Adaptation
Adaptation

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Adaptability is the gift that life's genetic machinery gives to all living things. We can marvel at it in the natural world, and we can study it in the lab. We can decipher its mechanisms to understand and improve our own health. Finally, we would be wise to design and run our own institutions to be just as doggedly resilient and adaptive, especially at this moment in history.

We're in a time of unprecedented upheaval in science and medicine. Scientific advances are transforming the practice of medicine at a dizzying pace. Physicians enter the profession today knowing that they will offer their patients treatments and diagnostics that were scarcely dreamt of just 20 years ago. As scientists, we now have scientific and computational tools to investigate basic biological processes and human health to an extent that was only hinted at with the sequencing of the first human genome in 2003.

Even as we embrace these opportunities in science and medicine, we are faced with daunting challenges. Our nation's much-needed health care reform initiatives are rightfully forcing us to address health care quality, cost, and access. But such reforms limit the ability of academic health centers to support research to the extent that they traditionally have. Meanwhile, federal support of research through the National Institutes of Health (NIH) has, in purchasing power, been stagnant for several years. The most recent NIH data show that the University of Pittsburgh's NIH funding is on the rise, but it is clear to me that our institution must nonetheless adapt to changing realities.

“The art of life is a constant readjustment to our surroundings.”

KAKUZO OKAKURA
In the pages of this report, you’ll learn how we at the University of Pittsburgh School of Medicine remain inventive, innovative, and entrepreneurial in the face of these challenges. We do this through strategic partnerships and through well-structured, institutional support for developing physicians and scientists. We commit our resources to emerging areas of biomedical research, and we focus on the translation of basic science discoveries to clinical care. To give just a few examples:

- Pitt’s new Center for Medicine and the Microbiome earned top billing at a March 2016 White House event announcing the launch of the National Microbiome Initiative. This important project aims to improve our understanding of the trillions of microbes that exist throughout the human body and make major contributions to our health and physiology. These insights hold tantalizing promise for improving human health.

- In July 2016, Pitt’s Clinical and Translational Science Institute was awarded a transformative $53 million grant under the NIH’s Precision Medicine Initiative Cohort Program. One of the first such awards in the nation, it makes Pitt a key player in the nationwide effort to enroll and sequence the genomes of 1 million volunteers to dramatically expand the base of knowledge that allows us to personalize medical treatments based on genomic information.

In the educational arena, our medical students learn in year one that our curriculum is, by necessity, supremely adaptive. They are invited to participate as faculty, staff, and students evaluate the curriculum in light of our evolving understanding of science and the changing practice of medicine. By the time they graduate, our students have witnessed and helped to guide important changes in the teaching of certain subjects as our knowledge grows deeper and more nuanced.

What never changes is that we are fully committed to preparing our students to be skilled, science-based, compassionate clinicians and innovative biomedical scientists. Those are the qualities that enable us to adapt to any state of affairs. I invite you to discover for yourself how the University of Pittsburgh School of Medicine fulfills that commitment on the pages of this report.

ARTHUR S. LEVINE, MD
Senior Vice Chancellor for the Health Sciences and
John and Gertrude Petersen Dean of Medicine
NIH RANKING

In the only truly objective metric by which the overall stature of research-focused institutions can be assessed in a nationally competitive context, the University of Pittsburgh moved into the TOP 10 list of recipients of National Institutes of Health (NIH) funding in 1998. In recent decades, there have been very few newcomers among this elite group of institutions; Pitt not only cracked the top 10 but steadily rose over the ensuing years to the extent that it is now firmly anchored in the heart of this enviable echelon that comprises the nation’s leading research institutions. In fiscal year 2015, Pitt faculty received more than $475 million in total funding, with the lion’s share of that funding going to the School of Medicine.

Our Shared Ancestry

“UPMC was created out of the University of Pittsburgh (and) the two have risen together in national and international prestige,” Pittsburgh-area historian and author Mary Brignano notes in Beyond the Bounds: A History of UPMC. “UPMC’s founders followed one core principle: Research and clinical success are synergistic and interdependent. What is good for one is good for both.”

The visionary spirit of those early leaders has continued through to today, more than 40 years after the great “Pittsburgh experiment” began. Much about the region’s landscape has changed over the decades, with education and health care assuming the economic pride-of-place once reserved for heavy industry. Together, the University and UPMC have grown into one of the nation’s leading academic medical centers, medical schools, and training grounds for physicians, scientists, and other health care professionals. We proudly continue to serve the people of our community—delivering superb care to neighborhoods throughout the region and across the country.

Today, Pitt and UPMC’s vital collaboration still drives a circular bond from research to clinical care, and back to research—but now, it’s moved forward from transforming Pittsburgh to transforming health sciences education and clinical care across the globe.
In early July 2016, the National Institutes of Health (NIH) released $55 million, with $4.2 million of that awarded to the University of Pittsburgh, to build the foundational partnerships and infrastructure needed to launch the Cohort Program of President Obama’s Precision Medicine Initiative (PMI). The PMI Cohort Program is a landmark longitudinal research effort announced in the 2015 State of the Union address that aims to engage 1 million or more research participants across the country to revolutionize how disease is prevented and treated based on individual differences in lifestyle, environment, and genetics.

Over five years, the total amount awarded to Pitt is expected to top $46 million, pending progress and availability of funds. Pitt is one of four organizations receiving awards to support a network of Healthcare Provider Organizations (HPO)—the others being Columbia University Health Sciences, Northwestern University, and the University of Arizona. The awards set the NIH on course to begin initial enrollment into the PMI Cohort Program during 2016, with the aim of meeting its 1 million person enrollment goal by 2020.

“As an HPO, the University of Pittsburgh, in collaboration with UPMC (University of Pittsburgh Medical Center), has an essential role in the PMI Cohort Program, one of the National Institutes of Health’s most ambitious research efforts since the Human Genome Project,” noted med school dean Arthur S. Levine, MD. “We are on the cusp of a new era in medicine in which we can apply knowledge in genetics and genomics, combined with lifestyle and environmental data and other disciplines, to improve disease prevention strategies and tailor treatment options for everyone,” he added.

Led by Pitt’s Clinical and Translational Science Institute (CTSI)—a collaboration of the University of Pittsburgh Schools of the Health Sciences and UPMC—the Pitt PMI project, called the Precision Approach to healthCARE (PA CARES), is being launched at 11 enrollment sites across the western half of Pennsylvania and neighboring states. In its first year, PA CARES aims to recruit and enroll 10,000 volunteer participants, primarily from CTSI’s Research Participant Registry of more than 103,000 participants as well as an additional 165,000 individuals over the five-year award period.

“This project is a testament to the strength and value of the integrated research resources and expertise we’ve been able to build through CTSI over the past 10 years at Pitt,” said principal investigator Steven E. Reis, MD, associate vice chancellor for clinical research, health sciences, Distinguished Service Professor of Medicine, and CTSI director. “The PMI Cohort Program will provide individuals from across the region, and the nation, with an unprecedented opportunity to contribute to the development of individualized approaches to prevent and treat disease. What we learn now by working together will benefit our children, grandchildren, and generations to come.”

“Every patient is different; every patient has a unique story. This comprehensive massive collection of patient information, combined with our advanced analytics approach eventually will enable us to treat each patient in a personalized way to produce the best possible results,” said Steven D. Shapiro, MD, UPMC’s chief medical and scientific officer.

PMI Cohort Program volunteers will be asked to contribute a wide range of health, environment, and lifestyle information. They also will be invited to answer questions about their health history and status, share their genomic and other biological information through simple blood and urine tests, and grant access to their clinical data from electronic health records.

In addition, mobile health devices and apps will provide lifestyle data and environmental exposures in real time. All of this data acquisition
Pitt Receives $62.3 Million, Five-Year NIH Award To Accelerate Translational Scientific Research into Implementable Solutions

The University of Pittsburgh Clinical and Translational Science Institute (CTSI) will receive nearly $62.3 million over five years from the National Institutes of Health (NIH) to broaden its mission of speeding translation of scientific research into realistic treatments for the people who need them.

In 2006, CTSI was among the first 12 recipients of NIH’s Clinical and Translational Science Awards (CTSA). Since then, Pitt’s CTSA funding has totaled more than $221 million. Including the recently announced funding for Pitt’s participation in NIH’s Precision Medicine Initiative Cohort Program, CTSI-supported programs have been awarded approximately $108 million in research funding over the next five years.

“This award is emblematic of the significant contribution that University of Pittsburgh researchers and physicians are continuing to make to advance our understanding of biomedical science and improve clinical care,” said Arthur S. Levine, MD, Pitt’s senior vice chancellor for the health sciences and John and Gertrude Petersen Dean of Medicine.

Over the past 10 years, CTSI has built an infrastructure of programming to support all avenues of scientific investigation, from guidance in regulatory requirements and study design to career/workforce development, education and training, community engagement, biomedical informatics, pilot funding of early-stage research, and innovation. It has trained 850 investigators and supported more than 2,000 investigators who have conducted more than 4,000 research studies.

“Among our most important goals for the next five years is engaging a broader range of people and communities in research,” said CTSI director Steven E. Reis, who is also associate vice chancellor for clinical research, health sciences, and a professor of medicine. “We will also expand CTSI’s reach by launching several new programs, including a focus on entrepreneurship in research and in translating discoveries to practice.”

New initiatives during the upcoming grant period include:

- Innovation as a Discipline
- Biomedical Modeling
- Integrating Special Populations
- Clinical Trial Recruitment and Efficiency
- Clinical Trial Innovation
- Multidisciplinary Team Science

Funding is being provided through NIH’s National Center for Advancing Translational Sciences.

Welcome to the West Wing

Since the 1950s, Scaife Hall has served as the hub of medical education on Pitt’s campus. Directly connected to UPMC Presbyterian and Montefiore Hospitals, not to mention research facilities in Biomedical Science Tower 3 and the Thomas E. Starzl Biomedical Science Tower, Scaife Hall’s educational and research facilities have been modernized many times over the years. But those improvements don’t even come close to the blockbuster expansion that planners and architects now envision for the School of Medicine.

While the plans are still in development and have hurdles to clear before the first med student crosses the threshold, the School of Medicine envisions a new west wing with more than 200,000 square feet dedicated to medical education. Students would be the chief beneficiaries of the seven-story expansion. The glass entry, high ceilings, limestone and wood surfaces, and open spaces will make for a welcoming atmosphere filled with natural light. New learning environments will be state of the art, with technology fully integrated into the design.

These include a top-floor anatomy lab, a team-based learning room, and a divisible lecture hall that reuses the original wood from Scaife’s stately lecture rooms. This major, multiphase project is expected to create an unparalleled destination for medical education.

While planners wait for the word “Go!” on the major expansion, a $4.5 million renovation centered on the fifth floor of Scaife Hall is already approved. It, too, is focused on improving student services and student facilities, and it will pave the way for the complete west wing overhaul to come.
Pitt Recruits Prominent Physician-Scientists

The School of Medicine has been able to tempt top biomedical scientists to call Pittsburgh home more than once over its 130-year history. Now, 2016 brings a trifecta of exceptionally stellar talent to Pitt—both homegrown and recruited.

One of the world’s foremost clinician-scientists in vision research, José-Alain Sahel, MD, joined the faculty on July 1 as Eye and Ear Foundation Professor and chair of ophthalmology.

“José-Alain Sahel is a gifted scientist whose transcendent goal is to apply the results of research to patient care with immediacy,” said dean Arthur S. Levine, MD. “I believe his influence here will have great institutional impact.”

Sahel has been recruited to the University from Paris, where he served as professor of ophthalmology at the Université Pierre-et-Marie-Curie, the medical school of the Sorbonne. He is also chair of departments of ophthalmology in the largest eye hospitals in the country, as well as founding director of Paris’ Vision Institute, a translational research center housing 320 investigators and staff focused on understanding vision and finding therapies for currently untreatable genetic and age-related eye diseases.

Areas of research interest for Sahel include investigations of the cellular and molecular mechanisms associated with retinal degeneration (particularly genetic rod-cone dystrophies), as well as developing and evaluating innovative treatments for retinal diseases using pharmacologic approaches, prosthetics, optogenetics, gene therapy, and stem cells.

In milestone work, Sahel and his collaborators discovered rod-derived cone viability factor (RdCVF), a protein secreted in the normal retina that protects cone photoreceptors. This finding provided the biological basis for paracrine interactions between rods and cones, which, the Sahel team demonstrated, play a critical role in maintaining photoreceptor cell viability. RdCVF has been shown to preserve central vision in several models of genetic human diseases causing blindness. His laboratory has also conducted research on the development of high-resolution in vivo cellular imaging, relevant biomarkers, and disease models.

In addition, he is a co-inventor on more than 20 patents, several of which formed the basis of start-up companies, including the Sahel-founded Fovéa Pharmaceuticals, which later became an ophthalmologic division of Sanofi-Aventis. He is also scientific cofounder of several
companies, including GenSight Biologics S.A., a company focusing on gene therapy-based approaches to treat mitochondrial and neurodegenerative diseases of the eye and central nervous system, and Pixium Vision, which develops innovative bionic vision restoration systems.

Gwendolyn Sowa, MD, PhD, newly named Physical Medicine and Rehabilitation Professor and department chair, formerly served as associate professor of physical medicine and rehabilitation and of orthopaedic surgery (School of Medicine) and of bioengineering (Swanson School of Engineering). She succeeds Michael L. Boninger, MD, who has taken on an administrative role as vice president for medical affairs for UPMC’s Division of Community Provider Services, the umbrella organization that manages all community-based and post-acute clinical programs.

Sowa also serves as associate dean for medical student research, codirector of the Ferguson Laboratory for Orthopaedic and Spine Research, and medical director of UPMC Total Care—Musculoskeletal Health. She is also an associate editor for *PM&R*, the official journal of the American Academy of Physical Medicine and Rehabilitation, and serves on the board of trustees of the Association of Academic Physiatrists.

Sowa completed her PhD in biochemistry and MD at the University of Wisconsin–Madison, and her physical medicine and rehabilitation (PM&R) residency at the Rehabilitation Institute of Chicago, Northwestern University. A PM&R clinician-scientist for more than 10 years, she has been active in developing new models of care, assessment of patient-reported outcomes, and interdisciplinary work groups to improve care quality. In particular, she has encouraged multidisciplinary collaboration to enhance treatment for patients with low back pain.

Sowa is also a noted educator, mentoring more than 65 trainees—more than half of whom have received awards for their research. Her research interests have focused on the effects of mechanical loading on musculoskeletal tissues and targeted biomarker discovery to inform the development of individualized treatment programs for low back pain—the most common cause of global disability.

“Dr. Sowa’s many accomplishments demonstrate her ability to cross specialties and to collaborate effectively in the clinical, research, and educational arenas. She is the definition of a committed teacher and mentor,” said Levine.

Terence S. Dermody, MD, has been appointed the Vira I. Heinz Professor and chair of pediatrics, physician-in-chief at Children’s Hospital of Pittsburgh of UPMC, and scientific director of the Rangos Research Center. He was recruited from Vanderbilt University School of Medicine, where he served as the Dorothy Overall Wells Professor of Pediatrics and director of both the Division of Pediatric Infectious Diseases and the Medical Scientist Training Program.

Dermody is a virologist with interests in viral pathogenesis and vaccine development. He has focused mainly on reovirus, an important experimental model for studies of viral encephalitis in infants, and on chikungunya virus, an arthropod-borne virus that causes epidemics of febrile arthritis.

He received his MD from Columbia University, interned at New York-Presbyterian Hospital, and completed infectious diseases and molecular virology fellowships at Brigham and Women’s Hospital and Harvard Medical School.

“His academic interests, which included running Vanderbilt’s MD/PhD training program, are unusually broad,” noted Levine. “An exceptional physician and scientist, he will be an asset to our faculty, residents, and students.”

In addition to his own NIH-supported virology research, Dermody’s priorities at Children’s include addressing autism, childhood cancers, and the so-called “social determinants” of health—the many socioeconomic and related factors that influence diet, lifestyle, and quality of life.
Among the first projects to be funded by the Pittsburgh Health Data Alliance are several Pitt-led innovations developed through the University’s Center for Commercial Applications of Health-care Data (CCA), an initiative led by Michael J. Becich, MD, PhD, Distinguished Professor and chair of biomedical informatics.

Launched in March 2015, the Pittsburgh Health Data Alliance is a unique collaboration involving UPMC, the University of Pittsburgh, and Carnegie Mellon University with a focus on building new companies that create data-intensive software and services to potentially revolutionize health care and wellness.

With this infusion of funding, four teams of University of Pittsburgh researchers now have the resources to advance their technologies aimed at reducing patient falls, preventing and monitoring pressure ulcers, improving the accuracy of cancer diagnoses, and providing personalized treatment recommendations. UPMC’s funding for these innovations is expected to total more than $3 million as the commercial potential of these products is further explored.

**FUNDED CCA PROJECTS ARE:**

The **Tumor-Specific Driver Identification (TDI) System** is a software package that will provide personalized genomic information to cancer clinicians about the genetic drivers of an individual patient’s tumors. The TDI algorithm will be used for real-time mining of genetic “big data” that will enable personalized treatments for cancer patients. TDI also is expected to lead to the discovery of new cancer drivers and may be used by pharmaceutical companies to identify novel drugs. Investigators on this project are Xinghua Lu, MD, PhD, professor, and Gregory F. Cooper, MD, PhD, professor and vice chair, both of the Department of Biomedical Informatics.

**Fall Sentinel**, led by Richard D. Boyce, PhD, assistant professor of biomedical informatics, is an automated system that will make it possible for clinical pharmacists to continuously monitor patients in nursing homes, especially for potential multidrug interactions that might lead to falls. Nursing home falls are one of the most common and dangerous events for patients, with treatment costing the nation’s health system more than $4 billion each year.

The **Pressure Ulcer Monitoring Program** is an approach to reducing hospital-acquired pressure ulcers, a condition that affects an estimated 3 million patients annually. The monitoring and alert solutions, using wearable devices and hospital bed sensors, will provide real-time documentation of patient repositioning and a process to improve compliance with these preventive measures. J. Peter Rubin, MD, UPMC Professor and chair of plastic surgery, is spearheading this effort.

**SPDx (Spatial Pathology Powers Cancer Diagnosis)** is a software program that will aid pathologists in delivering more accurate diagnoses from complex tumor images. Initially, the focus is on breast cancers, in which misdiagnosis can have deadly consequences. The principal investigators are Chakra Chennubhotla, PhD, associate professor of computational and systems biology, and D. Lansing Taylor, PhD, Allegheny Foundation Professor of Computational and Systems Biology and director of the University of Pittsburgh Drug Discovery Institute.

**New Faces**

**Welcome to Your New Faculty Orientation**

New faces bring a special energy to the School of Medicine, which, according to recent data, tallies 31 departments and more than 4,700 full-time and volunteer faculty members. Among notable new faculty members recruited to the School of Medicine during the past year are:

**Nathan Urban, PhD**, is professor and vice chair of neurobiology, vice provost for special projects, associate director of the University of Pittsburgh Brain Institute, and codirector of the joint Pitt-Carnegie Mellon University Center for the Neural Basis of Cognition. Urban received a PhD in neuroscience from the University of Pittsburgh and completed a postdoctoral fellowship at the Max Planck Institute for Medical Research in Germany, where his mentor was Nobel Laureate Bert Sakmann, PhD. Among his research interests are physiological and computational analyses of neural circuit function and the development and application of physiological and optical techniques to facilitate studies, including of the olfactory bulb. In his role in the provost’s office, Urban will be involved in supporting the development and promotion of University-wide strategic initiatives in neuroscience research and education.

**Don Taylor, PhD, MBA**, is assistant vice chancellor for commercial translation in the health visiting sciences; visiting associate professor of biomedical informatics and of plastic surgery, School of Medicine; and associate professor of bioengineering, Swanson School of Engineering. Taylor received his PhD in bioengineering from the Swanson School of Engineering at the University of Pittsburgh and an MBA from the Joseph M. Katz Graduate School of Business. A longtime life sciences entrepreneur, Taylor recently served as CEO of healthStratica LLC and as an executive-in-residence at the Pittsburgh Life Sciences Greenhouse. His responsibilities include working across the six health sciences schools to accelerate commercial translation of Pitt’s discoveries and inventions, in concert with the Innovation Institute, Clinical and Translational Science Institute, and University administration. Taylor also codirects the Center for Commercial Applications of Healthcare Data under the Pittsburgh Health Data Alliance Initiative and is associate director of the Center for Medical Innovation at the University of Pittsburgh.
“Science magazine is a huge voice and plays an outsized role in matters of policy and all things associated with the pursuit of new knowledge and scientific advances.”
Five School of Medicine faculty members have been tapped to join the prestigious Association of American Physicians (AAP) and the American Society for Clinical Investigation (ASCI). Induction into these societies is considered among the highest honors in biomedical science.

