittsburgh, an organization committed to empowering African Americans, wants to eliminate health disparities. The New Pittsburgh Courier, one of the nation’s oldest and most prestigious black newspapers, is read throughout the city. Bring them together and a unique, successful collaboration is born.

Each month, these partners work together to create a spread that runs in the Courier. Each spread focuses on a specific health disparity and provides health information, community resources, and relevant research findings. Recent topics include infant mortality, heart disease, mental health, and asthma, among others. Because it’s important to have volunteers from diverse backgrounds in clinical studies so that research findings can apply to all populations, the articles encourage participation in research, describing what volunteers can expect and presenting information about specific studies needing volunteers.

The information is reaching its intended audience. The newspaper’s circulation is more than 10,000, and the first year’s segments received almost 50,000 hits online. The second year’s segments are on track to be viewed by even more people.

Along with providing helpful information to the community, the partnership itself has been successful. Funded by a community-based participatory research (CBPR) pilot award from the National Center for Advancing Translational Sciences; the project is managed by Elizabeth Miller, MD, PhD, codirector of CTSI’s Community PARTners (Partnering to Assist Research and Translation) Core, associate professor of pediatrics, and chief of adolescent medicine at Children’s Hospital of Pittsburgh of UPMC. Of the partnership, she says, “This collaboration has been fantastic. We have mutual ownership, flexibility, and communication; and each partner is getting something it values. It really defines what CBPR is all about.”
P eople who want to have more of a say in their health care may be getting more opportunities to have their voices heard. As funding for basic science research is dwindling, funding for research that can be translated quickly into better health care practices is increasing. And researchers need patient input to help improve the quality of care and lower costs. Patient-centered outcomes research addresses problems prevalent in the community and, in turn, improves health care for everyone. Federal health care reform legislation (specifically, the Affordable Care Act of 2010) established the Patient-Centered Outcomes Research Institute (PCORI) and will allow for an estimated $3.5 billion in federal funding through 2019. PCORI is authorized by the U.S. Congress to use comparative effectiveness research (CER) to speed the best prevention, treatment, and information to patients and their families.

In the first cycle of awards, PCORI gave two grants to University of Pittsburgh researchers out of only 25 projects funded across the country. James Schuster, MD, MBA, chief medical officer for Community Care Behavioral Health (a nonprofit behavioral health managed care organization and part of UPMC) and adjunct associate professor of psychiatry, received $1.7 million to examine two promising ways to promote the health, wellness, and recovery of adults with serious mental illness. Nearly 3,000 Medicaid-enrolled adults will be invited to participate because they are at risk for chronic medical conditions and receive care at local community mental health centers. (Charles F. Reynolds III, MD, UPMC Professor of Geriatric Psychiatry, is also a principal investigator on this grant.)

“While there are proven strategies that can prevent and manage significant medical conditions that are common among adults with serious mental illness, providers need a better understanding of how to shape and deliver these interventions so that they can effectively support the outcomes that matter most to patients,” says Schuster.

Michael Schneider, PhD, assistant professor of physical therapy in the School of Health and Rehabilitation Sciences, also received a PCORI award to study senior citizens’ involvement in community exercise programs to evaluate nonsurgical treatment methods for patients with lumbar spinal stenosis. Schneider’s study will randomly assign seniors who have pinched nerves in their lower backs to either standard medical care, such as oral or injected medications; individualized manual therapy, such as traction and exercise guided by physical therapists and chiropractors; or exercise in a group setting at two senior centers in Pittsburgh. Medicare rates show that lumbar surgery for spinal stenosis has increased dramatically in the last decade, according to Schneider. These surgical procedures are associated with significant health care costs, risks, complications, and rehospitalization rates.

“Evidence is lacking for the effectiveness of the various nonsurgical treatments offered to patients with this condition,” he says. “We aim to bridge this knowledge gap with a project that will compare interventions and help us develop clinical practice guidelines to choose the best treatment for individual patients based on their particular circumstances.”

In the second cycle of awards announced in mid-2013, two more Pitt researchers received funding. Rachel Berger, MD, MPH, associate professor of pediatrics, School of Medicine, and director of child abuse research at Pitt’s Safar Center for Resuscitation Research, received funding for her project “Using the Electronic Medical Record to Improve Outcomes and Decrease Disparities in Screening for Physical Abuse.” Lakshmanan Krishnamurti, MD, associate professor of pediatrics, School of Medicine, received an award for his project “Comparative Effectiveness of a Decision Aid for Therapeutic Options in Sickle Cell Disease.”