New AAP members are David Brent, MD, Professor of Suicide Studies, of psychiatry, and of pediatrics, School of Medicine, and professor of epidemiology, Graduate School of Public Health; Anne B. Newman, MD, MPH, Katherine M. Detre Professor of Population Health Sciences and professor and chair of epidemiology, Graduate School of Public Health, and professor of medicine and of clinical and translational science; and Brian Zuckerbraun, MD, Henry T. Bahnson Professor of Surgery.

Founded in 1885, AAP is dedicated to the pursuit of medical knowledge, experimentation and discovery in basic and clinical science, and the application of new findings to clinical medicine. Each year, 60 people are chosen for AAP membership.

ASCI inductees are Stephen Chan, MD, PhD, visiting associate professor of medicine and director of the Center for Pulmonary Vascular Biology and Medicine at Pitt’s Vascular Medicine Institute; and Bernhard Kühn, MD, associate professor of pediatrics and of cell biology, Richard King Mellon Institute for Pediatric Research scholar, and director of research, Division of Pediatric Cardiology.

The two join 51 other Pitt colleagues on the membership rolls of ASCI, an organization of more than 2,800 physician-scientists who have achieved notable success relatively early in their careers.

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 50 or younger at the time of their election.
Peter L. Strick, PhD, Thomas Detre Professor of Neuroscience, Distinguished Professor and chair of the Department of Neurobiology, has been named to the systems neuroscience section of the Proceedings of the National Academy of Sciences (PNAS) editorial board. Strick, a leading expert on the neural basis of movement and cognition, is director of Pitt’s Brain Institute and was elected to membership in the National Academy of Sciences in 2012.

He joins Angela M. Gronenborn, PhD, UPMC Rosalind Franklin Professor, Distinguished Professor and chair of the Department of Structural Biology, who is an editorial board member of the biophysics and computational biology section at PNAS.

PNAS is one of the world’s most-cited and comprehensive multidisciplinary scientific journals, publishing more than 3,800 research papers annually that span the biological, physical, and social sciences.

Center for Medicine and the Microbiome Launched

PITTSBURGH SCHOOL OF MEDICINE AND UPMC ESTABLISH JOINT VENTURE

Our bodies host a vast ecosystem, with microbes far outnumbering human cells. They assist in digestion, fight off disease, produce vitamins, and otherwise partner with us in a symbiotic tango of life. Some, though, may increase our risk for diseases or flat out make us sick.

Pitt’s new Center for Medicine and the Microbiome is bringing together scientists and clinicians to explore how the microbiome affects health and disease—and how it can be harnessed to develop new therapies to help patients. The initiative aims to advance the understanding of microbiome behavior and enable protection and restoration of healthy microbiome function, including investigations of fundamental principles that govern microbiomes across diverse ecosystems and development of new tools to study microbiomes.

“The very nature of the microbiome involves many organs and affects many areas of medicine—from infectious disease, to cancer biology, to inflammatory bowel disease, to immunology—requiring collaboration between the many disciplines of science and medicine, something UPMC and Pitt have a proven track record of achieving,” said Mark T. Gladwin, MD, Jack D. Myers Professor, Distinguished Professor and chair of Pitt’s Department of Medicine.

The center is being led by Alison Morris, MD, MS, UPMC Professor of Translational Pulmonary and Critical Care Medicine in the Department of Medicine, and Barbara Methé, PhD, visiting professor of medicine and former professor at the J. Craig Venter Institute.

“There is a lot of enthusiasm on campus,” said Morris, adding that a project to analyze the oral microbiome is currently ongoing in collaboration with Alexandre Vieira, DDS, MS, PhD, professor of oral biology and director of clinical research, School of Dental Medicine. Vieira is also principal investigator of the school’s Dental Registry and DNA Repository, a collection of some 3,500 saliva samples and dental phenotypes matched with DNA and clinical health data.

Other collaborations include fecal transplant research with John Mellors, MD, professor of medicine, Global Elimination of HIV and AIDS professor, and chief, Division of Infectious Diseases, and Tatiana Bogdanovich, MD, PhD, MSc, clinical assistant professor of medicine in the infectious diseases division, as well as commercial application projects with UPMC Enterprises.

Elite Journal Honors Pitt Partner in China

TSINGHUA UNIVERSITY’S YIGONG SHI, PHD, RECOGNIZED FOR MENTORSHIP

The School of Medicine congratulates a key figure in its Pitt-Tsinghua University partnership, Yigong Shi, PhD, vice president of Tsinghua University and dean of Tsinghua’s School of Life Sciences, who has received the 2015 Nature Award for Mentoring in Science. Held annually, each Nature-hosted awards ceremony focuses on a specific country or countries and seeks to champion the importance of mentoring and inspiring young scientists.

The 49-year-old Shi received the journal’s mid-career award in Northern China, along with a prize of 50,000 yuan. Shi is a world leader in the structural biology of cell signaling and macromolecular assemblies. He is known for demonstrating the first three-dimensional structure of an intact yeast spliceosome at a resolution of 3.6 angstroms, a landmark achievement that increases the mechanistic understanding of pre-messenger RNA splicing. His team uses the tools of structural biology to elucidate the functional mechanisms of several key classes of proteins that control apoptosis, or programmed cell death. Apoptosis plays essential roles in the development of multicellular organisms and in preventing diseases like cancer and autoimmune disorders.

Beginning in 2012, medical and graduate students from Tsinghua University have come to Pittsburgh to participate in a two-year training program in biomedical research. To date, 67 scholars have completed their School of Medicine training and returned to Tsinghua University.

Honors for Burns, Tan

Timothy F. Burns, MD, PhD, assistant professor of medicine in the Division of Hematology/Oncology, and Roderick J. Tan, MD, PhD, assistant professor of medicine in the Division of Renal-Electrolyte, have received the 2016 Young Physician-Scientist Award from the American Society for Clinical Investigation.

Burns studies ways to develop therapies for non-small cell lung cancer targeting the KRAS mutant oncogene, and Tan studies the molecular mechanisms underlying both acute kidney injury and chronic kidney disease and fibrosis.
Goldstein Receives Presidential Honor

It isn’t every day you suit up for a photo op in the East Room of the White House with the leader of the free world and formal, full-length portraits of George and Martha Washington on the wall for company.

But that’s just what happened to Tina Goldstein, PhD, associate professor of psychiatry, in May, when she and other top talent in research gathered in the nation’s capital to receive 2016 Presidential Early Career Awards for Scientists and Engineers, the highest honor given by the U.S. government to science and engineering professionals who are in the initial stages of independent research careers.

Goldstein joined the Pitt faculty in 2006 after completing a psychology internship and postdoctoral fellowship in child and adolescent psychiatry at Western Psychiatric Institute and Clinic of UPMC. She received her PhD in clinical psychology from the University of Colorado, Boulder.

Goldstein’s work focuses on the assessment and psychosocial treatment of young people who have or are at risk for bipolar disorder, with a particular interest in suicide prevention. She aims to develop improved prevention and intervention strategies for young people informed by an enhanced understanding of the complex relationship between biological and psychosocial determinants of mood disorder and suicide. She is principal investigator for National Institute of Mental Health-funded grants to study early assessment and intervention and improving medication adherence among adolescents with bipolar disorder.

Goldstein has widely disseminated her work, collaborating on more than 60 peer-review publications in high-impact journals, including The American Journal of Psychiatry, Journal of the American Academy of Child & Adolescent Psychiatry, and Archives of General Psychiatry, as well as numerous book chapters, and is coauthor of a book on the treatment of depressed and suicidal youth.

Established by President Bill Clinton in 1996, the Presidential Early Career Award honorees are selected for their pursuit of studies at the frontiers of science and their commitment to community service through scientific leadership, public education, and outreach.
Patrick M. Kochanek, MD, Ake N. Grenvik Professor of Critical Care Medicine, has been selected to receive a Lifetime Achievement Award from the American College of Critical Care Medicine. The organization’s highest award, which recognizes “pioneering contributions to the field of critical care through the advancement of medical science, medical education, and medical care,” will be presented at the 46th Congress of the Society of Critical Care Medicine in January 2017.

A 2014 special report by ScienceWatch called Kochanek “the most prolific of authors” on traumatic brain injury (TBI), noting that he had contributed to 300 reports, which had generated more than 3,800 citations. He has a long track-record of investigation in traumatic and ischemic brain injury and neurointensive care and is funded by the U.S. Army, National Institutes of Health, and the Laerdal Foundation.

“This is a reflection of the hard work and dedication of the entire team involved in pediatric critical care,” said Kochanek, who is vice chair of critical care medicine, professor pediatrics and of clinical and translational science, and professor of bioengineering, Swanson School of Engineering.

Kochanek received his MD from the University of Chicago, completed a pediatrics residency at the University of California, San Diego, and a pediatric critical care fellowship at Children’s National Medical Center in Washington, D.C.

Kochanek has been a faculty member at the University of Pittsburgh since 1986 and director of the Safar Center for Resuscitation Research since 1994. His major research interest is in mechanisms of secondary damage after severe TBI. He is principal investigator of a $10.4 million multicenter preclinical drug screening consortium funded by the U.S. Army to identify new TBI therapies.

In a burgeoning annual tradition begun in 2015, a diverse community of faculty, physicians, students, and trainees from the medical school gathered together with spouses and partners to socialize, to celebrate their accomplishments, and to envision ways this community might grow more diverse, vibrant, and powerful. Held each fall at the Senator John Heinz History Center, the most recent iteration of the Toast to Diversity and Call to Action attracted more than 200 attendees, especially those who self-identify...
Coming together to celebrate a campus-wide commitment to diversity

as members of groups underrepresented in the medical profession.

It was just one of many recent University events celebrating diversity, as the 2016-17 academic year was officially declared the Year of Diversity at Pitt by Provost Patricia Beeson. The campus-wide focus gives a significant boost to the many ongoing diversity programs supported by the Office of Health Sciences Diversity. In addition to academic talks and informal mentoring, these include special events like an evening reception at the Carnegie Museum of Art exploring the exhibit She Who Tells a Story: Women Photographers from Iran and the Arab World, the work of 12 photographers who are challenging representations and perceptions of Middle Eastern identity. Dozens of attendees, including med students, enjoyed a presentation and discussion with one of the featured artists.
Pitt, Pharma Take On Rare Diseases in New Partnership

The University of Pittsburgh has begun a research collaboration with global biopharmaceutical company Shire plc (LSE: SHP, NASDAQ: SHPG) to advance potential treatments for rare diseases, where sizable unmet need exists. The collaboration combines the expertise of Pitt’s top-ranked health sciences schools, led by the School of Medicine, with Shire’s research, development, and commercialization experience.

“We’re very excited to enter into a partnership with Shire Pharmaceuticals,” said Pitt Chancellor Patrick D. Gallagher. “For decades, Pitt has been a leading research university; and, as we move into our next phase, finding external partnerships with companies like Shire is critical for our future and a priority for Pitt.”

Pitt has an extensive legacy of delivering groundbreaking health solutions, such as creating the first safe, effective polio vaccine, pioneering organ transplantation, and developing imaging technology to identify the protein plaques characteristic of Alzheimer’s disease in the living brain.

“This collaboration has enormous potential to take what our scientists have already learned and will discover about rare illnesses and apply this new knowledge to improve the care of patients who have otherwise garnered little attention,” said Arthur S. Levine, MD, Pitt’s senior vice chancellor for the health sciences and Petersen Dean of Medicine.

“We want to make a difference for these families.”

This kind of partnership is relatively new for Pitt but is the type of relationship the University has identified as a strategic priority. Under the agreement, Pitt and Shire have selected an initial three projects that will be funded by Shire and could ultimately result in a licensing agreement.

• Solomon Ofori-Acquah, PhD, associate professor of medicine, will be investigating a molecular pathway that may lead to drug targets against sickle cell anemia.
• David Whitcomb, MD, PhD, Giant Eagle Foundation Professor of Cancer Genetics and professor of medicine and of cell biology, will be researching a molecular pathway relevant to pancreatitis.
• Peter Wipf, PhD, Distinguished University Professor of Chemistry, Dietrich School of Arts and Sciences, and Stephen Meriney, PhD, professor of neuroscience, Dietrich School, will be studying a newly identified molecule that may lead to drug targets against the autoimmune disorder Lambert-Eaton myasthenic syndrome.

“"These projects are now being fleshed out to define a three-year plan to codevelop a new molecule and lead compound that demonstrates effectiveness in an animal model of disease," said Dietrich Stephan, PhD, who is leading the collaboration for Pitt, and is professor and chair of the Department of Human Genetics at Pitt’s Graduate School of Public Health. "In addition to our teams, we have access to all of Shire’s capabilities and contract research organizations, which includes custom chemistry on the molecules and preclinical work.”

According to patient advocacy organization Global Genes, rare diseases affect more than 320 million people worldwide—10 times the number affected by all cancers combined and approximately the same number who suffer from the global epidemic of diabetes. Scientists have identified thousands of rare diseases, often having origins in genetic mutations that can pass through generations. These diseases are usually extremely severe, cause significant suffering, and very often result in early death. While each individual disease generally affects fewer than several hundred thousand people, they collectively account for a massive global burden of underserved patients.

PSC Welcomes New Supercomputer

"Bridges" AIDS BIG DATA STUDIES

During 2016, the Pittsburgh Supercomputing Center (PSC) has been celebrating its 30th anniversary with expanded capabilities and recognition from the high-performance computing (HPC) world. A joint effort of the University of Pittsburgh and Carnegie Mellon University, PSC began with a machine that could perform up to 840 million arithmetic operations every second. Shortly thereafter, new acquisitions started getting Burgh-flavored nicknames like “Mario” and “Warhol.”

The latest, “Bridges,” was developed with a $9.65 million grant from the National Science Foundation to support investigators working in a wide range of fields, including genomics, physical sciences, engineering, neuroscience, and the social sciences.

“First and foremost, Bridges is about enabling researchers who’ve outgrown their own computers and campus computing clusters to graduate to supercomputing with a minimum of additional effort,” says Ralph Roskies, PhD, PSC scientific director and professor of physics, University of Pittsburgh.

Bridges and PSC’s other upgrades have not gone unnoticed. HPCowire, a leading trade publication, cited PSC’s work for “Best Use of HPC Applications in Life Sciences” and “Best Use of High Performance Data Analytics,” with a particular shout-out to the Pittsburgh Genome Resource Repository (PGRR).

PGRR is a resource for storing, accessing, and analyzing large, de-identified national sets of data like The Cancer Genome Atlas (TCGA) from the National Institutes of Health, which are important for personalized medicine. PGRR is funded by Pitt’s Institute for Precision Medicine (IPM) and University of Pittsburgh Cancer Institute (UPCI) and includes collaboration of faculty and staff from IPM, UPCI, the Department of Biomedical Informatics, the University of Pittsburgh Center for Simulation and Modeling, PSC, and UPMC.

PGRR facilitates the large-scale profiling of TCGA’s 11 petabytes of data, consisting of data on tumor samples from 11,000 cancer patients, to better understand genetic pathways and eventually enable personalized cancer treatments.
NCI Recognizes Pitt Cancer Researchers

Make way for the Outstanding Investigator Award, a National Institutes of Health funding mechanism that rewards preeminent researchers with significant funding for seven years. The award, also known as an R35 grant, is intended to provide stable support for more adventurous research ideas.

Although the awards are fairly new (the first class of recipients was announced in summer 2015), faculty associated with the University of Pittsburgh Cancer Institute (UPCI) are already well represented among National Cancer Institute (NCI) honorees—acknowledgment that their work has unusual potential to advance cancer research.

Olivera J. Finn, PhD, Distinguished Professor of Immunology, and director of UPCI’s Immunology Program, has received $6.3 million to continue her investigations into identifying specific mechanisms of human antitumor immunity and developing prophylactic cancer vaccines. In particular, her group has identified a novel immune response to a tumor-associated antigen, MUC1, expressed on breast, pancreatic, colon, ovarian, and other carcinomas of epithelial cell origin. MUC1-based vaccines were tested in several clinical trials in patients with these cancers. Finn also received the American Association of Immunologists’ highest honor in 2016, the AAI Lifetime Achievement Award.

Thomas W. Kensler, PhD, professor of pharmacology and chemical biology and coleader of the Cancer Epidemiology and Prevention Program at UPCI, has been awarded $6.3 million to support his studies on dietary chemoprevention—foods that may be used to reduce the risk of developing cancer caused by unavoidable environmental toxins. Studies done by Kensler’s team in China have examined the bioactive molecules in broccoli and how they may help people there detoxify air pollutants. Broccoli and other cruciferous vegetables contain a naturally occurring molecular compound, sulforaphane, which activates protective protein pathways in cells that dampen risk from exposure to carcinogens.

Patrick S. Moore, MD, MPH, Pittsburgh Foundation Professor of Innovative Cancer Research and Distinguished Professor of Microbiology and Molecular Genetics, has received $6.4 million to continue exploring links between viruses and cancer. Together with his research partner and wife, Yuan Chang, MD, Moore has identified two different viruses that cause Kaposi sarcoma and Merkel cell carcinoma. The award will fund investigations that help to elucidate the mechanisms by which these viruses lead to the development of cancer and identify new ways to find cancer-causing viruses. Recently, the Moore-Chang lab found a new mechanism that cancer viruses use to regulate how cells translate RNA into proteins and developed an assay to discover a class of viruses called polyomaviruses.
At the University of Pittsburgh School of Medicine’s annual curriculum colloquium in 2012, med school dean Arthur S. Levine, MD, proposed a new program to neatly complement the school’s basic science strengths. He suggested pairing students with a moderately complex case, a patient whom they would follow through the course of their education. The only other longitudinal experience, after all, is the Scholarly Project—the four-year research endeavor Pitt med students undertake. This was like adding another, very different pillar to support the curriculum.

Robin Maier, MD, MA, assistant professor of family medicine and director of medical student education in that department, attended that colloquium and thought the program sounded interesting. What impressed her, she says, is that “there’s this sense of seeing the medical system from the inside out, from the patient perspective,” rather than the usual doctor-side perspective. After telling the dean as much, she was quickly asked to head the pilot program.

Maier launched the Longitudinal Alliance Project (LAP) in 2013. Med student Mike Bruno, who was in the inaugural class of 10, says that the program “flips our roles and lets us sit beside the patient. And it has a whole different tone to it. Because after the visit, we don’t just go and talk to the doctor and debrief with the doctor: So what do you think of this lab value? Instead, we’re debriefing with the patient: So what do you think about what the doctor said? Did you get everything out of that? That is really what distinguishes this experience—and why I think it’s valuable.”

Each year of LAP is loosely guided by a theme. Getting to know the patient is the bulk of year one. Getting to know the health care team and its interprofessional interactions makes up year two. Maier arranges for other health professionals to join small-group discussions that year, starting the tilt toward medicine-as-team-sport thinking. In the third year, the focus is on the different specialties of medicine and how they interact—how a family doctor might refer her patient to a cardiologist, who then refers him to a radiologist for imaging and then sends the result back to the patient and the primary doctor. Ultimately, as students grow in their medical knowledge, LAP grows with them.

By the end of that first year, Bruno was expected to understand the biology of his patient’s conditions. As a capstone, he and the other students each gave a presentation to the small group on the medical science behind their patients’ health concerns and wrote reflective papers on their experience with the patient and LAP.

The learning that goes on in these group sessions, though difficult to quantify, is a huge part of LAP’s success, the students say. The sheer breadth of conditions and individual circumstances each student encounters—and therefore shares with the others in his group—range from children with Down syndrome to adults with cancer, from people on dialysis to those newly diagnosed as diabetic. When, as has happened twice, a patient in the program dies, the students grieve together. When another patient’s diabetes comes under control—because of a dental procedure, of all things—they celebrate.

So far, only a half-dozen or so of the nearly 100 patients enlisted have left the program. The most recent LAP group numbers nearly 60, and next year’s group is expected to be even bigger. “It’s giving students real insight into how it is to deal with the medical system … which is something that makes every kind of physician a more effective physician,” says Maier. At its best, the program helps med students learn what kind of doctors they want to be.
Bolstering Clinical Research Careers

Preparation of Medical Students for 21st-Century Medicine

Physician-scientists—docs who work in the clinic and also pursue research—are invaluable in translating insights from the bench to patient care. Yet, physicians with this double expertise are an endangered species, says Wishwa Kapoor, MD, MPH, Distinguished Service Professor and Falk Professor of Medicine, chief of the Division of General Internal Medicine, and director of Pitt’s Institute for Clinical Research Education. According to a comprehensive assessment by the National Institutes of Health last year, the average age of physician-scientists is rising, and pressures in today’s funding climate create additional challenges for young trainees. Kapoor notes that many programs at Pitt are attempting to address the shortage—from summer institutes for kids to seminars on work-life balance for junior faculty.

What are some of the factors contributing to the leaky pipeline?

Becoming a physician-scientist requires more training, and you often start out with more debt; research salaries are also lower than clinical salaries at the start. Also, in my view, these careers are a lot harder than being a physician in practice. Not that being a physician is easy, but the path is relatively straightforward: You join a practice and, generally, patients keep coming. As a physician-scientist, though, you have to take the reins and guide your career in a creative way—ask the right questions, develop your research program, get the grants. There’s a significant degree of burnout because of the stress of trying to get funding.