The Comparative Effectiveness Resource Core (CERC) was established at the University of Pittsburgh’s Clinical and Translational Science Institute to offer training in CER methodology, provide guidance on promoting stakeholder involvement, assist researchers in obtaining external funding, and foster collaborations between researchers and established CER/PCORI methodologists.

CERC director Sally C. Morton, PhD, professor and chair of biostatistics, Graduate School of Public Health, serves as a statistical methodology expert to PCORI’s methodology committee. She describes comparative effectiveness research as “all about asking patients to be part of research” and “taking the results of research and getting them into practice.”
J. NADINE GRACIA, MD, MSCE

Has it really only been 11 years since J. Nadine Gracia, MD, MSCE, wore the cap and gown of Pitt’s School of Medicine? Her post-Pitt accomplishments seem like significantly more than one decade’s work. After graduation in 2002, she stayed on for a pediatrics residency and chief residency at Children’s Hospital of Pittsburgh of UPMC, completed a pediatrics research fellowship at Children’s Hospital of Philadelphia, and earned an MS in clinical epidemiology from the University of Pennsylvania. In 2008, she was selected to join the prestigious White House Fellows program, a one-year leadership and public service training program for future policymakers. As a fellow, she contributed to several initiatives in the Office of the Secretary at the Department of Health and Human Services (HHS) and served as a policy advisor in the Office of the First Lady, where she assisted with the development of the childhood obesity initiative.

Currently, Gracia is deputy assistant secretary for minority health and director of the Office of Minority Health (OMH) at HHS. As such, she oversees an office of more than 60 staff members based in Rockville, Md., near the nation’s capital, as well as colleagues in the 10 HHS regions. OMH’s primary responsibility is to improve health and health-care outcomes for racial and ethnic minority communities by developing or advancing policies, programs, and practices that address health, social, economic, environmental, and other factors that affect health. Gracia’s office works in partnership with communities and organizations in the public and private sectors. These collaborations support a systems approach for eliminating health disparities, national planning to identify priorities, and coordinated responses through focused initiatives. The office provides funding to state offices of minority health, community and faith-based organizations, institutions of higher education, tribes and tribal organizations, and other organizations dedicated to improving minority health.

In her leadership role, Gracia advocates for minority health and health equity at forums around the nation, at White House events, and in talking with citizens in communities across the country.

RONALD L. KRALL, MD

Shortly after graduating from Pitt’s medical school, Ronald L. Krall, MD, received some foundational research training in the Epilepsy Branch of what was then the National Institute of Neurological and Communicative Disorders and Stroke (now the National Institute of Neurological Disorders and Stroke). Since departing NIH and completing a neurology residency at the University of Rochester, he has had a long and varied medical career in the pharmaceutical industry. In a nice bit of symmetry, Krall is now back with a new role at NIH. In 2012, he was elected to the Board of Directors of the Foundation for the National Institutes of Health (FNIH).

“A long time ago I was privileged to train at the National Institutes of Health. I feel honored to be able to return to now serve the institution,” said Krall. “I hope to bring my 25 years of research and development experience to better serve patients through research.”

FNIH is an independent nonprofit organization committed to facilitating and accelerating the work of NIH. Specifically, FNIH aims to support NIH in its mission to improve health by forming and facilitating public-private partnerships for biomedical research and training. Among the board members’ responsibilities are ensuring effective organizational planning; ensuring adequate resources and managing them...
effectively; reviewing, monitoring, and strengthening FNIH’s programs and services; and enhancing FNIH’s public standing. Krall is a member of the executive board of the Observational Medical Outcomes Partnership—an initiative to help devise a better system for monitoring existing drugs, devices, and procedures so that the health care community can reliably identify risks and opportunities to improve patient care.

“The FNIH continues to build relationships with the pharmaceutical industry, and we know that Ronald’s insight will be very valuable as we further our private-public partnerships,” said Charles A. Sanders, MD, FNIH chairman.