How can institutions help trainees succeed?

We need to make this track more accessible to younger researchers and to train and retain more women and minorities. There is no magic-bullet solution. The focus must be not just on recruitment but on sustaining and supporting these investigators. But I think the most important component of success is mentorship. Young investigators need mentors who can devote time to them and who are committed to promoting their careers—both at the home institution and with outside colleagues.

How has Pitt been a leader in efforts to recruit, train, and sustain the careers of physician-scientists?

The School of Medicine has developed programs for medical students to do substantive research. These programs (described on pages 20–24 of this report) help spark interest and are the beginning of research careers.

Q&A with Wishwa Kapoor, MD, MPH

The best physicians have a solid grounding in the scientific method. They don’t have to be scientists, but they understand how research works and how the latest scientific discoveries can lead to better health for their patients. At Pitt, we challenge medical students to contribute to scholarly research during their med school years. In each graduating class, without fail, there are med students who seize this opportunity and produce extraordinary results. Pitt’s innovative Scholarly Project requirement was introduced more than a decade ago. At the time, some said it would drive away applicants (who didn’t want to do research, presumably), but the opposite has proven true. Today, admission is more competitive than ever. Pitt graduates are increasingly sought after by top residency programs, partly because of their research experience. Even more telling, some of the nation’s other elite medical schools now emulate Pitt’s Scholarly Project. A few key features developed over the years have greatly enhanced the success of the program, according to Donald B. DeFranco, PhD, associate dean for medical student research and professor and vice chair of pharmacology and chemical biology. “What is unique to Pitt, I think, is the direct connection to preparatory coursework. Methods and Logic in Medicine is a small-group, mentor-led class that prepares them to do research, and it happens in the fall and winter of their first year.” Following that course, every med student is invited to take part in summer research between the first and second years of med school. “We are close to an all-time high,” DeFranco notes, “with about 85 percent of the class doing summer research.” For the Scholarly Project, students are paired with established scientists, including some of Pitt’s most accomplished faculty members. Program organizers have created a culture in which there is a clear focus on providing guidance and tools for mentors. The mentor-student relationship is structured and supported from beginning to end. Depending on their interests, med students delve into everything from wet-bench laboratory research to computational biology. Some formulate clinical research projects with clinician mentors; others explore the subtleties of the doctor-patient relationship or mine public health data for new insights into disease trends. In these and scores of other ways, med students build their own scientific knowledge and develop skills that will help them to become clinicians who can make difficult diagnoses and help patients make decisions based on evidence.
Addiction Medicine and the Opiate Abuse Epidemic

Health professionals from all disciplines are joining forces to address substance abuse, with a particular focus on opiate abuse. Pitt medical students begin learning about these conditions early in the first year and continue the process throughout the curriculum during sessions that provide essential knowledge and patient-counseling skills in pain management and addiction. New Web-based instructional modules are being introduced to provide students with added exposure to patient cases in these areas.

In spring 2015, Pitt’s Schools of the Health Sciences introduced a unique presentation that was delivered to every student graduating this year from Pitt’s Schools of Medicine, Dental Medicine, Pharmacy, Nursing, Health and Rehabilitation Sciences, and Public Health. The program, “A Man-Made Epidemic: Uses and Abuses of Opioids,” is the brainchild of med school dean Arthur S. Levine, MD, who is also senior vice chancellor for the health sciences, to convey the urgency and importance of the latest information on opioid addiction to students as they embark on their careers as health professionals.

In addition, the med school joined more than 60 American medical schools in an Association of American Medical Colleges–organized pledge to, beginning in fall 2016, require all medical students to undergo prescriber education in line with the newly released Centers for Disease Control and Prevention Guidelines for Prescribing Opioids for Chronic Pain.
In-Depth Study for Med Students

Through a raft of specialized programs, diverse research opportunities, and areas of concentration, med students at Pitt are able to explore their interests in depth. Many 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 devote a full year to research through either the Clinical Scientist Training Program (CSTP) or the Physician Scientist Training Program (PSTP).

CSTP

The Clinical Scientist Training Program offers a leg up for medical students who show an interest in and a talent for clinical research. Select students whose mentored scholarly projects meet the NIH definition of clinical research are invited to delve deeper into their research during a fifth year of training. Interested students apply to 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, 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. After leading the program for 12 years, Amber E. Barnato, MD, MPH, MS, associate professor of medicine and of clinical and translational science, stepped down as CSTP director in 2015. Margaret B. Conroy, MD, MPH, associate professor of medicine, School of Medicine, and of epidemiology, Graduate School of Public Health, will lead the program going forward. Conroy, who is also assistant dean for medical student research, plans to formalize a CSTP peer mentoring program and further strengthen the continuity between the Scholarly Project and the research that CSTP students conduct during the research year.

Several members of the Class of 2016 are products of Pitt’s CSTP, having previously completed the research year.

CSTP GRADUATES AND THEIR RESIDENCY PROGRAMS:

<table>
<thead>
<tr>
<th>Name</th>
<th>Residency Match</th>
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<tbody>
<tr>
<td>JULIE BOIKO, MD, MS</td>
<td>Pediatrics, University of California, San Francisco</td>
</tr>
<tr>
<td>JEE-HONG KIM, MD</td>
<td>Otolaryngology, University of Southern California, Los Angeles</td>
</tr>
<tr>
<td>DOUGLAS HOLT, MD</td>
<td>Preliminary Internal Medicine, University of Utah Affiliated Hospitals, Salt Lake City</td>
</tr>
<tr>
<td>OLUBUSOLA OLUWOLE, MD, MS</td>
<td>Internal Medicine/Global Health, UPMC Medical Education Program/University of Pittsburgh</td>
</tr>
<tr>
<td>ALEXANDER KHALAF, MD</td>
<td>Neurological Surgery, UPMC Medical Education Program/University of Pittsburgh</td>
</tr>
<tr>
<td>XIAORAN ZHANG, MD, MS</td>
<td>Neurological Surgery, UPMC Medical Education Program/University of Pittsburgh</td>
</tr>
</tbody>
</table>

Mentors:
- Paul Szabolcs, MD, Professor of Pediatrics and of Clinical and Translational Science; Chief, Division of Blood and Marrow Transplantation and Cellular Therapies
- Vivien L. Parry, MD, Associate Professor of Neurological Surgery and of Clinical and Translational Science
- Howard Aizenstein, MD, PhD, Professor of Neurological Surgery and of Clinical and Translational Science
- Marguerite F. Peroni, MD, Professor of Radiation Oncology and of Clinical and Translational Science
- Michael T. Lotze, MD, Professor of Medicine, Division of Hematology/Oncology, and of Clinical and Translational Science
- Enrico Novelli, MD, MS, Assistant Professor of Neurological Surgery and of Clinical and Translational Science
- Nduka Amankulor, MD, Assistant Professor of Medicine, Division of Hematology/Oncology, and of Clinical and Translational Science
- Michael T. Lotze, MD, Professor of Surgery and Vice Chair for Research, Department of Surgery; Professor of Immunology and of Clinical and Translational Science; Professor of Bioengineering, Swanson School of Engineering

Mentor:
- Howard Aizenstein, MD, PhD, Professor of Psychiatry and of Clinical and Translational Science; Associate Professor of Bioengineering, Swanson School of Engineering
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 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 2016 included three graduating PSTP students who matched to top residency programs in some of the most competitive medical specialties. Three members of the Class of 2016 are products of Pitt’s PSTP, having previously completed the research year.

**PSTP GRADUATES AND THEIR RESIDENCY PROGRAMS:**

**MICHAEL BURROW, MD**
Residency Match: Ophthalmology, University of Utah, Salt Lake City
Mentor: James Funderburgh, PhD, Professor of Ophthalmology and of Cell Biology

**ERIN CUMMINGS, MD**
Residency Match: Pediatrics, UPMC Medical Education Program/University of Pittsburgh
Mentor: Gary Silverman, MD, PhD, Harriet B. Spoehrer Professor and Chair of Pediatrics, Washington University in St. Louis School of Medicine

**BHAVANA CHAPMAN, MD**
Residency Match: Preliminary Internal Medicine, University of Texas MD Anderson Cancer Center, Houston
Radiation Oncology, Baylor College of Medicine, Houston

Mentors:
Jennifer Grandis, MD, American Cancer Society Professor, Associate Vice Chancellor for Clinical and Translational Research, and Professor of Otolaryngology, University of California, San Francisco
Saleem Khan, PhD, Professor of Microbiology and Molecular Genetics

**PSTP GRADUATES AND THEIR RESIDENCY PROGRAMS:**

**TOLANI OLONISAKIN**
Residency Match: Preliminary Internal Medicine, University of Texas MD Anderson Cancer Center, Houston
Mentor: Christopher Bakkenist, PhD, Associate Professor of Radiation Oncology

**THIAGU MEYYAPPAN**
In Vivo Induction of Antigen Specific Tregs To Prevent the Onset of Type 1 Diabetes
Mentors: Steven R. Little, PhD, William Kepler Whiteford Professor and Chair, Department of Chemical and Petroleum Engineering, Swanson School of Engineering

PSTP Students Win Prestigious HHMI Fellowships for 2016–17

All three PSTP students graduating with the Class of 2016 shared something in common: Each was awarded a highly coveted research training fellowship through the Howard Hughes Medical Institute (HHMI) Medical Research Fellows Program. Carrying on this distinguished tradition, five current PSTP students were also named HHMI fellows in 2016. The students will be supported through a one-year leave of absence, during which they’ll dedicate themselves to their research projects and associated research training. Pitt’s success in this prestigious arena stems in part from the specialized grant writing course offered to PSTP students between the first and second years of med school. In addition to learning widely applicable keys to successful grant writing, the course provides very specific feedback on each student’s HHMI proposal.

**THE AWARD-WINNING STUDENTS AND THEIR PROJECTS:**

**POOJA KARUKONDA**
Investigating the Role of Radiation Therapy in Promoting an Anti-Tumor Response in the Host
Mentor: Christopher Bakkenist, PhD, Associate Professor of Radiation Oncology

**MONDIRA RAY**
Construction and Validation of Pathway-Oriented Features for Use in Machine Learning Programs To Predict Breast and Lung Cancer Outcomes
Mentor: Rebecca S. Jacobson, MD, MS, Professor of Biomedical Informatics and of Clinical and Translational Science
Ziv Bar-Joseph, PhD, Professor of Computational Biology, Carnegie Mellon University

**Pooja Karukonda**
Investigating the Role of Radiation Therapy in Promoting an Anti-Tumor Response in the Host
Mentor: Christopher Bakkenist, PhD, Associate Professor of Radiation Oncology

**Cyrus Tsang**
The Role of Synaptic Zinc in Tinnitus-Related Hyperactivity
Mentor: Thanos Tsounopoulos, PhD, Professor of Auditory Physiology and Associate Professor of Otolaryngology

**MONDIRA RAY**
Construction and Validation of Pathway-Oriented Features for Use in Machine Learning Programs To Predict Breast and Lung Cancer Outcomes
Mentor: Rebecca S. Jacobson, MD, MS, Professor of Biomedical Informatics and of Clinical and Translational Science
Ziv Bar-Joseph, PhD, Professor of Computational Biology, Carnegie Mellon University

**Cyrus Tsang**
The Role of Synaptic Zinc in Tinnitus-Related Hyperactivity
Mentor: Thanos Tsounopoulos, PhD, Professor of Auditory Physiology and Associate Professor of Otolaryngology
**It’s an MSTP Match**

Match Day is a big deal for all graduating med students, but for those in the Medical Scientist Training Program (MSTP), Pitt’s combined MD/PhD program, the anticipation has been building for an especially long time. Most classmates with whom they entered med school are long gone, because MSTP students begin with two years of MD training then break for a few years of PhD research before returning to complete the MD. While in the midst of their PhD research, they watch most of the MD students they entered with celebrate graduation and move on to residency positions. Match Day for MSTP students typically arrives about seven years after they begin medical school. In 2016, Pitt said farewell to four of these budding physician-scientists. “In 2016, our graduating students matched into top-tier programs,” said Richard Steinman, MD, PhD, associate dean for MSTP and associate professor of medicine and of pharmacology and chemical biology. “More notably, the academic programs that they chose for residency training have a tradition of supporting physician-researchers. Across the board, our graduates will continue both their clinical and scientific training with guidance from outstanding role models at their new institutions.”

**PITT’S 2016 MSTP GRADUATES AND THEIR RESIDENCY MATCHES:**

<table>
<thead>
<tr>
<th>KAREN CHIU, MD, PHD</th>
<th>Niyathi Hegde Shah, MD, PhD</th>
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<tbody>
<tr>
<td>Residency Match:</td>
<td>Internal Medicine, Weill Cornell Medical College, New York, NY</td>
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<tr>
<td>Mentor:</td>
<td>Michael J. Palladino, PhD, Associate Professor of Pharmacology and Chemical Biology</td>
</tr>
<tr>
<td>ANDREY FINEGERSH, MD, PHD</td>
<td>Jeffrey Walch, MD, PhD</td>
</tr>
<tr>
<td>Residency Match:</td>
<td>Otolaryngology, University of California, San Diego</td>
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<tr>
<td>Mentor:</td>
<td>Gregg Homanics, PhD, Professor of Anesthesiology and of Pharmacology and Chemical Biology</td>
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<td>Preliminary Surgery, University of Maryland, Baltimore</td>
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<td></td>
<td>Fadi Lakkis, MD, Frank and Athena Sarris Professor of Transplantation Biology, Department of Surgery; Professor of Immunology and of Medicine</td>
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On average over the past six years, MSTP students have coauthored six scientific publications (three as first author) by the time they graduate. Other MSTP bragging points include Pitt’s enviable success rate in winning F30 awards from the National Institutes of Health. Also known as Ruth L. Kirschstein National Research Service Awards, F30s are granted to MSTP students who demonstrate the potential to become highly trained, productive, and independent physician-scientists. NIH’s ultimate goal with this program is to increase the number of future investigators with both clinical knowledge and skills in basic, translational, or clinical research. In recent years, roughly half of Pitt’s MSTP students have earned NIH grants.

**F30 AWARDS TO CURRENT MSTP STUDENTS:**

<table>
<thead>
<tr>
<th>Colin Beckwitt</th>
<th>Annie Liu</th>
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<tr>
<td>Oxygen’s Impact on Tumor Metastasis Dormancy and Therapy</td>
<td>Organization and Plasticity of Post-Synaptic Targets of Individual Gliomeruli in the Mammalian Olfactory Bulb</td>
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<tr>
<td>National Cancer Institute</td>
<td>National Institute on Deafness and Other Communication Disorders</td>
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<tr>
<td>Mentor: Alan H. Wells, MD, DMS, Thomas J. Gill III Professor of Clinical Pathology and Executive Vice Chair for Clinical Pathology, Department of Pathology; Professor of Computational and Systems Biology; Professor of Bioengineering, Swanson School of Bioengineering</td>
<td>Mentor: Nathan Urban, PhD, Professor and Vice Chair of Neurobiology</td>
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<tr>
<td>Joel Kuttken</td>
<td>J. Randall McAuley</td>
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<td>Tsp1-Cd47 Signaling Limits Signalsome in Osteosarcoma Metastasis</td>
<td>The Carma3/Bcl10/Malt1</td>
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<tr>
<td>National Institute of Biomedical Imaging and Bioengineering</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>Mentor: Bruce Freeman, PhD, UPMC Irwin Fridovich Professor and Chair of Pharmacology and Chemical Biology</td>
<td>Mentor: Peter Lucas, MD, PhD, Associate Professor of Pathology and of Pediatrics</td>
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<td>Eric Zimmerman</td>
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<td>Nucleus Reuniens Regulation of Ventral Tegmental Area Dopamine Neuron Activity: Relevance to Psychosis</td>
<td>National Institute of Mental Health</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases</td>
<td>Mentor: Anthony A. Grace, PhD, Distinguished Professor of Neuroscience and Professor of Psychology, Dietrich School of Arts and Sciences</td>
</tr>
<tr>
<td>Mentor: Jeffrey S. Isenberg, MD, MPH, Associate Professor of Medicine; Associate Professor of Bioengineering, Swanson School of Engineering</td>
<td>Mentor:</td>
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Pitt’s MSTP has 80 students currently—big enough to maintain a lively and diverse group dynamic. In the 2016–17 academic year, MSTP boasts its highest level of NIH support since its founding 30 years ago, with 20 Pitt MD/PhD students funded by NIH per year.

As usual, students in the program welcomed an influx of fresh faces at the start of the academic year. The research interests of the incoming class reflect a few of the many research strengths...
of the University, ranging from molecular pharmacology to epidemiology, with individual students focusing on immunology, clinical and translational science, neuroscience, structural biology, and molecular biophysics.

“The 14 new students who make up this year’s incoming class stood out for their research accomplishments and their smart plans for how they would use our program to further develop their already outstanding skills,” said Steinman. “They were drawn to Pittsburgh by specific faculty members and research programs that buoy our national reputation in biomedical science.”

Medical School Isn’t Just for MDs

In addition to the approximately 600 students in the four-year MD program, there are nearly 300 students pursuing PhD degrees in 12 programs that include neuroscience, biomedical informatics, computational biology, molecular biophysics and structural biology, and clinical and translational science. The breadth and depth of research activity at the University are extensive enough that graduate students in a wide range of disciplines receive training that allows them to conduct research at the cutting edge of biomedical science.

Of note in 2016, Tianyu (Emma) He, a fifth-year PhD student in the Cellular and Molecular Pathology program, was awarded a Young Investigator Prize at the 21st International AIDS Conference in Durban, South Africa, for her abstract presentation of a new strategy for reactivating HIV from reservoirs. The $2,000 prize is a means of supporting young researchers who demonstrate innovation, originality, rationale, and quality in HIV research. Her thesis advisor is Ivona Pandrea, MD, PhD, professor of pathology, School of Medicine, and of infectious diseases and microbiology, Graduate School of Public Health.

Class of 2016 Remakes Match Day Experience

On Match Day 2016, Pitt med’s senior class scored a record number of residency placements in 30 states and the nation’s capital, with 38 graduating students continuing their medical training right here in the City of Champions. Match Day is a familiar annual ritual, but while the residency assignments of the 141 individuals in the Class of 2016 were still sealed up in neat stacks of envelopes, the grand spectacle of Match Day 2016 was—dare we say it—divergent.

Seniors elected to forgo the lively, one-by-one chaos of “hear the dean call your name, get an envelope,” in favor of a mass opening of match letters. The tearing of envelopes was quickly followed by group rejoicing and opportunities for students to grab a microphone and share their results from the stage.

“I liked the format change, because there was less pressure for students to open their envelopes in front of everyone,” said Jacqueline Birken, now a pathology intern at Johns Hopkins Hospital. “I matched into my top choice!” she said.

“I was happy to have my parents and closest friends there to share the moment of me opening my envelope,” said Debra Okafor, former president of the Student National Medical Association at Pitt. “My friends and I did a countdown together. I was overjoyed and cried as soon as I saw my results.”

Okafor is now a pediatrics resident at Yale-New Haven Hospital. While at Pitt, she assisted in neonatology and gastroenterology research studies at Magee-Womens Hospital of UPMC and Children’s Hospital of Pittsburgh of UPMC.

“You should be applauded and celebrated,” said Joan Harvey, MD, associate dean for student affairs. “You should know how proud of each and every one of you we are.”

Malcolm Dombrowski was quick to return Harvey’s praise, saying he “couldn’t be happier” with his med-school experience. He described the med school as a “strong collegial and academic environment” with a diverse student body that shares common goals. In fact, he holds the Pitt environment in such high esteem that it was his first choice for residency. He was pleased to open his envelope and find that he’ll remain here for the next six years as an orthopaedic surgery resident.

“Pitt’s clinical teaching is definitely among the top in the nation,” Dombrowski added. “And based on the reactions and immediate respect I was given when interviewing, you could tell that faculty across the country know what type of training happens at Pitt.”

In addition to those in Pitt’s residency programs, large cohorts of 2016 Pitt med graduates are also training at Harvard, Johns Hopkins, and Case Western Reserve Universities, among many others.
ANDY SAYS, “WELCOME PITT MED!”

A new med-school rite of passage was introduced in August 2015, and now two entering classes have enjoyed a fun and funky evening to celebrate their first week of med school.

**THE PLACE:**
The Andy Warhol Museum on Pittsburgh’s North Side

**THE VIBE:**
From Warhol Hipster/Chic to Business Casual

**THE SCENE:**
Music, silk-screening, scavenger hunt, and more, all kicked off by the sorting of students into “houses,” which are led by their advisory deans.
Second-year med student Sangki Oak has been named a Tillman Scholar by the Pat Tillman Foundation. This prestigious honor is reserved for a small number of post-9/11 military veterans (or their spouses) who demonstrate strength in character, academic excellence, and extraordinary potential in the fields of medicine, law, business, education, and the arts. Founded in 2004, the foundation honors the memory of Pat Tillman, who passed on a lucrative professional football contract to enlist in the U.S. Army and was killed in action in 2004. Tillman Scholars receive academic scholarships and support for study-related expenses.