“Dr. Krall is one of the nation’s most distinguished drug developers and a well-known authority on the safety of medicines,” added Freda C. Lewis-Hall, MD, FNIH board member. “His expertise in translational research—the science of driving promising compounds from laboratory concept to a therapy proven in the clinic as safe and effective—will be highly welcomed by all of us on the FNIH board as well as by millions of patients awaiting new cures.”

Kral was most recently senior vice president and chief medical officer of GlaxoSmithKline. He has held a variety of leadership positions in drug development and drug safety, overseeing the development of more than 20 medicines. Krall is a member of the Institute of Medicine Forum on Drug Discovery, Development, and Translation and was an associate fellow at the University of Pennsylvania Center for Bioethics for many years.

JOHANNA SEDDON, MD, SCM

J ohanna Seddon, MD, ScM, grew up just outside of Pittsburgh in Bethel Park. Small wonder, then, that the University of Pittsburgh was integral to her dreams of higher education. She earned her undergraduate degree at Pitt. And though she had no family members in the medical profession and women made up less than 10 percent of medical students at the time, she enrolled in medical school here as well. She worked summers assisting surgeons, and that is how she met a female ophthalmologist who talked to her about how rewarding it was to help people improve their vision. This early role model started Seddon down a path that led her to a residency in ophthalmology at Tufts—New England Medical Center (now Tufts Medical Center) and two clinical fellowships at Massachusetts Eye and Ear Infirmary, Harvard Medical School.

A 1974 graduate of the School of Medicine, Seddon recently returned to campus to accept the University’s 2013 Distinguished Alumni Fellow Award and the School of Medicine’s 2013 Philip S. Hench Distinguished Alumnus Award. (Philip Hench, MD, graduated from the University of Pittsburgh School of Medicine in 1920. In 1950, he received the Nobel Prize in Physiology or Medicine, along with Dr. Edward C. Kendall and Dr. Tadeus Reichstein, “for discoveries about the hormones of the adrenal cortex, their structure and biological effects.”)

Seddon also attended the Harvard School of Public Health, where she earned a master’s degree in epidemiology. She was the founding director of the epidemiology unit in the Department of Ophthalmology at Harvard Medical School, where she began her academic career in 1982. In 2007, she joined the faculty at Tufts University School of Medicine, where she is currently professor of ophthalmology and founding director of the Ophthalmic Epidemiology and Genetics Service of Tufts Medical Center.

Seddon has had remarkable success in the field of age-related macular degeneration (AMD), the leading cause of blindness in older people. Her research into modifiable factors led to the recognition of the beneficial effects of exercise and higher dietary intake of lutein and omega-3 fatty acids—as well as the adverse effects of smoking—and has changed the management of patients with macular degeneration worldwide.

In the 1980s, Seddon began twin and family studies, a pioneering effort into the genetic epidemiology of AMD. To date, her research team has discovered 10 of the 20 known genetic variants associated with AMD. Seddon’s discovery of the association between AMD and a novel rare mutation is one of the first instances in which a common complex disease variant led to the discovery of a rare pathogenic mutation. She also developed and validated the first comprehensive models to predict progression of AMD.

Seddon has been recognized internationally for her contributions to the field. She is a gold fellow of the Association for Research in Vision and Ophthalmology and a recipient of the inaugural Maurice F. Rabb Jr. Award from Prevent Blindness America for her pioneering work and continued dedication to the field of macular degeneration research.
The success of the University of Pittsburgh School of Medicine depends on the generosity of our benefactors. Through the years, they have responded to urgent needs with contributions for immediate use. Visionary donors have seen the importance of establishing enduring support through gifts to endowed funds. They have seen not only what the School of Medicine is today but also what it can become. We are sincerely grateful for this support and pleased to recognize in the following pages those who have invested in the School of Medicine.

During the 2011–12 fiscal year, approximately 9,000 contributors made more than $95 million in gifts and pledges to the School of Medicine, University of Pittsburgh Cancer Institute, and Western Psychiatric Institute and Clinic of UPMC. Through donor support, the School of Medicine contributed significantly to the completion of the University of Pittsburgh’s $2 billion Building Our Future Together campaign, which reached its goal in fall of 2012, nearly two years early, and concluded in June 2013. The campaign was the most ambitious ever undertaken by the University; and it resulted in more than $691 million raised for the School of Medicine, approximately $184 million of which was designated for the endowment.

The impact of these contributions can be seen throughout this publication. Gifts to the School of Medicine help to attract and retain exceptional scientists and physicians, provide essential funding for research projects, help to transfer medical discoveries into lifesaving clinical treatments, and decrease the loan burden of medical students. In fiscal year 2012, nearly $4 million in scholarship awards were made to 247 students in the School of Medicine. At Pitt, 88 percent of medical students graduate with an average debt of more than $145,000. Donor support helps offset this burden.

The current trajectory of the School of Medicine suggests continued and even greater success in the years to come. Pitt’s medical school would not be the first-class institution that it is today without donor support. We look forward to ongoing and strengthened partnerships with our friends and alumni to further promote medical education, research, innovation, and discovery.

CLYDE B. JONES III
Vice Chancellor for Health Sciences Development and President, University of Pittsburgh/UPMC Medical and Health Sciences Foundation
Study a map of the University of Pittsburgh main campus and one name will jump out again and again. At the top of a steep climb from Pitt’s bustling main avenue is the Petersen Sports Complex, a 12-acre parcel of land that’s home to beautiful, state-of-the-art baseball, softball, and soccer facilities. Midway up the hill is the windowed façade of the John M. and Gertrude E. Petersen Events Center. Grand in scale, the “Pete” is home to Pitt’s basketball programs, student fitness and recreation facilities, and the athletics department. Directly across the street in Scaife Hall is the latest addition to the Petersen legacy on Pitt’s campus, but you won’t find this one on the map. It’s the office of Arthur S. Levine, MD, senior vice chancellor for the health sciences and, as of 2013, John and Gertrude Petersen Dean of Medicine.

The creation of an endowed chair for the medical school dean is a special occasion. It’s not only a testament to the generosity of the Petersens but also a mark of distinction for the institution and the individual who holds the chair. Mr. and Mrs. Petersen have given many gifts to the University, including a flat contribution for the Gertrude E. and John M. Petersen Institute of NanoScience and Engineering and numerous scholarships. Nevertheless, they aren’t a couple who seeks attention—far from it. The Petersens are quiet people who know and recognize hard work and intelligence. Their admiration for Dr. Levine and the work he has done on behalf of the University moved them to create an endowment that would further his work and honor his accomplishments.

Dr. Levine has steered the course of Pitt’s biomedical research enterprise and medical education programs since 1998. He has led Pitt to an enviable position among the top five universities for research funding from the National Institutes of Health. The School of Medicine is known as one of the premier medical schools in the country. Under his direction, the Schools of the Health Sciences have seen a dramatic increase in and improvements to research facilities, including construction of the Biomedical Science Tower 3, a cutting-edge high-rise that acts as a front door to Pitt’s collaborative research community. Under Dr. Levine’s leadership, the School of Medicine has established several new departments—including critical care medicine, biomedical informatics, urology, physical medicine and rehabilitation, immunology, plastic surgery, cardiothoracic surgery, developmental biology, structural biology, and computational and systems biology—reflecting the institution’s position at the leading edge of medical education, clinical practice, and basic science research.

For many of these fields, similar departments are still rare in American medical schools.

“I believe in Dr. Levine deeply,” says Mr. Petersen. “He has a wonderful organization, and he has made it highly successful. The extent of his knowledge is staggering. He can talk about three different subjects with tremendous depth in the same meeting; I just sit there in awe.”

Mr. Petersen knows what hard work is. The son of a commercial fisherman, he grew up in Erie, Pa. Money was tight, and he says, “There was no such thing as an allowance.” He worked for a fish company on Erie’s busy waterfront throughout high school and full-time in the summers, with a starting wage of $.25 per hour. When he got out of the Army, he attended Pitt on the GI Bill. He majored in business administration, and he finished his degree in five semesters. Mr. Petersen worked for General Electric in Connecticut before joining Erie Insurance Group as its first investment officer in 1962. The company’s net worth was around $7 million when he started and $2.1 billion when he retired in 1995 as president and chief executive officer. At age 85, Mr. Petersen is still involved in business, running several start-up companies.