A veteran of the U.S. Navy, Oak served as senior medic for a team of Marines deployed to Afghanistan in 2009 and 2010. In addition to providing medical care to their Marines, Oak and his team worked on improving public health and health infrastructure for the local population. In Afghanistan, Oak developed a passion for helping those in medically underserved communities worldwide. His position as a medic, as well as the team member in charge of aid and development efforts for the local population, familiarized him with the needs and struggles of those in remote parts of the world and those caught in the crossfire of armed conflict.

Since leaving the military, Oak’s passion for medicine has been reinforced by visits with Syrian refugees in camps near the Iraq border and through providing medical care to those affected by the earthquake in Nepal. He credits the military with providing him the temperament and skills to operate in these harsh and remote places and the aptitude to develop solutions with limited resources.
Global Partnerships
Expanding and Maturing

THE SCHOOL OF MEDICINE OPERATES ON A GLOBAL STAGE, WITH ACTIVE COLLABORATIONS CONNECTING PITTSBURGH WITH AFRICA, ASIA, EUROPE, AND SOUTH AMERICA. OF PARTICULAR NOTE OVER THE PAST FIVE YEARS, PROGRAMS LINKING US WITH CHINA AND KAZAKHSTAN HAVE MATURED INTO THRIVING PARTNERSHIPS.

Through the School of Medicine’s partnership with Tsinghua University School of Medicine in Beijing, medical students at this most prestigious of Chinese scientific institutions undergo a rigorous, two-year biomedical research training program in Pittsburgh. Initiated in 2012, the historic agreement was recently renewed for a second five-year term. As of August 2016, Pitt’s Tsinghua Scholars program has 67 alumni and 25 active scholars on campus, working in the labs of some of Pitt’s most accomplished biomedical researchers.

The 2016 edition of the annual Pitt-Tsinghua Joint Symposium was held in Beijing. Eight Pitt faculty members made the journey from Pittsburgh and took part in scientific presentations alongside their peers from Tsinghua University. Cutting-edge topics included cryo-electron microscopy and viral protein assembly, computational modeling, the use of advanced quantitative methods to improve bedside care, advances in precision medicine, Big Data and computational modeling to counter epidemics, and advanced clinical decision analysis. The 2017 joint symposium will be held in Pittsburgh.

The School of Medicine initiated a collaboration with China’s renowned Central South University Xiangya School of Medicine in 2012, as well. Under the five-year agreement, Pitt provides two years of rigorous biomedical research training to medical students, most of whom have already undergone six years of medical school, including clinical clerkships. As of September 2016, 24 of these medical students are on campus, and 10 have recently returned to Changsha to graduate from medical school after their two years in Pittsburgh. In 2014, spurred on by the success of this global collaboration between universities, Xiangya Hospital formed a partnership with UPMC to establish an international medical center that will improve access to high-quality care for patients within the region.

In 2012, the School of Medicine was selected to guide the Republic of Kazakhstan’s Nazarbayev University (NU) as it establishes its own medical school, which aims to educate physician-scientists to become this Central Asian nation’s next leaders in health care, medical education, and biomedical research. Pitt has partnered with NU to institute a U.S.-style curriculum; design and develop teaching facilities; recruit and train school leadership and faculty; plan organizational and administrative structures, policies, and procedures; and develop courses, syllabi, and clinical experiences with the participation of physician-educators from Kazakhstan and around the globe. In August 2015, the NU School of Medicine welcomed its first class of 20 students, followed by a second class of 32 students in August 2016.

Alumnus Ryan McGarry Returns for Graduation Keynote

The Class of 2016—and all those in attendance for the awarding of diplomas—were treated to an engaging keynote address by Pitt med alumnus Ryan McGarry, MD, emergency medicine physician at NewYork-Presbyterian Hospital and a clinical instructor in emergency medicine at Weill Medical College of Cornell University.

McGarry has had a lifelong interest in filmmaking, which he explored while a med student at Pitt. During his emergency medicine clerkship at Los Angeles County General Hospital, he began filming the daily events in the hospital’s emergency department. This project eventually became the riveting and poignant documentary film Code Black, which received critical acclaim and was named Best Documentary at the 2013 Los Angeles Film Festival.

It captured the interest of CBS, too, and the television network premiered the scripted series Code Black on its Wednesday-night lineup in September 2015, with McGarry as an executive producer. After a very successful first season, Code Black was renewed for a second season with CBS, beginning in fall 2016.

While in Pittsburgh for the Class of 2016’s graduation ceremony, McGarry took in the full Pittsburgh nostalgia experience, including a visit to Primanti’s for a sandwich with the works. He also delivered a special presentation, “Code Black and the Television Doctor Paradox: Popular and Powerless in the 21st Century,” sponsored by Pitt’s Center for Research on Media, Technology, and Health.

Med Student is One of Forbes Top 30 under 30

After a baseball injury during high school, Christopher Murawski showed such interest in the treatment plan for his damaged ankle ligament that he was invited to shadow his orthopaedic surgeon on rounds—once his ankle was healed. Murawski studied neuroscience as a Pitt undergrad, but he never strayed far from his interest in orthopaedics. In fact, his keen interest led to an invitation to work in the lab of Freddie Fu, MD, Distinguished Service Professor, David Silver Professor and chair of the Department of Orthopaedic Surgery. Murawski helped Fu’s team with sophisticated anatomical explorations of normal and damaged anterior cruciate ligaments, and he evaluated the effectiveness of different types of surgical reconstructions—all as an undergrad.

Since beginning med school in 2014, he’s continued to work on research projects through the Department of Orthopaedic Surgery. The third-year medical student’s research portfolio has grown to more than 55 peer-reviewed publications, and he’s participated in more than 60 conference presentations.

In January 2016, Murawski was named one of Forbes magazine’s Top 30 under 30 in health care. The magazine describes this group as “the brightest young entrepreneurs, breakout talents, and change agents” worldwide.
We aim to bring about transformational changes in American medicine by exploring the most fundamental and important areas in biological science and clinical care.

Linked Genes Provide Novel Insight on Disease
PITT-DEVELOPED WEBSITE PROVES BOON TO EVOLUTIONARY BIOLOGY RESEARCHERS

DNA travels its own peculiar path over time to ensure that we come out on the right side of the “adapt or die” equation. And at the genetic level, we share the dance floor with creatures great and small whose response to evolutionary pressures can bring new clarity to the cellular functions, proteins, and other regulatory molecules linked with human disease.

Developed by Nathan Clark, PhD, assistant professor of computational and systems biology, and colleagues, this bioinformatics approach—known as evolutionary rate covariation (ERC)—correlates branch-specific evolutionary rates of a chosen pair of genes. The fundamental concept behind ERC is that functionally related genes should respond similarly to evolutionary pressures and, therefore, be easier to track and characterize.

By parsing such genetic “guilt by association” in Drosophila and other species, Clark and colleagues have been able to identify new protein networks that influence reproduction (PLOS Genetics, 2014), amino acid transporters that affect signal transmission in the glutamatergic neuromuscular junction (Nature Scientific Reports, 2016), and key evolutionary signatures among a variety of disease genes that could help to untangle previously unknown relationships between clinically distinct disease processes (PLOS Genetics, 2015).

Over the past year, the Clark team has built a publicly accessible Internet portal to assist researchers at Pitt and elsewhere with ERC-based investigations.

“Imagine you’re a kidney disease researcher interested in sodium permeability on the cell surface. Take a gene that you know influences that pathway, put it into the portal, and it will serve you up genes that are highly correlated with your gene,” says Clark. “We’ve shown now through a number of published studies that this works.”

Portal structure is described in the August 2015 issue of the journal Bioinformatics. It contains data on three taxonomic groups—33 mammal species, 12 Drosophila species, and 18 kinds of yeasts. Website analyses are designed to provide statistically supported results that are easy to interpret, he says, adding that as of the 12 months ending in July 2016, more than 3,000 unique users representing “all inhabited continents” had used the portal.

Clark’s lab recently used a modified ERC method to correlate evolutionary patterns of genes with environmental influences in marine mammals compared to their terrestrial compatriots. These analyses traced molecular-level contributions to morphological and physiological adaptations necessary to support species transition from landlubber to sea dweller.

Published in the July 2016 issue of Molecular Biology and Evolution, the Clark team reported on accelerated changes in genes affecting muscle formation, lipid metabolism, sensory systems, skin, lung, and connective tissue—broadly recognized functional adaptations for which underlying mechanisms are not well understood.

“We’re advancing this work now to look at subterranean mammals and the changes going on in these animals that are essentially blind,” Clark says of an ongoing collaboration with Kanwal Nischal, MD, professor of ophthalmology and chief of the Division of Pediatric Ophthalmology, Children’s Hospital of Pittsburgh of UPMC. “We’re looking to see what new eye genes we might uncover.”

Visit the ERC website: csb.pitt.edu/erc_analysis/index.php.

A kidney disease researcher interested in sodium permeability on the cell surface can select a gene known to influence that pathway, put it into the portal, and receive a list of other, highly correlated genes, including some surprises.
Rooky S. Tuan, PhD, Arthur J. Rooney Sr. Professor of Sports Medicine and Distinguished Professor of Orthopaedic Surgery, has received a $500,000 grant from the Center for the Advancement of Science in Space (CASIS) to support experiments on a 3D microphysiological system (MPS) that will be implemented on board the International Space Station (ISS) to evaluate the accelerated aging and degeneration processes of bones that occurs under microgravity conditions during space travel.

The award, announced at the White House Organ Summit in June 2016, is part of the 3D Microphysiological Systems for Organs-on-Chips Grand Challenge by CASIS, which was chosen by the U.S. National Aeronautics and Space Administration (NASA) to manage the ISS U.S. National Laboratory in 2011.

“Studying such rapid progression of the disease offers great advantages to developing treatments for osteoporosis faster and more effectively, in ways that are not possible on Earth,” said Tuan. “Our research will benefit not only the health of astronauts who may face long stays in space on the ISS or a future journey to Mars but also will help people on Earth, providing capabilities for the screening of drug therapies, enhancing personalized medicine, and developing bioreactor technologies for tissue engineering.”

Tuan is internationally known for his research in stem cell biology, musculoskeletal tissue engineering, and regenerative medicine and for innovative leadership in biomedical education. He is also associate director of the joint Pitt/UPMC McGowan Institute for Regenerative Medicine, director of the Center for Military Medicine Research, and director of the Center for Cellular and Molecular Engineering.

Under Tuan, Pitt’s Center for Cellular and Molecular Engineering focuses on the science of treating injuries and diseases of the musculoskeletal system, using stem cells and biomaterials in combination with bioreactor and biofabrication technologies, including 3-dimensional printing, for functional skeletal tissue engineering and regeneration.

The MPS project has also been partially funded by the Ri.MED Foundation, a collaborative effort of Italy’s government, the University of Pittsburgh, and UPMC. The foundation, based in Palermo, Italy, promotes, supports, and leads biomedical and biotechnological research projects, with an emphasis on the translation of innovative results into clinical practice.
NEW METHODS TO TRACK PLACENTAL HEALTH

The trophoblast—the outermost layer of the placenta—regulates maternal-fetal gas exchange, nutrient delivery, waste removal, immunological defense, and production of hormones. Recently, scientists discovered that this layer also secretes tiny, bubble-like vesicles containing RNA into the mother’s bloodstream. By analyzing this RNA, researchers hope to better monitor placental health. A team including Pitt and Magee-Womens Research Institute (MWRI) researchers are collaborating with researchers at Carnegie Mellon University, Penn State University, and Massachusetts Institute of Technology in developing “acoustic tweezers” that use sound waves to separate placental vesicles based on their size and other properties. The research project is one of the 19 selected by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, that comprise the five-year Human Placenta Project. For the fiscal year, NICHD committed approximately $46 million to the effort, with Pitt receiving more than $3.5 million. Placental function is key to fetal development and maintaining the health of the mother and baby. Monitoring for signs of dysfunction can indicate common pregnancy complications, said principal investigator Yoel Sadovsky, MD, Distinguished Professor of Obstetrics, Gynecology, and Reproductive Sciences, Elsie Hilliard Hillman Professor of Women’s and Infants’ Health Research, and MWRI director. “A fundamental challenge in perinatal medicine arises from our limited ability to diagnose placental disorders in real time throughout the pregnancy.” Researchers hope the new technique will help track placental health in real time and shed more light on placental function and its effect on mothers’ and babies’ health.

UPCI’S COMPREHENSIVE CANCER CENTER DESIGNATION RENEWED

The National Cancer Institute (NCI) renewed the University of Pittsburgh Cancer Institute’s (UPCI) accreditation as a Comprehensive Cancer Center and one of just 45 NCI-designated Comprehensive Cancer Centers in the United States. The renewal comes with a Cancer Center Support Grant Parent Award totaling $25.6 million. “The award recognizes our strength in basic, clinical, and population research; education; and community outreach and reflects the dedication of everyone here who is working toward a future without cancer,” said Nancy E. Davidson, MD, Distinguished Professor of Medicine, Hillman Professor of Oncology, professor of pharmacology and chemical biology and of clinical and translational science, and UPCI director. In 2015, UPCI received $68 million in funding from NCI to support cancer research. Since the last renewal, UPCI program members, including the 337 Pitt faculty members, have collectively published more than 6,000 articles in peer-reviewed journals. UPCI was established in 1985, received NCI-designated Comprehensive Cancer Center status in 1990, and has retained it since.

Grants of Note

RESEARCHERS AT PITTSBURGH SCHOOL OF MEDICINE

Researchers at Pitt’s Center for Vaccine Research (CVR) received nearly $4 million through five federal grants to study a variety of mosquito-borne viruses and further develop vaccines to fight their associated diseases. The research will be conducted in Pitt’s Regional Biocontainment Laboratory, a high-security facility that can safely contain and handle dangerous pathogens. Incidence of the related diseases remains small, yet they’re a significant threat, said William B. Klimstra, PhD, associate professor of microbiology and molecular genetics at the CVR. “While the number of people who get these diseases is relatively small, the severity of disease and their potential emergence in larger populations or for use as bioweapons drive the necessity for development of countermeasures,” he said. Klimstra is principal investigator on two National Institutes of Health grants to research eastern equine encephalitis virus (EEEV), a rare but deadly disease of the Atlantic and Gulf states. He is also principal investigator on a $1.2 million U.S. Department of Defense (DOD) grant to develop a novel, inactivated vaccine to counter three strains of alphavirus, which comprise about 30 different mosquito-transmitted viruses. Klimstra will work with investigators at Washington University in St. Louis and Oregon Health and Science University. An additional grant from the DOD is being used to investigate how mosquito-borne viruses gain entry into the brain, while another was used to explore harnessing anti-EEEV antibodies from cows that have been genetically altered to produce human antibodies.

CENTER FOR VACCINE RESEARCH RECEIVES FEDERAL GRANTS FOR MOSQUITO-BORNE VIRUSES RESEARCH

Researchers at Pitt’s Center for Vaccine Research (CVR) received nearly $4 million through five federal grants to study a variety of mosquito-borne viruses and further develop vaccines to fight their associated diseases. The research will be conducted in Pitt’s Regional Biocontainment Laboratory, a high-security facility that can safely contain and handle dangerous pathogens. Incidence of the related diseases remains small, yet they’re a significant threat, said William B. Klimstra, PhD, associate professor of microbiology and molecular genetics at the CVR. “While the number of people who get these
PITT INFECTION DISEASE RESEARCHERS HELP GUIDE HIV DRUG ROLLOUT IN AFRICA

Around 25 million people in sub-Saharan Africa have HIV, representing nearly 70 percent of the global total. As part of a plan for a large-scale rollout of drugs and microbicides in that region to prevent HIV infection, Pitt infectious disease researchers have been tasked with monitoring for drug resistance. With a $5 million agreement from the U.S. Agency for International Development, researchers from the Department of Medicine’s Division of Infectious Diseases—including project director John W. Mellors, MD, Global Elimination of HIV and AIDS Professor, professor of medicine and of pathology, chief of the Division of Infectious Diseases, School of Medicine; professor of infectious diseases and microbiology, Graduate School of Public Health; and Urvi M. Parikh, PhD, assistant professor of medicine—will conduct research to develop evidence-based policies for monitoring drug resistance during HIV-drug distribution. Pre-exposure prophylaxis (PrEP) and antiretroviral (ARV)-based microbicides will be provided via daily pills or a monthly vaginal ring that releases medication. Should someone become infected with HIV while on PrEP or an ARV-based microbicidal, a drug-resistant strain could arise and spread. The project will assess the frequency of drug resistance and develop strategies to reduce it. The researchers are also developing models and simulations to analyze the costs, frequency, and effectiveness of regular HIV testing for populations at risk. They will later advise the World Health Organization and the Joint United Nations Programme on HIV/AIDS on PrEP and microbicide prevention initiatives.

SPORE GRANT RENEWAL EXPANDS HEAD AND NECK CANCER RESEARCH

Incidence of differentiated thyroid cancer is rising at a faster rate than all cancers in the United States and worldwide. With a $10.9 million grant renewal from the National Cancer Institute’s Specialized Program of Research Excellence (SPORE), Pitt researchers will continue to explore differentiated thyroid cancer and other head and neck cancers. The thyroid cancer project will use next-generation sequencing to reduce unnecessary surgeries for less aggressive tumors while helping identify patients with more aggressive disease. Three of the four projects outlined by this SPORE grant focus on head and neck squamous cell carcinoma, an often deadly cancer with few drug therapies. The award is one of four SPORE grants active at Pitt. The others support melanoma, lung, and ovarian cancer research.

GRANT SUPPORTS DEVELOPMENT OF DRUGS TO COUNTERACT RADIATION EXPOSURE

Pitt’s multidisciplinary Center for Medical Countermeasures against Radiation has previously developed and patented two drugs to mitigate the effects of radiation on the body. Now, researchers are working to develop new drugs and are exploring methods to administer drugs individually or in combination using microneedle arrays. These new efforts are propelled by a five-year $18.7 million grant from the National Institute of Allergy and Infectious Diseases (NIAID) to the School of Medicine, the University of Pittsburgh Cancer Institute, and Pitt’s Graduate School of Public Health to develop drugs that can protect against radiation from deliberate attacks or accidental exposure. It marks the third renewal of the grant for Joel S. Greenberger, MD, Claude Worthington Benedum Foundation Professor and chair of the Department of Radiation Oncology. “Patients suffering from radiation damage may be too sick to take an oral therapy, and delivering drugs intravenously would be too impractical and costly. We need a safe and effective way to make sure these drugs are given appropriately,” Greenberger said. The researchers are also investigating molecular mechanisms behind radiation disease. In addition to emergency preparedness, such drugs might be used to lessen side effects of radiation therapy for head and neck cancer patients.

LONG-TERM STUDY TO TRACE IMPACT OF SUBSTANCE USE ON BRAIN DEVELOPMENT

Pitt Department of Psychiatry investigators are joining the multi-site Adolescent Brain Cognitive Development (ABCD) Study that plans to follow more than 10,000 9- and 10-year-old children for 10 years to study the developing brain—from early years, through adolescence, and into young adulthood—and how it’s affected by marijuana, alcohol, and other drugs. Due to inconsistent findings in smaller studies, the NIH provided $30 million per year for the ABCD Study to comprehensively investigate brain changes, said Duncan B. Clark, MD, PhD, professor of psychiatry, School of Medicine, and leader of the local research site, where more than 500 Pittsburgh children are expected to participate. The funding will support 19 research sites across the United States, with Pitt receiving $5 million total, and the study will address the effects of regular versus occasional substance use on brain development; substance use and mental illness, physical health, development, and academic achievement; and factors that influence substance use. The Pitt team also includes David A. Lewis, MD, Thomas Detre Professor of Academic Psychiatry and chair of psychiatry, School of Medicine, and professor of neuroscience, Dietrich School of Arts and Sciences; Rolf Loeb, PhD, Distinguished Emeritus Professor of Psychiatry, School of Medicine; and Beatriz Luna, PhD, Staunton Professor of Pediatrics and Psychiatry, School of Medicine, and professor of psychology, Dietrich School of Arts and Sciences. “This will be the first research project to study such a large group of individuals from early in development, when most would not have used drugs, to possibly peak use in adolescence and to explore different pathways that contribute to decreases in substance use with maturation,” Luna said.