Despite their success, the Petersens are humble, refuse the limelight, and are guided by a spirit of forthright generosity. They’ve endowed many scholarships at their respective high schools in center city Erie for students with B and C averages because they believe these students have potential, may have had difficult backgrounds, and deserve a chance to earn college educations. The Petersens know that they can change lives with their gifts. But they don’t dwell on the opportunities they’ve provided individually or through Pitt; they simply want to encourage people to create success in their own lives.
“We’ve worked hard. We’ve been frugal,” says Mr. Petersen. “All my life, I’ve always saved 10 percent of whatever I’ve earned and invested it. We don’t have a desire to have more now than we did 25 years ago.”

Even though the Petersen legacy at Pitt is highly visible around campus, they originally didn’t want their names on buildings. They were convinced otherwise when they realized that doing so might inspire others to support Pitt and, in turn, encourage others to strive for excellence. The Petersens can rest assured that Dr. Levine, whose position now bears their name and who understands the transformative power of hard work, can always be inspired and guided by everything they stand for just by looking out his office window at the Pete.

With grateful appreciation for their generosity, we acknowledge the following individual, corporate, and foundation donors whose contributions of $500 or more to the University of Pittsburgh School of Medicine, University of Pittsburgh Cancer Institute, and Western Psychiatric Institute and Clinic between July 1, 2011, and June 30, 2012, have supported us in our academic, research, and clinical missions.

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Sitting in the Southwestern Pennsylvania Eye Center he founded and directs, E. Ronald Salvitti, MD, recalls a memorable patient. She was 93 years old, always sharply dressed, and drove herself 25 miles each way to her appointments. She was having eye problems, and Dr. Salvitti performed cataract surgery that restored her vision. When he didn’t see the patient again for a while, he thought she had died. But two years later, she returned, having driven herself again to her appointment.

“I am truly amazed by the level of independence that patients can maintain at progressively older ages,” Dr. Salvitti says. “It just shows how we need to support eye care at a level that will allow aging patients to maintain their quality of life and function independently. If we can do something to enhance vision quality through research, that’s important.”

A philanthropist for many years to different regional organizations and schools, he established the E. Ronald Salvitti, MD, Chair in Ophthalmology Research at the University of Pittsburgh. He chooses his philanthropic activities carefully and is loyal to the institutions and locations that are dear to him. Education, research, and Southwestern Pennsylvania, the area in which he grew up, mean a great deal to him, so creating a chair meant to benefit all three was a perfect fit.

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“Dr. Salvitti wanted his chair to be held by someone whose work was a perfect combination of translational and basic research focused on retinal repair. He was pleased when the Department of Ophthalmology hired Dr. Nasonkin, who specializes in new ways to repair and regrow the retina through the use of stem cell therapies and novel epigenetic techniques.

“Our population is aging, and their vision is going to deteriorate,” Dr. Salvitti says. “I believe that the best way to advance patient care is by investing in the future of ophthalmology, in educating up-and-coming physicians, and in research that will reveal new understanding.”

Dr. Salvitti was chief resident while training at Pitt’s Department of Ophthalmology in the early 1970s. He worked for six years in family practice before deciding to specialize in ophthalmology. It was during Dr. Salvitti’s residency that he began to appreciate what his father, who was partially sighted because of a congenital vision problem, lived with his whole life. Knowing he wanted to take care of his parents as they aged, Dr. Salvitti returned to the area in which he started his career in family medicine. He had a full schedule of patients in his ophthalmology practice from day one.

Dr. Salvitti’s commitment to research partially stems from his own innovative work. He says he was inspired to learn new technologies in his residency, especially with regard to the eye surgery he loved doing. He eventually designed a popular intraocular lens for cataract surgery and has contributed to the development and advancement of new technologies for several decades. Dr. Salvitti is also well known as a medical educator; he spent many years traveling to 26 states and internationally to train doctors in cataract and refractory surgery. But he remains committed to Southwestern Pennsylvania and its people.

The E. Ronald Salvitti Chair in Ophthalmology Research is held by Igor O. Nasonkin, PhD, who is also assistant director of the Louis J. Fox Center for Vision Restoration and heads the Department of Ophthalmology’s Retinal Repair and Epigenetics Research Lab. Dr. Salvitti wanted his chair to be held by someone whose work was a perfect combination of translational and basic research focused on retinal repair. He was pleased when the Department of Ophthalmology hired Dr. Nasonkin, who specializes in new ways to repair and regrow the retina through the use of stem cell therapies and novel epigenetic techniques.