RESEARCH ON HIV AND ACCELERATED AGING HIGHLIGHTED BY TWO GRANTS

People with HIV can live for decades thanks to medication, yet they’re more likely to have cardiovascular, lung, kidney, and liver diseases, osteoporosis, and other conditions compared to healthy peers; their bodies often resemble someone years or even decades older. A $3 million grant from the National Heart, Lung, and Blood Institute will permit investigators at Pitt’s Center for Vaccine Research to study the accelerated-aging characteristics and processes linked to HIV infection. Ivona Pandrea, MD, PhD, professor of pathology, School of Medicine, and of infectious diseases and microbiology, Graduate School of Public Health, and grant principal investigator, and colleagues will research the relationship between excessive blood clotting—which is common and often deadly for HIV patients—and accelerated aging. Cristian Apetrei, MD, PhD, professor of microbiology and molecular genetics, School of Medicine, and of infectious diseases and microbiology, Graduate School of Public Health, is principal investigator on another $3.3 million National Institute of Allergy and Infectious Diseases grant to explore activating cellular reservoirs for HIV in the body. Reactivating the virus could reduce the size of the reservoir and lead to virus eradication from the infected individuals.
**Pitt-Developed Test Has Potential To Diagnose Myriad Conditions with Drop of Blood**

A unique way of detecting antibodies in blood introduces the possibility of new diagnostic test development for autoimmune diseases, cancers, and other conditions for which causes are elusive, according to University of Pittsburgh research.

As reported in the August 2016 edition of the *Journal of Immunological Methods*, the proof-of-principle study demonstrates the first evidence on which to base development of a potential blood test for any infectious disease by screening random libraries of non-biological molecular shapes.

“The method does not rely on starting with known viral components,” said senior author Donald S. Burke, MD, Graduate School of Public Health dean and Distinguished University Professor of Health Science and Policy. “This is important because there are conditions for which there isn’t a known antigen, such as newly emerged epidemics, autoimmune diseases, or even responses to traumatic injury.”

When confronting antigens caused by infectious disease or injury, the immune system produces antibodies which, like puzzle pieces, can fit themselves to molecules on the invader or damaged tissue by shape.

Pitt researchers used a technique pioneered by coauthor Thomas Kodadek, PhD, of the Scripps Research Institute, that can synthesize differing molecular shapes (called “peptoids”) that are then attached to microscopic plastic beads. These peptoids are not organic, but if they match to the corresponding shape on an antibody, that antibody will connect to them, allowing the scientist to pull out each bead and examine the peptoids and their corresponding antibodies.

Burke’s team chemically generated a huge library of random molecular shapes. Researchers then used blood from HIV-infected and uninfected people to screen 1 million candidate shapes to identify those binding to antibodies present in the blood of HIV-infected patients but not the healthy controls. Despite the fact that no HIV proteins or structures were used to construct or select the peptoids, the approach successfully detected the best molecular shapes to use in screening for HIV antibodies.

The team subsequently synthesized mass quantities of the HIV-antibody-targeting peptoid and tested it by screening hundreds of samples from the Multicenter AIDS Cohort Study (MACS), a confidential research study of the natural history of treated and untreated HIV/AIDS in men who have sex with men. Study coauthor Charles Rinaldo, PhD, chair of Pitt Public Health’s Department of Infectious Diseases and Microbiology, and director of the Pittsburgh arm of the MACS, selected the samples but blinded the testers to which samples were positive or negative for HIV. The test distinguished between the samples of HIV-positive blood and HIV-negative blood with a high degree of accuracy.

“This technology means that we may be able to take a single drop of blood from a patient and detect antibodies to all manner of infections, cancers, or other conditions to which they’ve been exposed. We hope that this is the first step toward development of an ‘Epi-chip’ that can be used to reconstruct a person’s entire exposure history,” said Burke, who is also UPMC Jonas Salk Professor of Global Health.

“We hope that this is the first step toward development of an ‘Epi-chip’ that can be used to reconstruct a person’s entire exposure history.”

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**PITT TO COORDINATE, MANAGE A NUMBER OF CLINICAL TRIALS TARGETING BREATHING DISORDERS**

The University of Pittsburgh’s School of Medicine and Graduate School of Public Health are leading a $16.8 million, five-year federal initiative to oversee national clinical trials to develop new treatments for a variety of breathing disorders. With funding from the National Heart, Lung, and Blood Institute, National Institutes of Health, researchers will conduct clinical studies on chronic lung conditions such as interstitial lung disease, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and obstructive sleep apnea. Chronic lung diseases comprise some of the most common medical conditions worldwide, and more than 15 million people in the United States alone suffer from COPD. A Network Management Core headed by Pitt will coordinate and support trials carried out by the Pulmonary Trials Cooperative, which includes lung disease researchers from across the nation.

**U.S. DEPARTMENT OF DEFENSE PROMPTS ALPHAVIRUS BIOTERRORISM COUNTERMEASURES**

The U.S. Department of Defense (DOD) has consistently funded a range of research initiatives under way at Pitt’s Center for Vaccine Research (CVR). With a recently awarded $7.6 million grant to explore countermeasures against bioterrorism attacks, CVR investigators aim to home in on developing drugs and vaccines to counter alphaviruses, which comprise about 30 mostly mosquito-transmitted viruses. The group includes eastern, western, and Venezuelan encephalitis viruses, which are rare yet highly deadly and cause natural outbreaks in the Americas. The alphaviruses’ potential use as bioweapons has prompted the researchers to better understand the biological mechanisms through which the viruses harm people upon inhalation. They’re also working to determine the best timing for providing antiviral medications and are exploring therapies that could be tested in human clinical trials, said coprincipal investigator Amy L. Hartman, PhD, assistant professor of infectious diseases and microbiology, Graduate School of Public Health, and grant principal investigator William B. Klimstra, PhD, associate professor of microbiology and molecular genetics.
When It All Goes Wrong: Surgical Rescue as a Discipline

On call one Saturday a little more than two years ago, surgeon Andrew B. Peitzman, MD, had an epiphany. Peitzman spent that whole Saturday in surgical suites at UPMC Presbyterian Hospital attending to complications of operations or procedures done previously at Presby and at facilities throughout the region. While unexpected and serious complications can arise during or after any surgery, risks are greater for patients undergoing emergency operations.

“It struck me that this was probably the most vulnerable population for whom we provide care,” says Peitzman, Mark M. Ravitch Professor of Surgery and Distinguished Professor of Surgery, School of Medicine.

Fully two-thirds of UPMC Presbyterian patients arrive as transfers from other facilities that initiated emergency or other surgical care, he explains. “What we’re doing is trying to identify who these patients are and what to do to get them out of trouble.”

In two recent publications, Peitzman describes these cases in terms of “surgical rescue,” requiring immediate intervention—and, in the majority of cases, additional surgery.

Saving these critically ill patients requires a skilled team with access to resources that include immediate availability of operating rooms, intensive care expertise, surgeons practiced in treating complicated, “reoperative” surgery, and broad surgical subspecialty support, Peitzman and colleagues write in the September 2015 Scandinavian Journal of Surgery.

“As acute-care surgeons, we’ve taken care of patients with these complications, but nobody has focused on it as a unique problem,” he says, explaining that medical or surgical complications account for more than 1 million hospitalizations a year in the United States. Although diagnoses that require surgery vary, these most fragile of patients are more likely to be older with underlying health issues.

“Almost any patient will tolerate a well-thought-out, well-done operation. What they don’t tolerate is that first complication.”

Effective surgical rescue requires vigilance for symptoms like elevated white count or generalized decline and early recognition that additional surgery is mandatory to save these patients. “There should be no delaying and hoping these issues won’t turn into a more serious problem,” he says. 
The Brain and Behavior Research Foundation provided two $100,000 National Association for Research on Schizophrenia and Depression (NARSAD) Independent Investigator Grants to Pitt Department of Psychiatry faculty members who will use the awards to further research on molecular rhythms and psychiatric disorders and on sleep disturbance in adolescents with bipolar disorder. Studies have revealed that bipolar disorder, major depression, and schizophrenia are associated with significant disruptions to circadian rhythms. Disruptions to normal circadian rhythms have also been known to trigger mood changes and psychotic episodes. Pitt researchers, led by Colleen A. McClung, PhD, associate professor of psychiatry, will explore whether such alterations are present at the molecular level in human brain regions that regulate mood and cognition. They will investigate if stabilizing rhythms can lead to therapeutic advancements. The research will also help investigators to determine the importance of molecular rhythmicity in the primary pathology of psychiatric disorders. Peter L. Franzen, PhD, assistant professor of psychiatry, will use support from the award to lead research on the neural mechanisms by which sleep disturbance influences suicide risk and treatment response to adjunctive dialeactical behavioral therapy (DBT) in youths with bipolar disorder. DBT is hypothesized to significantly improve suicidality and mood symptoms by enhancing emotion regulatory abilities; sleep disturbance is hypothesized to disrupt this activity. The research also builds on Franzen’s collaboration with Tina R. Goldstein, PhD, associate professor of psychiatry, to examine the neural circuitry underlying emotion regulation and cognitive control via functional magnetic resonance imaging (fMRI) in bipolar participants at baseline and mid-treatment.

Researchers can analyze a set of mutated genes in a cancerous tumor and use the raw data as predictors of cancer outcomes, such as recurrence and metastasis. However, with developments in data analysis based on machine learning, an alternative approach involves finding patterns in the data that represent biological processes, such as aberrant cell signaling pathways, and using those patterns to predict cancer outcomes. Moreover, the combined use of biological patterns and clinical data holds promise to further improve such predictions, which can affect clinical care. To advance this work, Big Data researchers at Pitt received a $5 million, three-year grant to develop better methods to analyze and model large amounts of cancer-patient data. Pennsylvania’s Department of Health provided this Commonwealth Universal Research Enhancement, or CURE, grant as part of the Big Data for Better Health (BD4BH) project, which also includes UPMC, Carnegie Mellon University, the Pittsburgh Supercomputing Center, and Lincoln University. While the investigators will focus on breast and lung cancers to develop analytical software and tools, their methods can apply to other diseases, said Gregory F. Cooper, MD, PhD, professor of biomedical informatics, of computational and systems biology, School of Medicine, and of clinical and translational science.

“The basic approach is to process raw molecular data, such as gene sequence and expression data, to derive highly informative biological patterns in the data that are then used along with clinical data to predict patient outcomes. We are evaluating the hypothesis that this approach will predict cancer outcomes significantly better than current methods,” Cooper said.

Adults with Down syndrome typically show symptoms of Alzheimer’s by their 40s and have a 70 to 80 percent chance of developing clinical dementia by their 60s, said Benjamin L. Handen, PhD, professor of psychiatry and coprincipal investigator on a $12.5 million, five-year grant from the National Institute on Aging, National Institutes of Health. The grant will enable Alzheimer’s disease research experts to better explore Alzheimer’s biomarkers and cognitive function in people with Down syndrome. Pitt is one of four sites in the United States and the United Kingdom taking part in the Neurodegeneration in Aging Down Syndrome study funded by the grant. The study will monitor and track amyloid in blood and cerebrospinal fluid, structural and functional MRI scans, and cognitive and functional measures in 180 individuals with Down syndrome and 40 without. Individuals with Down syndrome have three copies of chromosome 21, each of which contains a copy of the gene linked to the precursor protein for beta-amyloid, which is heavily present in the brains of Alzheimer’s patients. “It’s apparent from Down syndrome patients that amyloid deposition is not sufficient to produce dementia,” Handen said. “These individuals have these deposits for more than a decade before cognitive decline is apparent. Understanding the relationships between Down syndrome, disease biomarkers, and cognitive decline is critically important to help us design better therapies for all people with Alzheimer’s.”

During pregnancy, women normally undergo striking metabolic and cardiovascular adaptive changes that help to ensure that their babies develop and grow normally and are carried to term. Magee-Womens Research Institute (MWRI) researchers study these pregnancy changes to look for abnormalities that may signal a predisposition to later-life cardiovascular disease (CVD) in women. With a four-year $3.7 million grant from the American Heart Association, the MWRI researchers will investigate whether certain blood vessel changes that occur during pregnancy can point to mechanisms behind CVD in women. They hope to also help develop treatments for and better identify women at risk for CVD. Heart disease can damage the inner walls of blood vessels and lead to spasms and decreased blood flow to the heart muscle, which is known as microvascular dysfunction, a potentially undetected condition. “Microvascular dysfunction is a devastating public health challenge, because almost two-thirds of women who die suddenly of coronary heart disease have had no previous symptoms. We hope to build on the research of our previous studies by identifying mechanisms of CVD in women that are unmasked or perhaps affected by adverse pregnancy outcomes,” said Carl Hubel, PhD, MWRI investigator and associate professor of obstetrics, gynecology, and reproductive sciences.
I argue that intuition often forms the basis of physician decision-making—particularly in critical cases like trauma triage, sepsis, and stroke. People remember stories—if a videogame can allow us to recalibrate intuition, it can be a new tool to help people make the right decisions faster.”

Deepika Mohan, MD, MPH

NIH Director’s New Innovator Award Funds Study of Physician Decision-Making

In critical care medicine, the difference between life and death can often be measured in the treating physicians’ split-second decisions. For Deepika Mohan, MD, MPH, assistant professor of critical care medicine and of surgery, the most important question isn’t which decisions are made—but why.

“Most efforts to reduce physician error begin with the idea that decisions reflect knowledge, attitudes, and external constraints,” she says. “I argue that intuition often forms the basis of physician decision-making—particularly in critical cases like trauma triage, sepsis, and stroke.”

Mohan is studying ways to possibly improve the decision-making process with funding from a five-year, $2.3 million National Institutes of Health Director’s New Innovator Award, one of 41 awarded by NIH in 2015 to fund “unusually creative new investigators with highly innovative research ideas” early in their careers when supportive data for an R01 application may be scarce.

Her study, “A Novel Intervention To Make Heuristics a Source of Power for Physicians,” uses game technology to translate behavioral science principles about how people learn into a new method of modifying physician judgment.

A videogame, called “Night Shift,” has been developed by Pittsburgh-based Schell Games for use in a random-ized, controlled trial during a 2016 American College of Emergency Physicians conference. Players will be asked to play the game or an educational control followed by a virtual simulation, to see which intervention has an effect on choices made during the simulation.

“People remember stories,” says Mohan. “If a videogame can allow us to recalibrate intuition, it can be a new tool to help people make the right decisions faster.”
HARRINGTON SCHOLAR AWARD SUPPORTS LUNG TRANSPLANTATION RESEARCH

Every year, the Harrington Scholar-Innovator Program of the Harrington Discovery Institute selects up to 10 physician-scientists to receive Harrington Scholar-Innovator awards, which provide funding to help researchers bridge basic discoveries into clinical practice. Rama K. Mallampalli, MD, UPMC Professor of Acute Lung Injury; chief of the Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine; and professor of medicine and of cell biology, was named a 2016 Scholar-Innovator. With up to $700,000 in support, Mallampalli will continue to advance his research surrounding lung transplantation. He aims to assess the efficacy of a lead compound that inhibits a protein involved with acute cellular rejection during lung transplantation. Acute cellular rejection is strongly associated with chronic allograft rejection, which can impede long-term success after lung transplantation and lead to allograft loss and death.

RESEARCHERS TO PINPOINT HOW THE ANIMAL NOSE LOCALIZES SMELL

The animal nose and brain can detect the smell of mates and food. It enables bloodhounds to track the scent of a missing person or rats to find landmines in Angola. Yet we don’t fully understand the olfactory system, said co-principal investigator Nathan Urban, PhD, professor of neurobiology, and doing so could enable the creation of artificial chemical detection systems and a better understanding of other sensory systems.

To investigate how the animal nose can localize smells, Pitt researchers received a $6.4 million three-year National Science Foundation grant as part of a multi-institutional project to explore sense of smell. Localizing where a smell is coming from is challenging, because it requires sampling odors that waft through turbulent air a distance away from their origin. Thus, the multidisciplinary research team includes experts in mathematics, airflow physics, neuroscience, and evolutionary biology who are constructing models to quantify odors and are using algorithms to model their dispersal. The researchers believe these models could be useful for national security and law enforcement by helping to improve methods for detecting explosives and could also advance the development of technologies that inhibit the flight navigation of disease-carrying mosquitoes and crop pests.

STAND UP TO CANCER AWARDS TWO PITT INVESTIGATORS

Two Pitt investigators each received $750,000 Innovative Research Grants in April from Stand Up to Cancer, which funds scientists and clinical trials engaged with cancer research, among other initiatives. Greg M. Delgoffe, PhD, assistant professor of immunology, will continue research on immunotherapy techniques that alter the tumor microenvironment. He will explore cancer-fighting measures that employ oncolytic viruses, which are re-engineered to alter the immunosuppressive nature of the tumor microenvironment and can infect and destroy tumor cells. By improving and evaluating simultaneous use of two effective types of immunotherapies, Delgoffe and colleagues hope for a more potent immune response when testing them against melanoma in laboratory mice and, hopefully, in patients. Kara A. Bernstein, PhD, assistant professor of microbiology and molecular genetics, will further her research on double-strand break repair proteins, which are vital for fixing DNA damage and preventing cancer. Her research focuses on double-strand break repair proteins known as RAD51 paralogs and their function. She will continue to explore how mutations in the RAD51 paralogs may lead to cancer development and assess new methods for treating patients harboring RAD51 paralog mutant tumors.

3D BIOPRINTED BREAST DUCT MODEL AIMS TO LIMIT OVERTREATMENT OF NONINVASIVE BREAST CANCER

Improvements in mammography screening have resulted in better detection of invasive breast cancer but have also meant increased detection of noninvasive breast cancer, such as ductal carcinoma in situ, or DCIS, the earliest form of breast cancer, in which the cancer is still contained in the milk duct. With a two-year, $800,000 grant from the U.S. Congressionally Directed Medical Research Program of the Department of Defense, University of Pittsburgh Cancer Institute researchers and Carnegie Mellon University biomedical engineers are creating a 3D bioprinted breast ductal structure to advance identification of low-risk lesions that may not require invasive treatment. The researchers are growing DCIS cells in a printed mouse-replica breast ductal system and exploring why some DCIS cases progress to invasion while others remain static. More than 60,000 women are diagnosed with DCIS each year in the United States, and the majority of cases will not progress to invasive diseases even if left untreated. However, many such women receive unnecessary surgeries, treatments, and therapies. “Our hope is that our research will reveal novel biomarkers that will be useful for predicting which DCIS are likely to progress. We can then offer personalized therapy to those who require intervention while reducing the overtreatment of DCIS in those who don’t,” said Adrian Lee, PhD, professor of pharmacology and chemical biology, School of Medicine, and of human genetics, Graduate School of Public Health.

ST. BALDRICK’S FOUNDATION FUNDS CHILDHOOD LIVER CANCER RESEARCH

Cancer cells alter their metabolism to provide the energy and metabolic building blocks needed to support their rapid division, said Edward V. Prochownik, MD, PhD, professor of pediatrics and director of oncology research at Children’s Hospital of Pittsburgh of UPMC. By observing how these cells generate their energy, Prochownik hopes to advance new ways of mitigating tumor growth. He is the recipient of a $100,000 research grant from the St. Baldrick’s Foundation, a charity dedicated to raising money for pediatric oncology research and clinical trials. The award is one of 70 grants distributed nationally and internationally by St. Baldrick’s. Prochownik and colleagues have identified some of the key mechanisms and processes that enable cancer cells to change their metabolism. He and his research team developed a model of hepatoblastoma, the most common childhood liver cancer. They found that the mitochondria of the hepatoblastoma cells appear to be reprogrammed to operate at maximum capacity, providing significant resources for cells to rapidly grow and divide. These metabolic changes correlate with loss of expression of the mitochondrial sirtuins, SIRT3 and SIRT4. By finding ways to re-express SIRT3 and SIRT4, the researchers hope tumor growth and toxicity from currently used therapies can be suppressed.
Publications of Note

ANGEWANDTE CHEMIE
JAN 2016   VOL 55   ISSUE 1
“HOT PAPER” DESCRIBES NEW PROCESS FOR DISTANCE MEASUREMENT IN PROTEINS

The editors of the journal of the German Chemical Society, Angewandte Chemie, designate “hot papers” to highlight important findings in rapidly evolving fields of high interest. In early 2016, the journal selected a paper by Angela M. Gronenborn, PhD, Distinguished Professor of Structural Biology, UPMC Rosalind Franklin Professor and chair of the Department of Structural Biology in the School of Medicine.

Structural biology is a field at the intersection of molecular biology, biochemistry, and biophysics, where scientists like Gronenborn, who is also a professor of bioengineering, explore the molecular structure of biological macromolecules, especially proteins and nucleic acids. She and her colleagues seek to understand how these molecules acquire the structures they have and how changes in structure affect function. This information is of great importance to biologists, because proteins and nucleic acids carry out most cellular functions.

One important element of Gronenborn’s work involves obtaining precise distance measurements in proteins. In her recent publication with research associate Elena Matei, PhD, Gronenborn describes using fluorine NMR paramagnetic relaxation enhancement as a technique to extract distance information in F-labeled proteins. The researchers found that the process provides a superior alternative to more traditional methods of distance extraction since it is not hampered by background noise. Therefore, it is particularly well-suited to large proteins, protein complexes, and membrane proteins—making it a useful tool that could lead Gronenborn and her colleagues to new insights into HIV pathogenesis.

TRENDS IN BIOCHEMICAL SCIENCES
MAY 2016   VOL 41   ISSUE 5
OVERVIEW OF RETROVIRUS CAPSID RESEARCH LAYS PATH FOR CONTINUED INVESTIGATION

In retroviruses, the capsid is involved with almost all stages of the life cycle, from early stages of post-entry to maturation of the viral particle. Capsid cores self assemble and house the viral genome, as well as several proteins that drive infection. The cores protect the viral genes so that they can enter the host’s nucleus. Angela M. Gronenborn, PhD, Distinguished Professor of Structural Biology and UPMC Rosalind Franklin Professor and chair of structural biology, recently provided an overview of findings surrounding the retroviral capsid cores and how their structure and properties contribute to viral infection. Capsid cores follow defined geometric rules; and understanding their precise shape and molecular structure, particularly at assembly interfaces, opens new possibilities for drug development. Further, elucidating the interactions and relationships between structure, dynamics, and function of capsid assemblies — studies that are under way in the Pittsburgh Center for HIV Protein Interactions — requires deciphering the interfaces between subcomponents and building blocks in order to map out detailed atomic models of the core, both alone and with interacting cellular components. It is anticipated that the results of such studies will yield new understanding that may advance targeted therapies.
Imagine that moment when you take your seat on a roller coaster—the big one with the agonizingly slow climb to the top and the terrifying plunge that follows. As the seatbelt clicks into place and you grip the bar in front of you, you will experience a rush of physiological responses to this situation. Roller coaster aficionado or not, everyone has experienced the adrenaline rush that is our natural response to fear or stress. Elevated heart rate, sweating, and pupillary dilation occur when our adrenal glands, which are right above the kidneys, are triggered by sympathetic neurons in the spinal cord to secrete hormones.

Though it’s often called our “fight or flight” response, most of us in line at Kennywood will do neither. We try to breathe normally and think positive thoughts. Clearly, our individual response to stress is subject to extensive “top-down” or cognitive control. Yet scientists have never been able to point to any neural networks that would permit the “mind,” generally associated with the cerebral cortex, to influence the involuntary endocrine responses that control internal organs—until now, that is.

In a groundbreaking study published in *Proceedings of the National Academy of Sciences*, researchers from Pitt’s Brain Institute, Department of Neurobiology, Systems Neuroscience Institute, and Center for the Neural Basis of Cognition used an experimental strain of rabies virus, which infects neurons and can be used to trace neural networks, to identify the areas of the primate cerebral cortex that communicate through multi-synaptic connections with the adrenal medulla, the inner part of the adrenal gland. Led by Peter L. Strick, PhD, Thomas Detre Professor of Neuroscience, Distinguished Professor and chair of neurobiology, professor of neurological surgery and of psychiatry, the team showed that two broad networks in the cerebral cortex have access to the adrenal medulla. One is an area involved in all aspects of skeletomotor control, including the selection of a physical response to a situation, preparation to act, and movement execution. Another is involved in higher order aspects of thinking and experiencing emotion. These results indicate that specific circuits exist to link movement, cognition, and affect to the function of the adrenal medulla. This circuitry may help explain the effects of internal states like chronic stress and depression on organ function and thus provide a concrete neural substrate for unexplained phenomena such as psychosomatic illness, which scientists have long viewed with suspicion.
JAMA PEDIATRICS

NOV 2015 \ VOL 169 \ ISSUE 11

E-CIGARETTE USE IS A GATEWAY TO TRADITIONAL SMOKING AMONG YOUNG ADULTS

Compared with those who do not use e-cigarettes, young people who use e-cigarettes are significantly more likely to start smoking actual cigarettes within a year, according to a study led by the University of Pittsburgh Center for Research on Media, Technology, and Health (CRMTH) and the Dartmouth-Hitchcock Norris Cotton Cancer Center. The research team analyzed data from a national sample of about 700 nonsmoking 16- to 26-year-old e-cigarette users and nonusers. At baseline, the participants all answered with “definitely no” after being asked in a 2012 survey if they would try a cigarette offered by a friend or if they believed they would smoke a cigarette within the next year. However, in a follow-up 2013 survey, 38 percent of the e-cigarette users had started smoking traditional cigarettes compared with only 10 percent of the nonusers. “These differences remained statistically significant and robust even when we controlled for multiple known risk factors for initiating cigarette smoking, such as age, sex, race, ethnicity, socioeconomic status, sensation seeking, parental smoking, and friend smoking,” said Brian A. Primack, MD, PhD, professor of medicine and of pediatrics, director of CRMTH, and assistant vice chancellor for research on health and society, health sciences. The study was the first to examine this association in a national sample of young people and to include people older than 18. The researchers plan to continue monitoring usage of e-cigarettes and cigarettes so that policymakers can create research-based regulations to mitigate e-cigarettes’ gateway potential.

MOLECULAR PHARMACOLOGY

JUN 2016 \ VOL 89 \ ISSUE 6

NEWLY DEVELOPED COMPOUND COULD SPELL BETTER TREATMENT FOR EPILEPSY, TINNITUS

Retigabine, a drug that has been used to treat epilepsy, can lead to side effects like retinal abnormalities, urinary retention, and skin discoloration. In response, Pitt researchers have redesigned retigabine to effectively treat epilepsy and deliver fewer potential side effects. The drug might also treat tinnitus and other disorders associated with erratic and volatile neural signaling, which characterizes epilepsy. Epilepsy drugs typically operate by influencing the transport of sodium, potassium, and chloride ions across the nerve cell membrane to reduce brain cell excitability. “We have been able to refine an existing medication so that it acts selectively on certain nerve cell membrane transport channels, which should make it more effective,” said Thanos Tzounopoulos, PhD, Professor of Auditory Physiology and associate professor of otolaryngology. Retigabine activates four out of the five types of potassium channels in the KCNQ category. However, only two of the channels, KCNQ2/3, are critical for stabilizing the membranes of brain cells involved in hyperexcitability-related disorders, such as epilepsy and tinnitus, Tzounopoulos said. The newly developed compound, RL648_81 (RL-81), targets only those two channels. Researchers found that RL-81 is 15 times more potent than retigabine and should have fewer side effects. The compound might help reduce tinnitus by preventing hyperexcitation of nerve cells in auditory pathways, Tzounopoulos said.

NATURE COMMUNICATIONS

JUL 2015

STUDY EXAMINES PROTEIN IN YEAST TO ELUCIDATE DNA REPAIR PROCESSES SURROUNDING CANCER

Protein mutations in the RAD51 paralogues are associated with breast and ovarian tumors, according to Kara A. Bernstein, PhD, assistant professor of microbiology and molecular genetics. Bernstein was senior investigator on a study exploring how RAD51 paralogs function with other proteins to repair breaks in the DNA strands. RAD51 paralogs were too complex to study in animal cells, so Bernstein and colleagues studied them in yeast. By studying the yeast Shu complex, which contains RAD51 paralogs, the researchers uncovered their function during repair of DNA strand breaks. The RAD51 paralogs work with the Shu complex to find homologous DNA regions in which both strands of the twisting DNA ladder are broken due to toxins, radiation, or other influences, which can result in missing chunks of genetic code. The proteins work together to repair the damage and fill in the pieces of missing genetic code through a process called homologous recombination. “Now that we understand what the proteins do, we can now design tailored therapies for patients who have cancer and mutations in these repair genes,” said Bernstein.
Chronic arsenic exposure can cause stem cell dysfunction, leading to impaired muscle healing and regeneration. Pitt researchers found. More than 4 million Americans chronically ingest arsenic in their drinking water, as arsenic is one of the most abundant metals in the earth’s crust. “Whereas previous research has examined the impact of arsenic and other environmental contaminants on stem cell function critical for fetal and child development, there is very little information about how such exposures may affect stem cells and their function in adulthood,” said senior investigator Fabrisia Ambrosio, PhD, MPT, associate professor of physical medicine and rehabilitation. In the study, mice drank water containing 10 times the federally safe arsenic level for humans, concentrations commonly encountered by more than 140 million individuals worldwide. After five weeks of exposure, mice were subjected to muscle injury. Compared to mice given clean drinking water, the exposed mice had significantly decreased ability to regenerate and recover strength after injury. Arsenic-exposed mice also showed structural deficits throughout their muscle tissue’s extracellular matrix. Researchers learned that arsenic caused heightened biochemical signals from protein complex NF-kB, which relates to matrix remodeling and tissue repair. They also revealed that, after blocking activation of NF-kB, the exposed mice recovered normally. The researchers believe it could be important to pay greater attention to environmental factors when assessing tissue recovery and hope to explore the possibility of reversing the impact of chronic arsenic exposure in humans.
Infections have been linked to causing inflammatory disorders, yet researchers have not been able to clearly identify the mechanistic associations between defined infectious agents and the onset of chronic disease. It’s a compelling question, given the prevalence of inflammatory disorders like inflammatory bowel disease, psoriasis, asthma, and others affecting barrier tissue. Timothy W. Hand, PhD, assistant professor of pediatrics and of immunology, and investigators from other institutions explored how a single acute infection can have dramatic and longstanding consequences for tissue-specific immunity. The research team exposed mice to a bacterium, Yersinia pseudotuberculosis, which causes gastrointestinal infection. After the pathogen had been cleared, “immunological scarring” remained: Microbiota-dependent inflammation in fat tissue, coupled with damage to the lymphatic system, disrupted communication between the immune system and the tissue. Homeostasis was compromised long-term, and the microbiota also perpetuated immune dysfunction post-infection. The researchers believe the study could provide a framework to understand how previous infections can induce breakdown of tissue immune homeostasis and contribute to disease and chronic inflammation later in life.

Even the simplest body movements are generated by complex patterns of muscle activity. A team of University of Pittsburgh Brain Institute (UPBI) researchers, including Peter L. Strick, PhD, Thomas Detre Professor of Neuroscience, Distinguished Professor and chair of neurobiology, professor of neurological surgery, and scientific director of UPBI, explored how the central nervous system creates these patterns of motor output. They recorded neuronal activity in the primary motor cortex as a monkey made 24 different movements. They studied the activity of a special set of cortical neurons that have direct connections with motoneurons that control muscles. These neurons are termed corticomotoneuronal (CM) cells. Strick and his colleagues found that CM cells are “functionally tuned.” Some CM cells are active when the muscle they control functions as an agonist (generated force), whereas other CM cells are active when the same muscle functions as an antagonist (braked movement). Different populations of CM cells govern the separate functional uses of a muscle. These results, and the concept of functional tuning, provide new insight into how the primary motor cortex generates the patterns of muscle activity that are so critical for dexterous movement.
The placenta anchors the developing fetus in the uterus, nourishes it, and provides a barrier against infectious agents from the mother—yet it is one of the least well-understood human organs. Researchers at Pitt and Magee-Womens Research Institute (MWRI) constructed a cell-based model of the human placenta to investigate how pathogens that cause birth defects cross from mother to fetus. While researchers have studied placental cell lines and human trophoblasts isolated from full-term placentas, they sought to overcome some shortcomings of these placental models by culturing a human placental trophoblast cell line in a microgravity bioreactor system to construct a new type of model. The trophoblasts were spun in a vessel to reproduce shear stress and rotational forces that better replicate the maternal-fetal microenvironment. The resulting cells fused to form syncytiotrophoblasts, which resemble the outermost layer of cells of the villous structure of human placenta. The researchers then exposed the model to a virus and to three different strains of Toxoplasma gondii, a parasite found in cat feces that can cause fetal infection resulting in miscarriage or congenital disease or disability. The three-dimensional model successfully replicated the barrier properties of the actual placenta and resisted infection, revealing its ability to further test various infectious agents like Zika virus to see if, and how, they can penetrate the placenta. “With our new model in the research toolkit, we and other scientists hope to advance our knowledge of the placenta, examine its function, and learn how it can prevent most, but not all, maternal infections from causing problems for the baby,” said corresponding author Carolyn Coyne, PhD, associate professor of microbiology and molecular genetics and of obstetrics, gynecology, and reproductive sciences. Contributors included Yoel Sadovsky, MD, Distinguished Professor of Obstetrics, Gynecology, and Reproductive Sciences, Elsie Hilliard Hillman Professor of Women’s and Infants’ Health Research, and MWRI director.
AGE-RELATED COGNITIVE DECLINE COULD BE INFLUENCED BY CHRONIC VIRAL INFECTIONS

Certain chronic viral infections may add to cognitive deterioration in otherwise healthy older adults, researchers at Pitt and Johns Hopkins University found. Previous studies have suggested a link between decreased cognitive function and exposure to cytomegalovirus, herpes simplex viruses 1 and 2, or the protozoan Toxoplasma gondii. However, these studies have assessed people at a single point in time, whereas the Pitt study examined blood samples from more than 1,000 participants age 65 and older who were annually evaluated for five years during a previous study on cognitive change. “Our study is one of the few to assess viral exposure and cognitive functioning measures over a period of time in a group of older adults,” said lead investigator Vishwajit Nimgaonkar, MD, PhD, professor of psychiatry, School of Medicine, and of human genetics, Graduate School of Public Health. “It’s possible that these viruses, which can linger in the body one’s entire life after infection, are triggering some neurotoxic effects.”

The researchers saw that the viral infections influenced different aspects of cognitive deterioration often seen as age-related decline, and they are working to determine whether certain people could be predisposed to greater decline based on more fine-grained analyses of viral infections.

SYMPTOMS OF DEPRESSION COULD SIGNIFY GREATER LIKELIHOOD OF POSTSURGICAL COMPLICATIONS, HOSPITAL READMISSION

Patients reporting significant symptoms of depression before certain complex cancer operations could be at increased risk for postoperative complications and unplanned hospital readmissions, University of Pittsburgh Cancer Institute (UPCI) researchers found. Their study looked at patients planning to receive hyperthermic intraperitoneal chemotherapy with cytoreductive surgery (HiPEC+CS), a complex procedure to remove abdominal tumors. Researchers evaluated 98 patients for depressive symptoms prior to HiPEC+CS and found that 28 percent exhibited clinically significant symptoms of depression. Within 30 days of leaving the hospital after surgery, 22 percent of these patients were readmitted to the hospital, and 31 percent experienced a complication such as infection. The researchers statistically adjusted for effects of demographic and disease-specific risk factors to conclude that patients with significant depressive symptoms were more than five times more likely than non-depressed patients to have a complication or hospital readmission within 30 days of discharge. “Postoperative complications and readmissions can be very stressful for cancer patients and their families, not to mention very costly,” said lead author Carissa Low, PhD, assistant professor of medicine and of psychology with UPCI’s Biobehavioral Oncology Program. “We don’t yet know the mechanisms responsible for these effects. In addition to psychological sources of depressive symptoms, there is evidence that the cancer itself may release factors that trigger some types of depressive symptoms, such as fatigue.”
More and more studies indicate that physical activity can help protect the brain from cognitive decline. Yet people tend to be more sedentary in old age, when the risk for developing Alzheimer’s disease and other dementias increases, said James T. Becker, PhD, professor of psychiatry and of neurology, School of Medicine, and of psychology, Dietrich School of Arts and Sciences, and investigator on a Pitt and University of California, Los Angeles, study that looked at physical activity and Alzheimer’s disease. The researchers found that physically active older persons have larger gray matter volume in areas of the brain associated with memory and cognition. They also found that people with Alzheimer’s disease or mild cognitive impairment who demonstrated high levels of exercise-associated calorie burn showed less gray matter volume reduction over time. The research team examined data collected over five years from 876 people age 65 and older who received brain scans and periodic cognitive assessments. Participants also shared how often they walked, played tennis, golfed, danced, or engaged in other physical activities to assess their caloric expenditure per week. Using mathematical modeling, the researchers determined that participants who burned the most calories had larger gray matter volumes in the frontal, temporal, and parietal lobes of the brain, which are connected with memory, learning, and performance of complex cognitive tasks. Participants at the Pitt site with the highest energy expenditure showed larger gray matter volumes on initial brain scans, and larger volumes in these regions significantly reduced the likelihood of developing Alzheimer’s disease five years later. “Our current treatments for dementia are limited in their effectiveness, so developing approaches to prevent or slow these disorders is crucial,” said Becker.
COMMON UTERINE TUMORS RESULT FROM MUTATION AND GENOMIC INSTABILITY

Uterine leiomyomas are benign tumors arising from smooth muscle cells of the uterus. They are clinically diagnosed in 25 percent of women of reproductive age and can cause bleeding, pain, and, in some women, infertility and miscarriages. They’re also the single largest cause of hysterectomy. Genomic sequencing showed that nucleotide variants in a gene called MED12 are associated with uterine leiomyomas, but their genetic influence and role in genomic instability are not well-understood. Researchers from Pitt’s School of Medicine and Magee-Womens Research Institute, including Aleksandar Rajkovic, MD, PhD, Marcus Allen Hogge Professor of Reproductive Genetics, Department of Obstetrics, Gynecology, and Reproductive Sciences, created a mouse model that expressed the most common MED12 variant and showed that it stimulated uterine leiomyoma formation in both regular mice and in those harboring a uterine mesenchymal cell-specific MED12 deletion. Compared with regular mice, expression of the gene variant in MED12 knockout mice resulted in earlier onset and larger leiomyoma lesions. The study concluded that this common human leiomyoma-associated MED12 gene variant can cause leiomyomas and genomic instability in mice, which is often observed in human leiomyomas.

PHYSICS PRINCIPLE FURTHER EXPLAINS THE WORKINGS OF OUR SENSE OF SMELL

Researchers from Pitt and other institutions have found that the mechanism underlying our sense of smell follows a simple physics principle known as cooperativity. After odor molecules bind to specialized receptors located on millions of olfactory neurons, the receptors send signals from the neurons to the brain, where the scent is interpreted. While individual neurons have only one type of receptor, hundreds of different types of olfactory receptors are found, or expressed, in approximately equal numbers across the entire population of neurons, said senior investigator Jianhua Xing, PhD, associate professor of computational and systems biology. This diversity permits detection of a wide variety of smells. “Neuroscientists have been trying to uncover how nature accomplishes these two goals: selecting one, and only one, type of olfactory receptor for each neuron, while at the same time ensuring that all receptor types are represented in the whole population of neurons,” Xing said. The researchers used existing experimental data to create a computational model to show how olfactory receptor expression can be uniform across a single neuron yet diverse across the full population of neurons. They confirmed their model’s accuracy by correctly predicting findings from other research groups. The model exhibited a three-pronged regulation of olfactory receptor gene expression that conforms to the physics principle called cooperativity, which describes how elements of a system influence the behavior of each other rather than operate independently.
Two years ago, the leading professional societies for critical care medicine appointed 19 critical care, surgical, infectious disease, and other doctors to revise the definitions of sepsis and septic shock to reflect advancements made in the pathophysiology, management, and epidemiology of sepsis. The new definition and updated treatment information were published through a series of *Journal of the American Medical Association* articles. The task force, which included Derek Angus, MD, MPH, Distinguished Professor and Mitchell P. Fink Professor and chair of critical care medicine, and Christopher W. Seymour, MD, MSc, assistant professor of critical care medicine and of emergency medicine, describes sepsis as a syndrome rather than a disease and calls for attention to early-stage sepsis symptoms like altered mental status, low blood pressure, and fast respiratory rate. Sepsis occurs when the body damages its tissues and organs in response to an infection, even a minor one. It is the number-one killer of hospital patients, yet does not exhibit identifiable biomarkers. The refined definition describes sepsis as a life-threatening organ dysfunction due to dysregulated immune system response to infection. Septic shock is now described as a subset of sepsis characterized by substantial and more deadly circulatory, cellular, and metabolic abnormalities.

Atrial fibrillation (AF) is the most common heart rhythm problem in the United States, affecting around 1 percent of the adult population and more than 5 percent of those 65 and older. AF is strongly associated with higher risk of stroke, heart failure, and mortality. According to research from Pitt’s School of Medicine, blacks with AF have nearly double the risk of stroke, heart failure, coronary heart disease, and mortality compared to their white counterparts. Researchers analyzed data from the Atherosclerosis Risk in Communities (ARIC) Study, which recruited more than 15,000 men and women from four states to investigate causes and track atherosclerosis and cardiovascular disease for more than 20 years. “We knew blacks were likely to have an increased risk of stroke, but the findings for heart failure, coronary heart disease (CHD), and mortality are novel and important,” said lead researcher Jared W. Magnani, MD, MSc, visiting associate professor of medicine. At the 20-year follow-up, incidence of stroke in black participants who developed AF was 21.4 per 1,000 person-years compared to 10.2 in whites. Rates of heart failure, CHD, and mortality were nearly double in blacks compared to whites. The researchers noted limitations to generalizability that included the geographic and biracial composition of the study.
About 1 million Americans are affected by Parkinson’s disease (PD), characterized by tremors, slowness, balance difficulties, and abnormal gait. To slow or halt the disease, researchers need to understand what causes the degeneration and loss of neurons in the brain that govern movement and coordination. The protein alpha-synuclein is a key component of Lewy bodies—the pathological hallmark of Parkinson’s—and Pitt researchers recently discovered that the protein disrupts mitochondrial activity, triggering toxicity. Lead investigator J. Timothy Greenamyre, MD, PhD, Love Family Professor of Neurology and professor of clinical and translational science, and colleagues used well-established rodent models to show that the alpha-synuclein protein attaches to a mitochondrial protein called TOM20 and prevents the mitochondria from properly functioning. The mitochondria, which generate power for the cell, operated suboptimally, producing less energy and creating excess cellular waste, which ultimately leads to neurodegeneration. “The effects of alpha-synuclein on mitochondria are like making a perfectly good coal-fueled power plant extremely inefficient, so it not only fails to make enough electricity but also creates too much toxic pollution,” said Greenamyre. The team also explored methods to prevent alpha-synuclein’s toxicity. They employed gene therapy that forced the neurons to make more TOM20 protein, thereby protecting them from alpha-synuclein. An additional protein proved able to prevent alpha-synuclein from sticking to TOM20, blocking harm to the mitochondria. The researchers are optimistic that these two nascent therapeutic methods can be tested in clinical trials.