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In 2009, Bruce Haney had a routine physical. Concerned by some blood work results, his physician ordered a computed tomography scan, which revealed a large tumor coiled around the vena cava in Mr. Haney’s liver. The diagnosis was cholangiocarcinoma, a rare cancer with a generally low survival rate. Almost all of the specialists he saw deemed the tumor inoperable.

“Cut it out and hope it doesn’t come back—that was our only chance with this cancer,” says Andrea Haney, Mr. Haney’s high school sweetheart and wife of 31 years. “We met with many surgeons, but none of them wanted to try surgery because it was in such a dangerous location. But then Bruce met Wallis.”

J. Wallis Marsh, MD, MBA, professor of surgery and director of advanced liver surgery, Thomas E. Starzl Transplantation Institute, told Mr. Haney that if they worked to shrink the tumor, he’d perform the surgery. Mr. Haney had chemotherapy for six months, followed by surgery. During the long operation, Dr. Marsh carefully removed the entire tumor. After the surgery, the Haney’s agreed they wanted to give back to the School of Medicine to support the kind of care they received here—care delivered with courage, skill, and compassion.

“Bruce had appointments at other big-name cancer hospitals, but he loved Dr. Marsh’s confidence and go-for-it attitude,” Mrs. Haney says. “We wanted to spread the word about the kind of care we have in Pittsburgh.”

The Haney’s heard about the Raizman Endowed Fund, established by Mrs. Dorothy Raizman in memory of her husband, Richard, who had fought a courageous battle with liver cancer, and decided to contribute to the worthy cause. In addition to being a successful businessman, certified public accountant, and commercial real estate developer, Mr. Haney was an avid golfer. To raise money, the Haney’s, their friends, and extended families organized two Bruce Haney Charitable Foundation Golf Outings, with sponsors like Pittsburgh business giants PNC and Giant Eagle. The events raised a considerable amount of money, and Mrs. Raizman renamed her original fund the Raizman-Haney Endowed Fund as a tribute to Bruce’s efforts and to support the critical work being done in liver disease and liver cancer research at the Starzl Institute’s Liver Cancer Center.

“I was apprehensive because Bruce was going through chemo, was continuing to work, and we have children; but he wanted to do the golf fundraisers on top of everything else,” Mrs. Haney says. “He had cancer, but he was selfless and devoted to raising money for this fund. We never expected to raise the money that we did.”

Mr. Haney died in early 2013, having conducted business throughout his battle with cancer. His family and friends remember him as a great father and husband and a very successful businessman. Even when fighting for his life, he was committed to raising money for people diagnosed with cholangiocarcinoma in the future.

“We’re hoping that the fund will help bring in surgeons who aren’t afraid to take risks to save people’s lives,” says Mrs. Haney. “The biggest gift Dr. Marsh gave us was time with Bruce. Bruce ended up having more than three years to spend with his daughters and to make a lot of good memories. And he was inspired by Dr. Marsh. Bruce was able to stay positive, keep his head up, and show people he wasn’t just going to lie down and die.”

Bruce and Andrea Haney: The Gift of Time
Every effort has been made to ensure the accuracy of these records. Any errors or omissions may be brought to the attention of the University of Pittsburgh and UPMC Medical and Health Sciences Foundation: 412-647-3379 or bac83@pitt.edu.

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On a cold evening in the late 1940s, Wallace H. Coulter went to his garage, where he had set up a laboratory to tinker with different experiments outside of his job in electronics. He found that the paint he was using for a particular experiment had frozen. Rather than go back out in the cold, Mr. Coulter brainstormed. He needed a substance that had the viscosity of paint and was readily available. Using his own blood, he developed an experiment that showed it was possible to use electronic impedance to count and size microscopic particles suspended in fluid. The Coulter Principle, as it became known, led to the invention of the Coulter Counter. The device replaced the tedious practice of manually counting blood cells and was the first of many such instruments used in a wide range of applications, including the complete blood count, which is one of the most commonly ordered diagnostic tests in the world. The Coulter Principle is also used to analyze paint, chocolate, cosmetics, and NASA’s jet fuel. Mr. Coulter’s garage inventions led to the creation of his company, Coulter Electronics.