Overdiagnosis surrounding thyroid cancer has been on the rise and can lead to costly, unnecessary treatment. However, some thyroid tumors are indolent, or nonprogressing, despite the presence of cellular abnormalities that are usually deemed cancerous, said senior investigator Yuri E. Nikiforov, MD, PhD, professor of pathology and director of Pitt’s Division of Molecular and Genomic Pathology. Pitt researchers have used ThyroSeq v2.1, a next-generation sequencing test developed by Nikiforov and colleagues, to examine potentially cancerous cells. Recently, however, they explored reassessing the classification of a thyroid cancer. Incidence of a thyroid tumor known as encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) has doubled or tripled in the past 20–30 years and represents 10–20 percent of all thyroid cancer diagnoses in Europe and North America. Studies have shown that EFVPTC is not dangerous, yet it’s typically treated as aggressively as other thyroid cancers. Per recommendation from the National Cancer Institute, an international panel of pathologists and clinicians led by Pitt researchers reclassified EFVPTC as a non-cancer to indicate that it’s noninvasive and has low recurrence risk, a move that should reduce the medical and psychological consequences of receiving a cancer diagnosis. The pathologist panel, composed of experts from seven countries, examined 268 tumor samples to analyze cellular features, tumor invasion, and other factors. “To my knowledge, this is the first time in the modern era a type of cancer is being reclassified as a non-cancer. I hope that it will set an example for other expert groups to address nomenclature of various cancer types that have indolent behavior to prevent inappropriate and costly treatment,” Nikiforov said.

A new drug therapy developed by Pitt’s Center for Vaccine Research (CVR) targets bacterial biofilms and has proven to be effective against a deadly respiratory virus, demonstrating an unprecedented ability to fight bacteria and a virus during a co-infection, said senior author Jennifer M. Bomberger, PhD, assistant professor of microbiology and molecular genetics. The research could advance treatments for drug-resistant bacteria, including “superbugs,” which continue to proliferate alarmingly and remain resistant to nearly all antibiotics. Chronic infections often resist the body’s efforts to clear them from the lungs, sinuses, or other areas and lead to formation of biofilms, which are communities of surface-associated bacteria that can be 400 times as resistant to antibiotics as a single bacterium. The researchers used an engineered cationic antimicrobial peptide, or eCAP, which has a structure similar to natural antimicrobial peptides, to rupture and destroy bacteria and viruses. The team grew biofilms of drug-resistant Pseudomonas aeruginosa bacteria on airway-lining cells and then administered an eCAP.
The destruction of certain sensory neurons could prevent onset of the most common and lethal form of pancreatic cancer, according to new research from Pitt and other institutions. Sensory neurons play a significant role in pancreatitis, or inflammation of the pancreas, which is a pancreatic cancer risk factor. The researchers believe that sensory neurons may harbor key proinflammatory inputs that can lead to early stages of pancreatic ductal adenocarcinoma. The team injected capsaicin, the active agent in chili peppers, into newborn mice that had the most common genetic defects found in humans with pancreatic cancer. Whereas these at-risk mice typically develop pancreatic cancer within six months, the capsaicin repressed sensory neurons that communicate with the pancreas. The mice injected with the chemical that experienced the most sensory neuron loss were cancer free after 18 months, the study’s end. More than 90 percent of those that received no capsaicin died within six months. Capsaicin reduced inflammation and neuronal damage to the peripheral and central nervous system and helped to stop pancreatic cells from invading the spinal cord through sensory neurons. By preventing migration of pancreatic cells, cancer development slowed or was prevented, said study leader Brian M. Davis, PhD, professor of neurobiology and of medicine.
**CANCER PREVENTION RESEARCH**

**JUL 2016 \ VOL 9 \ ISSUE 7**

**BROCCOLI SPROUT EXTRACT PROTECTS AGAINST ORAL CANCER AND MAY IMPEDE CANCER RECURRENTNESS**

Cruciferous vegetables like broccoli, cabbage, and garden cress have a high concentration of sulforaphane, a potent compound that has been shown to protect against carcinogens. University of Pittsburgh Cancer Institute researchers demonstrated that sulforaphane protected laboratory mice against oral cancer—an unprecedented finding. Moreover, a low-cost, easily distributed broccoli sprout extract that harnesses sulforaphane was shown to activate the same “detoxification” gene in the mouths of human volunteers and, thus, could prevent cancer recurrence in survivors of head and neck cancer, the researchers believe. Lead author Julie E. Bauman, MD, MPH, associate professor of medicine, Yan Zang, PhD, a postdoctoral researcher, and colleagues treated human head and neck cancer cells, as well as healthy mouth cells, with sulforaphane in the lab. In both cell types, the levels of a protein that activates genes that promote detoxification of carcinogens increased. In a small clinical trial, healthy volunteers drank a broccoli sprout and fruit juice beverage for several days, activating the same protective genetic pathway in their mouths that was activated in the lab. In a separate study, mice predisposed to head and neck cancer that received sulforaphane developed far fewer tumors than their untreated counterparts. “With head and neck cancer, we often clear patients of their first cancer, only to see them develop a second cancer with deadly consequences,” said Bauman, who has now launched a clinical trial involving cancer patients cleared of head and neck cancer. These participants take capsules containing broccoli seed powder in hopes of warding off a second head and neck cancer occurrence.

**IMMUNITY**

**FEB 2016 \ VOL 44 \ ISSUE 2**

**INTERLEUKIN-35 LIMITS ANTI-TUMOR IMMUNITY AND PROMOTES T-CELL DYSFUNCTION IN THE TUMOR MICROENVIRONMENT**

One of the goals of immunotherapy is to inhibit regulatory T cells, known as “Tregs,” and enhance the capabilities of tumor-specific T cells without causing inflammation, autoimmune complications, or other adverse outcomes. Although Tregs impede autoimmunity, they also restrain critical tumor-specific T-cell responses. While Treg depletion improves tumor rejection, the resulting adverse autoimmune conditions highlight the need to restrict Treg-targeted therapies to the tumor microenvironment. Researchers at Pitt, including Dario A. Vignali, PhD, professor of immunology, and other institutions explored Interleukin-35 (IL-35), a Treg-secreted cytokine, and its ability to limit anti-tumor immunity by inhibiting T-cell proliferation and function. The researchers manipulated IL-35 in mice by applying an IL-35-specific antibody or by inducing Treg-restricted deletion of IL-35 production that resulted in limited tumor growth across various mouse models of human cancer. Limiting intratumoral IL-35 enhanced T-cell proliferation, effector function, antigen-specific responses, and long-term T-cell memory. Treg-derived IL-35 promoted the expression of multiple inhibitory receptors, further highlighting newfound roles for IL-35 in limiting anti-tumor immunity and contributing to T-cell dysfunction in the tumor microenvironment.

**NATURE STRUCTURAL AND MOLECULAR BIOLOGY**

**JUN 2016 \ VOL 23 \ ISSUE 6**

**RESEARCHERS ELUCIDATE STRUCTURAL COMPONENTS OF HERPESVIRUS CAPSID**

Cryo-electron microscopy (cryo-EM) provides the necessary resolution and maintains the natural environment needed to study the mechanisms and interactions that govern the assembly and function of functional complexes like the protein shell of a virus. Pitt researchers, including James F. Conway, PhD, associate professor of structural biology, employed cryo-EM to study the herpesvirus capsid, a complex protein assembly that includes hundreds of copies of four major subunits and smaller collections of several essential minor proteins, which, combined, enable infectivity. The team solved two high-quality capsid structures, one from human herpes simplex virus type 1 and the other from animal pseudorabies virus. Based on their observations, the researchers developed a model to illustrate subunit and domain organization. They found extensive networks of subunit contacts that support capsid stability. The networks form a pathway, the researchers observed, that may indicate the completion of DNA packaging from the capsid interior to the outer surface, which would initiate a key part of the infection process called nuclear egress. The subunit domain’s variances in orientation and folding between capsids suggest that the common elements have been altered to carry out specific functions. Better understanding of the structure and function of these capsids could lead to improved therapies and vaccines.

**PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES**

**FEB 2016 \ VOL 113 \ ISSUE 8**

**PITT RESEARCHERS SHED NEW LIGHT ON REGULATION OF CELL SIGNALING PROCESSES BY ENDOCYTOSIS**

Endocytosis, or active transportation of molecules into cells, governs intracellular signaling. Exactly how the process regulates signaling is largely unknown, however. Researchers from Pitt’s Department of Cell Biology, including Alexander Sorkin, PhD, Richard Beatty Mellon Professor of Physiology and chair of cell biology, use the Ras protein to study signaling. In this study, Ras, which is central to normal and oncogenic signaling, was labeled with a fluorescent protein via gene editing so that it could be tracked in living cells stimulated with epidermal growth factor (EGF). The team observed that the activated EGF receptors are rapidly internalized deeper into the cell via endosomes. Ras, however, was not internalized and remained within the plasma membrane, which indicates that EGF receptors signal mitogen-activated protein kinases—which help govern cellular responses to stimuli and regulate cell functions—exclusively from the plasma membrane. Sorkin and colleagues believe this is the first time scientists have reported examining the localization of endogenous Ras in living cells stimulated with EGF.
A full picture of the structural composition of RNA Polymerase II (Pol II) featuring a complete nucleic acid scaffold has not been available to scientists. Recently, however, Pitt researchers reported and described the crystal structures of Pol II in complex with a complete nucleic acid scaffold that reveals the architecture of a Pol II transcribing complex. The research team, led by Guillermo Calero, MD, PhD, assistant professor of structural biology, School of Medicine, explored the mechanisms and shape of Pol II to reveal a complete transcription bubble. While exploring the structure, they saw that an upstream duplex stretches over a wedge-shaped loop from the Rpb2 subunit, which comprises part of the structural framework during DNA elongation. By revealing the structural composition, the researchers permitted clearer visualization of the mechanisms and components of the enzyme. At the upstream transcription bubble fork, rudder and fork loop 1 residues coordinate strand annealing and the nascent RNA transcript. At the downstream fork, a network of Pol II interactions with the non-template strand forms a rigid domain with the trigger loop. The findings suggest that the varying open or closed arrangement of the trigger loop may be linked to interactions with the non-template strand and may be mechanically conducive to polymerase translocation. Ultimately, the cocrystal structure uncovers the large range of interactions between Pol II and the nucleic acid scaffold.

**Graphical Abstract**

**Crystal Structure of a Transcribing RNA Polymerase II Complex Reveals a Complete Transcription Bubble**

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**PITT RESEARCHERS REVEAL STRUCTURAL COMPOSITION OF ENZYME AND RELATED NUCLEIC ACID SCAFFOLD**

G protein-coupled receptors are the most abundant cell surface transmembrane receptors that activate or repress intracellular signaling pathways in response to extracellular stimuli. Of these medically important receptors, the parathyroid hormone receptor (PTHR) regulates calcium mineral-ion homeostasis. It is involved with maintaining steady concentrations of calcium and phosphate in extracellular fluids and with bone turnover and repair, and it’s a target for the treatment of osteoporosis. Researchers from Pitt’s Laboratory for G Protein-Coupled Receptors Biology, including Peter A. Friedman, PhD, professor of pharmacology and chemical biology and of structural biology, and Jean-Pierre Vilardaga, PhD, professor of pharmacology and chemical biology, investigated molecular and cellular processes by which PTHR transmits parathyroid hormone (PTH) signals in bone and kidney cells. Upon PTH stimulation, the PTHR moves into endosomes, where it engages the retromer complex, which promotes recycling of receptors to the cell surface. Sorting nexin 27 (SNX27) was identified as a new PTHR binding partner in isolated endosomes. The rate of PTHR recycling decreased following depletion of SNX27 or VPS35, a retromer subunit. Mutating the PDZ ligand of PTHR disabled the receptor’s interaction with SNX27 but did not affect the rate of recycling. This suggests that PTHR may directly bind the retromer complex. Recycling independent of SNX27 may involve the N-ethylmaleimide-sensitive factor, another protein that transfers vesicles from one cell compartment to another, to bind PDZ and mutant PTHRs. The researchers concluded that PTHR undergoes rapid recycling through both mechanisms. Such findings shed new light on cellular pathways of receptor signaling that are needed to develop new therapies for bone and mineral diseases.

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**TWO CELLULAR PROCESSES GOVERN RAPID CELLULAR RECYCLING OF RECEPTOR**

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**NITRIC OXIDE AND NITRITE REACTIONS ARE KEY TO PHYSIOLOGICAL FORMATION OF CELL SIGNALING MEDIATORS**

Nitric oxide induces a variety of signaling responses and chemical reactions under both physiological and metabolically-stressed conditions. Pitt researchers, including Bruce A. Freeman, PhD, UPMC Irwin Fridovich Professor and chair of pharmacology and chemical biology; Francisco J. Schofer, PhD, research associate professor of pharmacology and chemical biology; and Dario Vitturi, PhD, research assistant professor of pharmacology and chemical biology, identified new intermediates stemming from the reactions of nitrogen oxides that promote unique modes of cell and tissue signaling regulation. One product, symmetrical dinitrogen trioxide (ONONO), promotes both fatty acid nitration and thiol S-nitrosation at neutral pH. Theoretical models had predicted physiological formation of this compound, and this mass spectrometry-based study demonstrated its generation in aqueous reaction systems, in cell models, and in vivo. Autoxidation of nitric oxide instigates the reaction cascade leading to ONONO formation, which occurs in the absence of metal centers. These findings have revealed new biochemical reactions regulating biomolecule function and signaling network activity that involve nitric oxide and nitrite-dependent nitrosation and nitration reactions.
When Elizabeth Miller, MD, PhD, arrived at the University of Pittsburgh in 2011, she hit the ground running. Chief of the Division of Adolescent and Young Adult Medicine and relentless advocate for children and adolescents, Miller immediately noticed that Pittsburgh lacked a drop-in center for young people who do not have stable housing and need a connection to community services, supportive adults, and food, or who need a little bit of extra help with difficult life circumstances. She and community partners quickly pooled resources to set up a youth center in the Gay and Lesbian Community Center in downtown Pittsburgh.

While that center remains open, Miller’s vision for another drop-in center recently came to fruition—because, as she says, “it’s important for marginalized youths to have multiple portals through which to connect to support and services.” Funded by the Allegheny County Department of Human Services and led by the Auberle Foundation with the support of multiple community partners, including the Homeless Children’s Education Fund and Children’s Hospital of Pittsburgh of UPMC, 412 Youth Zone is a new, one-stop drop-in center to help young people live independently. It has showers, child care, prevention education, a reading room, and laundry. It houses trained staff members, youth coaches, case managers, an on-site nurse, and a clinician from Miller’s division once a week.

In addition to being professor of pediatrics, behavioral and community health sciences, and clinical and translational science and medical director of 412 Youth Zone and of other community health services—like the Children’s Hospital of Pittsburgh of UPMC/Ronald McDonald Care Mobile, a mobile van that links medical services to communities with little access to primary care—Miller is a tireless practitioner of community-engaged research. She is known for bringing to Pitt Coaching Boys into Men (CBIM), a prevention program that trains coaches to talk to their athletes about the importance of nonviolent behaviors toward women and girls, using the influence of athletic coaches as powerful messengers for violence prevention and male athletes as leaders in their communities. The successful program is being used in many high schools in Southwestern Pennsylvania, and the Federation of Independent School Alumnae (FISA) Foundation and the United Way partnered to support CBIM’s implementation in local high schools and colleges. The partnership also funded six domestic violence/sexual assault agencies to provide training for area schools and coaches, with a goal of training 2,000 coaches in the region. CBIM has gone international, with the program adapted for cricket players in India. Miller says the focus for CBIM now is on the best strategies for dissemination and implementation and doing smaller, more sociologic studies looking at the key characteristics of coaches effectively implementing the program.

What Miller calls her “dream project” is Manhood 2.0, which she developed and is funded by the Centers for Disease Control and Prevention (CDC). When CDC sent a call for proposals to engage men and boys in sexual violence prevention, she looked at the gender violence prevention work being done and noticed they were mostly in school- or clinic-based settings. She saw a need for community-based programming that includes in-depth discussion with young people over an extended period of time and implemented by people with whom they have some level of trust or connection. In a partnership with Promundo, a global gender violence prevention organization, the Urban League of Greater Pittsburgh is a city on the rise. As the city’s medical school, we seek to identify areas of need, contribute our expertise and energy, and strengthen partnerships to make a most livable city even better.
412 YOUTH ZONE is a new, one-stop drop-in center to help young people live independently. It has showers, child care, prevention education, a reading room, and laundry. It houses trained staff members, youth coaches, case managers, an on-site nurse, and a clinician from Miller’s Division once a week.
Pittsburgh, and the YMCA, Miller has implemented Manhood 2.0, which mixes comprehensive sexuality and sexual violence education and information about consent/communication and healthy relationships with critical analysis of rigid masculinity norms. It provides an 18-hour curriculum spread over six sessions and run by trained facilitators in community settings. Young people in local school districts can even participate in Manhood 2.0 as an alternative to out-of-school suspension.

“We have these amazing, intense, and wonderful conversations with young men about what it means to be a man, what they envision for their futures, media messages, the harmful effects of pornography, their experiences of racism and injustices, naming white privilege, and talking about male privilege,” says Miller. “You can see the gears working in their heads. It’s an immense amount of work and one of the most glorious, joyous projects.”

Miller mixes her research-community partnership work with her other many roles, like being codirector of community engagement for the Clinical and Translational Science Institute’s Community PARTners Core and offering clinical care at the division’s transgender clinic and at Shuman Juvenile Detention Center. She is involved with 18 active grants, administers $2 million in federal funds, and launched one National Institutes of Health and two CDC-funded studies this year. How does she remain fueled for her many responsibilities?

“Southwestern Pa. is an incredibly generous and compassionate place,” says Miller. “It’s a critically important characteristic that makes me optimistic about our ability to make a difference for kids here. Building research-community partnerships and collaborations is so important in translating research into community health impact. Collaboration has been really easy here. When you meet with other people who care deeply about the health of children, youths, and families, and when you sit with that kind of energy, it just keeps you going.”

JOSH BADSTIBNER, 18, FROM DUQUESNE, GETS SOME LAP TIME WITH GIBSON, A 3-YEAR-OLD BEAGLE DURING A “NATIONAL PUPPY DAY” VISIT IN THE 412 YOUTH ZONE COMMON ROOM.
For postdoctoral fellows and junior faculty new to the biomedical research workforce, navigating the first few years of academia can be difficult. Securing research funding is essential, but what do you do if you have had very little preparation in the nuts and bolts of being a researcher? Since 2005, training successful clinical researchers in Pitt’s resource-rich environment has been the task of the University of Pittsburgh’s Institute for Clinical Research Education (ICRE). Training programs are led by ICRE codirector Doris Rubio, PhD, who is also director of the center’s academic programs, director of the Office of Evaluation and Office of Lifelong Learning, and director of the data center of the Center for Research on Health Care. In discussions with colleagues at five minority-serving institutions (MSIs—specifically Charles R. Drew University of Medicine and Science, Howard University, Morehouse School of Medicine, University of Hawai‘i at Mānoa, and University of Puerto Rico), Rubio learned that these institutions sometimes struggled to launch the research careers of their junior faculty. She also saw an opportunity to foster and develop Pitt’s strengths in scientific mentorship while being a good citizen.

"Junior researchers at our partner MSIs have all had traditional classes, like biostatistics and research methods," says Rubio, professor of medicine, School of Medicine; professor of biostatistics, Graduate School of Public Health; professor of nursing, School of Nursing; and professor of clinical and translational science. "So we decided to provide some nontraditional training like how to write successful grants, how to publish papers, and training in biomedical writing."

Rubio received funding for two training programs—LEADS (Leading Emerging and Diverse Scientists to Success) and PROMISED (Professional Mentoring Skills Enhancing Diversity). Funded by the National Institute for General Medical Sciences, LEADS is a year-long program designed to meet the individual needs of trainees and junior faculty from participating MSIs who are underrepresented in the biomedical sciences and beginning their research careers. Once applicants are accepted into the program, they are assigned a career coach who helps the trainees identify which online modules they should complete (modules are readings, videos, research, and/or homework on different topics) and create a career plan for the year.