Mr. Coulter went on to amass honorary doctorates and 85 patents. The Coulter Corporation was widely considered to be an industry leader (it was acquired by Beckman Instruments and is now Beckman-Coulter), and it was driven by Mr. Coulter’s passion to improve health care through medical research and engineering. Prior to his death in 1998, Mr. Coulter established the Wallace H. Coulter Foundation to fund translational research in biomedical engineering, with the goal of accelerating the introduction of new technologies into patient care. The University of Pittsburgh was one of six universities nationwide to receive a Coulter Translational Partnership II grant—a $3.54 million award to the Swanson School of Engineering that was supplemented by $1.5 million in matching funds from the School of Medicine, the Swanson School, and the University’s Office of Technology Management. Harvey Borovetz, PhD, Distinguished Professor of Bioengineering, Robert L. Hardesty Professor in the School of Medicine’s Department of Surgery, and deputy director of the artificial organs and medical devices division of the McGowan Institute for Regenerative Medicine, is principal investigator. The coprincipal investigators are Stephen Badylak, DVM, PhD, MD, professor of surgery and director of tissue engineering for McGowan, and Marc S. Malandro, PhD, director of the Office of Technology Management and associate vice chancellor for technology management and commercialization at Pitt.

Pratap Khanwilkar, PhD, MBA, can relate to starting a business with intellectual curiosity, ambition, and a garage. Professor of bioengineering in the Swanson School, McGowan member, and executive-in-residence in the Office of Technology Management, Khanwilkar is the director of Pitt’s Coulter Translational Research Partners II Program (TPII). Armed with degrees in electrical and biomedical engineering, he developed an implantable left ventricular assist device drawn up from an initial napkin sketch in his own garage. With six companies, seven patents, and nearly three decades as an entrepreneur, medical device developer, and medical technology executive, Khanwilkar knows well the path from innovation to translational health care and is well suited to provide expertise at Pitt.

Khanwilkar has also taught bioengineering and business/technology management and conducted research at the University of Utah. He was recruited to guide the development of appropriate projects to be undertaken by Pitt researchers; ensure that they are properly vetted by a Coulter oversight committee composed of med-tech entrepreneurs, clinicians, and investors and advised by a similarly constituted advisory group; and facilitate the progress of securing additional funding, licensing intellectual property, and developing spin-off companies.

In addition to three other technologies funded in TPII’s first year of operation, the program recently selected four projects for one-year support of $100,000 each. The projects are a microneedle array technology initially targeted at curing and preventing skin cancer recurrence, developed by Louis Falo, MD, PhD, professor and chair of dermatology, and Larisa Geskin, MD,
associate professor of dermatology; an external electrostimulation technology that inhibits overactive bladder, developed by Changfeng Tai, PhD, and Mang L. Chen, MD, both assistant professors of urology; a regenerative medicine approach to replacing damaged meniscus in the temporomandibular joint, led by Bryan Brown, PhD, assistant professor of bioengineering, Swanson School of Engineering, Alejandro Almarza, PhD, assistant professor of oral biology, School of Dental Medicine, and of bioengineering, Swanson School of Engineering, and William Chung, MD, associate professor of oral and maxillofacial surgery, School of Dental Medicine; and a reverse thermal gel used to hold in place and provide infection resistance by delivering antibiotics to implanted pacemakers and defibrillators, led by Yadong Wang, PhD, William Kepler Whiteford Professor of Bioengineering, Swanson School of Engineering, and David Schwartzman, MD, professor of medicine.

“The Coulter experience is about getting an innovative technology—developed by a bioengineer and championed by a clinician—and providing the support and resources needed to get that technology to help as many patients as quickly as possible,” says Khanwilkar. “This objective is best achieved through commercialization, for which we provide mentoring, education, networking opportunities, and money. We add value by helping to ‘de-risk’ the technology within the academic setting so that investors and strategic partners are more comfortable taking the technology forward to clinical and commercial success. Our ‘get-to-patient’ mission drives an educational program that helps our researchers develop a business model, a commercialization plan, a product development plan, and an investor pitch. For some researchers, dealing with business is a culture shock, but we’re here to guide, refer, counsel, educate, support, and nudge in the direction necessary to get the technology to help patients.”

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5745–57, doi: 10.1242/jcs.109769
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doi: 10.1073/pnas.1110067109
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