"By the end of the year, our goal for the trainees is for them to have or be close to having a grant ready for submission," says Rubio.

LEADS allows for some funding for trainees who want to disseminate their research at conferences or travel to receive specialized training.

PROMISED is a program with an innovative approach to mentoring, funded by the National Research Mentoring Network. Rubio says, "Because the biomedical research workforce does not reflect the diversity in the United States, there's an effort to diversify the workforce. To do that, we need mentors who can specifically mentor people from diverse backgrounds. So, we developed PROMISED with the idea that mentors with strong leadership skills would be more effective mentors."

PROMISED provides online training modules that focus on leadership skills (including understanding academia and academic code, time management, executive shadowing, and managing others) and career coaching training. Rubio says that career coaching is about helping mentees take ownership of their careers and discerning for themselves, with some helpful guidance, what will help their career trajectories.

Rubio will host about 100 people at Pitt in the upcoming months to provide them with career coaching training. From that pool, 30 will participate in a one-year fellowship with PROMISED.

"The energy and excitement about the two programs has been incredible," Rubio says. "For both, I'd like to get to the point where the programs are available on the Web, and people could reproduce them at their own institutions or go through the programs independently. My goal is to disseminate them so they can have a much broader effect on the research workforce."

"We decided to provide some nontraditional training like how to write successful grants, how to publish papers, and training in biomedical writing."
Unexpected pregnancy can be a challenge for any woman, let alone a teenager. Teen mothers have higher rates of depression, have lower high school completion rates, are more likely to have a second unexpected pregnancy, and are more likely to have a baby with low birth weight and slower cognitive development, according to the Centers for Disease Control and Prevention. Recognizing that teen mothers are in great need of guidance and support, Jeannette E. South-Paul, MD, UPMC Andrew W. Mathieson Professor and chair, Department of Family Medicine, began a mentoring program for these mothers called the Maikuru Program.

"Maikuru" means "great aunt" or "wise woman of the village" in the Southern African Shona language. The Maikuru Program pairs teen mothers with volunteer mentors—maikurus—who offer support, experience, and a sympathetic ear for the new moms, who, like new mothers at any age, have a lot of questions and need reassurance.

The program, funded initially by the Heinz Endowments and now by the Grable, Poise, and Fine Foundations, offers six weekly meetings in Oakland, and participants are provided with transportation costs, dinner, child care, a chance to socialize with their maikurus and other mothers, and a presentation. The presentations cover timely topics like child development, depression, contraception, goal setting, healthy relationships, intimate partner violence, self-concept and spirituality, stress, and maintaining a positive outlook.

“The rate of depression in teen mothers is twice as high as depression is in the rest of the teen population,” says Yassmin Al Aaraj, MD, MPH, project coordinator for the Department of Family Medicine’s Maikuru Program, School of Medicine. “Depression is one of the problems that will prevent them from continuing their education, finding jobs, and establishing a family.” At the beginning and end of the program, South-Paul surveys the participants about issues like depression and problem-solving skills to measure whether the program is beneficial (and she refers them to social services if necessary). Follow-up interviews with participants who have completed the program demonstrate its benefit. Teen moms who had been through the program had a higher rate of completing high school than teen moms nationally or in Pennsylvania. Al Aaraj says that teen moms and maikurus often want to keep meeting, so the program offers a monthly continuation group meeting. Maikurus and their mentees often maintain their relationships for years after participating in the program.

South-Paul began the program in 2009 and recently expanded it to include a new program for mothers aged 19–25 and fathers or current partners. Participants attend weekly sessions and can be paired with a maikuru or a mentor couple.

“I just can’t begin to tell you how important it is for these teens to feel like they have social support and somebody that can coach them in life,” says South-Paul.
Residency Combines Family Medicine and Psychiatry for Integrated Care

A recent shift toward treating patients in integrated care settings bodes well for the School of Medicine’s combined family medicine-psychiatry residency program, which began in 2006 and is one of only five such programs in the country. Based on the concept of one physician being able to treat a patient’s entire brain-body system, the program provides residents with full training in both family medicine and psychiatry, leading to dual board certification. Applications to the program have doubled in the past few years and are expected to increase by 50 percent next year, according to Michael Travis, MD, associate professor of psychiatry, School of Medicine, and director of residency training, Western Psychiatric Institute and Clinic of UPMC.

“This integrated care training model isn’t a fad,” says Travis. “We firmly believe that combined training is the training of the future because of all the current emphasis on patients being able to see one doctor and have that person coordinating as much of their care as possible.”

Family medicine and psychiatry are a natural fit. Mental health is often entangled with physical health and vice versa, and primary care physicians are often the first health care providers to hear about any health issue. A physician trained to think about mental and physical health together can provide integrated care in one office visit.

Travis says that 30–40 percent of the residents’ patients in their family health center clinics have a behavioral health diagnosis in addition to whatever other comorbidities they have. “If people trust you as their primary care doctor, someone whom they might see regularly, they’ll also trust you to care for their mental health,” says Travis. “Combined family medicine-psychiatrists may be primarily dealing with a patient’s diabetes, but that physician is also able to recognize and treat the patient’s underlying anxiety and/or depression that’s making them feel even worse.”

Trainees in the program can have rotations in areas like geriatrics, mental retardation services, eating disorders, community psychiatry, and forensics and can see patients at the Birmingham Free Clinic, run by Pitt’s Program for Health Care to Underserved Populations and the Salvation Army. Graduates of the program are finding increasing career opportunities and have gone on to employment with state hospitals, integrated care settings, academic medical centers, and in research.

“Our trainees are seeing patients with extremely complex issues,” says Travis. “It’s exciting because they’re getting opportunities to be expert consultants for both family medicine and psychiatry categorical program colleagues. The trainees are family medicine physicians plus or psychiatrists plus. They’re going to be our future leaders and educators in medicine.”

“This integrated care training model isn’t a fad. We firmly believe that combined training is the training of the future because of all the current emphasis on patients being able to see one doctor and have that person coordinating as much of their care as possible.”
Remembering D.A. Henderson
1928–2016

Beginning on August 19, 2016, news of the death of D.A. Henderson, MD, MPH, 21st Century Professor of Medicine and Public Health, quickly circled the globe, accompanied by laudatory tales of his days with the World Health Organization (WHO). It was a fitting tribute to the leader of the successful global campaign to rid the world of smallpox. Henderson, 87, died from complications following a hip fracture.

Known to all as “D.A.,” he was born Donald Ainslee Henderson in Lakewood, Ohio. He received a medical degree in 1954 from the University of Rochester, then joined what later became known as the Centers for Disease Control and Prevention (CDC). He earned an MPH at Johns Hopkins University in 1960 and was elevated to chief of the CDC’s virus surveillance section. In this position, he came to the attention of the WHO and was tapped to lead its worldwide smallpox eradication program in 1966.

“The sense at the WHO was that this was an impossible mission, so they chose a young man who didn’t have a reputation to tarnish,” said Thomas V. Inglesby, MD, director of the UPMC Center for Health Security, where Henderson was a resident scholar.

For 11 years, Henderson traveled between the WHO’s Geneva, Switzerland, headquarters and global smallpox hot spots. The $300 million surveillance and vaccination campaign achieved success, with the last naturally occurring case of smallpox isolated in Somalia in 1977. The disease was officially declared eradicated in 1980.

Henderson left the WHO in 1977 for Johns Hopkins, where he later founded a center for civilian biodefense studies. In 2003, he joined the faculty of the University of Pittsburgh. Henderson served in the administrations of three presidents—George H.W. Bush, Bill Clinton, and George W. Bush—and received many honors, including the National Medal of Science (1986) and the Presidential Medal of Freedom, the nation’s highest civilian honor, in 2002.

Pitt’s Clinical and Translational Science Institute (CTSI) has reached a milestone: More than 103,000 people of all ages have signed up with its Research Participant Registry to learn about different health topics and/or participate in local health studies. The registry connects members of the community with investigators and studies that address their interests or health needs.

The registry launched in August 2008 with 18 participants, as Kerri Jackson, administrator for CTSI’s registry, recalls. “We’ve worked hard to engage as many people as we can since then,” Jackson says. “Our online recruitment through MyUPMC, UPMC’s online patient management system, has been incredible. Much of our enrollment can be attributed to word-of-mouth referrals and recruitment through UPMC and Children’s Hospital of Pittsburgh of UPMC outpatient offices.”

The feature that differentiates Pitt’s CTSI research participant registry from other registries nationwide is its focus on the participant. “We want to engage people for the long term, give them a different avenue to obtain information about research, and show people how research is relevant to their own health,” says Steven E. Reis, MD, associate vice chancellor for clinical research, professor of medicine and of emergency medicine, and director of CTSI. “The registry also is a partnership with investigators to help them gain access to populations they might otherwise have trouble reaching and to diversify their participant base.”

To find new ways to engage current and new participants, CTSI’s registry has launched a new campaign called Pitt+Me™ (researchrecruitment.pitt.edu/ctsi). Using a strong digital messaging presence, the campaign hopes to reach people wherever they are and whenever they might be most interested in learning more about certain health topics or ways to partner with research studies. “We’re hoping to use social media to drive people to the new website and, through a strong multimedia presentation, engage them in the registry once they’re there,” says Reis. “Using this approach is also getting investigators thinking about their studies in new ways.

“Investigators who haven’t yet used the registry and CTSI’s services should try them,” says Reis. “We all want to disseminate our research findings and see how our work is benefiting people.”

A Milestone of Participation

Beginning on August 19, 2016, news of the death of D.A. Henderson, MD, MPH, 21st Century Professor of Medicine and Public Health, quickly circled the globe, accompanied by laudatory tales of his days with the World Health Organization (WHO). It was a fitting tribute to the leader of the successful global campaign to rid the world of smallpox. Henderson, 87, died from complications following a hip fracture.

Known to all as “D.A.,” he was born Donald Ainslee Henderson in Lakewood, Ohio. He received a medical degree in 1954 from the University of Rochester, then joined what later became known as the Centers for Disease Control and Prevention (CDC). He earned an MPH at Johns Hopkins University in 1960 and was elevated to chief of the CDC’s virus surveillance section. In this position, he came to the attention of the WHO and was tapped to lead its worldwide smallpox eradication program in 1966.

“The sense at the WHO was that this was an impossible mission, so they chose a young man who didn’t have a reputation to tarnish,” said Thomas V. Inglesby, MD, director of the UPMC Center for Health Security, where Henderson was a resident scholar.

For 11 years, Henderson traveled between the WHO’s Geneva, Switzerland, headquarters and global smallpox hot spots. The $300 million surveillance and vaccination campaign achieved success, with the last naturally occurring case of smallpox isolated in Somalia in 1977. The disease was officially declared eradicated in 1980.

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Henderson left the WHO in 1977 for Johns Hopkins, where he later founded a center for civilian biodefense studies. In 2003, he joined the faculty of the University of Pittsburgh. Henderson served in the administrations of three presidents—George H.W. Bush, Bill Clinton, and George W. Bush—and received many honors, including the National Medal of Science (1986) and the Presidential Medal of Freedom, the nation’s highest civilian honor, in 2002.
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 of UPMC between July 1, 2014, and June 30, 2015, have supported us in our academic, research, and clinical missions.

Thank you.
After the School of Medicine Class of 1972’s 40th reunion in 2012, a few classmates met to continue reminiscing. In their discussions, they all realized that their time at the University of Pittsburgh had been such an influence in their lives that they wanted to honor those years and the mentors they had enjoyed. That night, they made a decision to organize members of the class to give a gift to the school. They continued planning in the weeks after in an informal group, which is currently composed of Richard B. Kasdan, MD, Leslie R. Laufman, MD, Gregory McClure, MD, Ernest E. Moore, MD, Bruce Coull, MD, John Loeb, MD, and Ivan Shulman, MD, MM.

Helping others was a core principle of the Class of 1972. “When we started in 1968, our class had a sense of social activism—there were protests, the Vietnam War was going on—it was a difficult time politically and socially,” says Dr. Shulman, voluntary assistant professor of surgery at the University of California, Los Angeles, longtime general surgeon in the Los Angeles area, and professional conductor and oboist. Many members of the class were greatly influenced by professors and mentors, including Ken Rogers, MD, chair of what was then the Department of Community Medicine at the School of Medicine. Dr. Rogers organized a rotation in the Navajo Nation in Arizona that influenced many class members.

“Ken saw the world from the downtrodden perspective,” says Dr. Shulman. “He saw medicine as a gift to give, and it fit well with our class’ social consciousness.”

Another memorable professor was Jack D. Myers, MD, chair of Pitt’s Department of Medicine from 1950 until 1970. “He was a structured, almost militaristic kind of guy who had very high standards, and you had to perform at a high level. You knew that you were doing well when he lit a cigar during rounds,” says Dr. Coull, William M. Feinberg, MD, Professor in Stroke Research, professor of neurology and of medicine, and vice dean for clinical affairs, University of Arizona School of Medicine.

“Jack was the model for a clear-thinking, compassionate but scholarly approach to patients,” says John Loeb, MD, a rheumatologist in private practice. “He gave brilliant talks; even if you’d been up all night, you tried to go to his rounds because he was such a great bedside teacher. He was the teaching-clinician role model that’s such a huge influence when you see patients yourself.”

To honor their mentors and the education they received at Pitt, the steering committee for the Class of 1972 decided to support student education. The summer after their first year, medical students typically work on their Scholarly Project, a longitudinal research experience throughout the four years of medical school, and the Class of ’72 Research Fund helps offset expenses of one selected student’s summertime research.

“The fund isn’t so much about turning med students into academic researchers; it’s about showing that bench and clinical research are important educational experiences for any doctor,” says Dr. Loeb. “We see it as a vital part of medical education.”

The School of Medicine made its first award for the summer of 2016. The recipient, Sheri Shiyu Wang, a Pittsburgher and rising second-year medical student, conducted research in the Plastic Surgery Adipose Stem Cell Research Laboratory. Ms. Wang juggled a few research projects in the summer of 2016, but her Scholarly Project research involved isolating lymphatic endothelial cells from the human adult dermis, examining the influence of mechanical stress on these cells and how stretching them in vitro leads to different cell signaling and possibly to lymphedema. Ms. Wang, who wants to pursue a career as a clinician-researcher in plastic surgery, says of the award, “It has done wonders for me. Otherwise, I would’ve had to get a summer job on top of my lab work. I feel as if I did a lot of hard science, and I built my management skills.”

“All of us had a research project, and we all benefited from it,” says Dr. Loeb. “We’re making a statement that we believe in paying back and showing gratitude to the people and the place that educated us.”
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In football, offensive linemen are the strength of the offense. They protect the quarterback and other teammates running or catching the ball. Usually the biggest men on the field, offensive linemen are known for strength, grit, and heart. James P. Covert embodies all of these characteristics. He played on the “O line” for three of his four years on the University of Pittsburgh Panthers football team that went 31–5 in the early 1980s. (The quarterback he was protecting then was his Pitt roommate, Dan Marino.) He was a first-round draft pick of the Chicago Bears and a member of the famous 1985 Super Bowl XX championship team coached by Pitt and National Football League legend Mike Ditka. Mr. Covert’s cocaptain on the Bears’ offense, Walter Payton, called him the “best offensive tackle in the NFL.”

So, what does a professional football player do when he retires from the game? He continues looking out for others—just in a different way.

In 2007, after several years in health care sales, marketing, and acquisition initiatives with different companies, Mr. Covert joined the Institute for Transfusion Medicine (ITX-M) as president and chief executive officer. ITX-M specializes in transfusion medicine and related services. With its two blood centers, Central Blood Bank in Pittsburgh and LifeSource in Chicago, it provides nearly one million units of blood products annually.

One of Mr. Covert’s first goals for ITX-M was to create a strategic plan, and a large part of that plan was research. He asked, why not forge a relationship with a biomedical powerhouse right here in Pittsburgh?

With Mr. Covert’s guidance, a relationship between ITX-M and the University of Pittsburgh was solidified to serve people with and conduct research on blood disorders and blood-related diseases. Using the strength in biomedical research and a joint gift from ITX-M’s Blood Science Foundation and ITX-M’s subsidiary, the Hemophilia Center of Western Pennsylvania, the partnership created the Pitt School of Medicine’s Vascular Medicine Institute (VMI), directed by Mark Gladwin, MD, Distinguished Professor of Medicine, Jack D. Myers Professor of Internal Medicine, and chair, Department of Medicine. Mr. Covert calls the partnership a “win.”

“We committed the seed dollars, and once Mark got started, BOOM, he really took off. He’s a dynamo,” Mr. Covert says. “That passion and energy is what has made VMI so successful.”

But he also credits another group of contributors that he feels is essential. “People who give us the gift of their blood in order for us to treat patients are doing an altruistic act. The dollars we earn that go into the Blood Science Foundation really come from the community, and I just feel strongly that the money needs to go back into the community. If we can develop lifesaving therapies for people with blood disorders and blood-related diseases through our research, if we can better the quality of life for people with diseases like sickle cell and hemophilia, then that’s what we need to do,” says Mr. Covert.

When he was asked to join the Board of Trustees at Pitt in 2014, Mr. Covert saw it as another chance to help.

“Pitt has given me so much in my life. I came from a small steel mill town near Pittsburgh and grew up and met my wife at Pitt,” he says. “As my career since football has gone through changes, Pitt has prepared me for that. You can’t say that about a lot of places.”
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Herb and Barbara Shear created the Shear Family Foundation with their children in August of 2014 as a means to fund—and propel—a set of nonprofit organizations and causes whose missions align with their own. They also see their foundation as an opportunity to teach their grandchildren about the joys and responsibilities of philanthropy.

“We’re still early in the game,” says Mr. Shear, “but we’re making some heartfelt and strategic decisions that we think will have long-term impact. That’s what gets us excited. We want to help make a measurable difference in areas we really care about.”

Mr. Shear is chairman and CEO of the Shear Family Office, which manages the Shear Family Foundation and Shear Family Investments. Formerly, he was the executive chairman and CEO of GENCO, where he earned an international reputation for pioneering work in reverse logistics. He grew the family business into the second-largest third-party logistics provider in North America, and then sold the company to FedEx in 2014, which enabled the Shears to focus on other passions.

The Shear Foundation’s focus areas include medical research, hunger insecurity, Jewish causes, and family issues.

“We both are interested in and encouraged by the advances we’ve seen in medicine and particularly the progress being made in cancer research,” says Barbara Shear. “We want to help continue this impressive momentum.”

To that end, the Shears recently made a significant gift and pledged multi-year support to the University of Pittsburgh Cancer Institute (UPCI), partner with UPMC CancerCenter.

“There are brilliant, dedicated researchers at UPCI doing transformative, life-saving work,” says Mr. Shear. “This is the type of project the Shear Foundation wants to get behind.”

“The Shears are helping us to advance our program in precision medicine, especially in the area of breast and ovarian cancers,” says Nancy Davidson, MD, director of UPCI and UPMC CancerCenter until December 2016. “The funds they’re providing will allow for the sophisticated infrastructure needs such as tissue banking, databases, and analytics needed to support the initiative.”

More specifically, the investment will support investigations into the genomics of breast cancer, as well as research projects ranging from work on a specific subtype of breast cancer called lobular cancer to a comprehensive genomic characterization of breast cancer metastases, to understand the molecular pathways that contribute to this advanced and generally lethal stage of the disease.

“The work supported by the Shears is focused on translational research—research that extends from the laboratory bench into the communities we serve,” explains Dr. Davidson. “UPMC CancerCenter is optimized for and excels in this type of research.”

The work will be led by Adrian V. Lee, PhD, professor of pharmacology and chemical biology, School of Medicine, and of human genetics, Graduate School of Public Health; director of Pitt’s Institute for Precision Medicine; and director of the Women’s Cancer Research Center, a collaboration between UPCI and Magee-Womens Research Institute.

“The more we heard, the more we wanted to be active and make a commitment there,” Mrs. Shear says. “We just think they’re on the cutting edge in a lot of areas.”

While the Shears prefer to maintain a low profile, they agreed to be featured here with a little prodding.

“If it will help spread the word about this new and exciting research in personalized medicine and gene sequencing and if it inspires other people to contribute in ways that they can,” says Mrs. Shear, “then it’s the right thing to do.”

“The scientific opportunities have never been better, and we appreciate the Shears’ commitment to support our UPCI investigators in their quest to develop high-impact ideas that can lead to advances in our ability to practice molecular cancer medicine,” says Dr. Davidson. “Their partnership and confidence in our work are extraordinary gifts to our research team and ultimately to our patients.”
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Adaptation in nature, as demonstrated by four birds from the genus Geospiza, which is endemic to the Galapagos Islands and was famously depicted in The Zoology of the Voyage of the H.M.S. Beagle, by Charles Darwin and John Gould