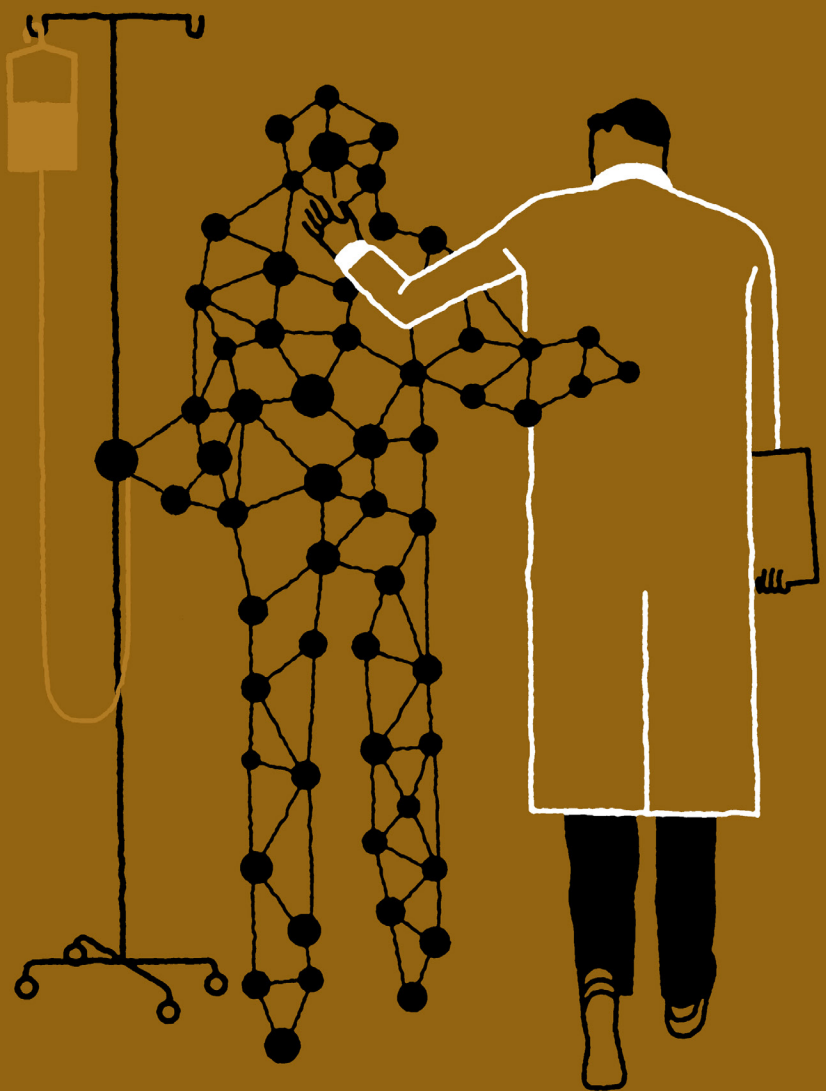
Future Tense



University of Pittsburgh
School of Medicine

2018 ANNUAL REPORT

Future Tense

COVER: A "future tense" interpretation of the clinical encounter encompasses doctor, patient, and countless data points.

A Future Tense Ethos

If you're not "future tense," it's possible that you're just not paying attention, because the near future should have us all on tenterhooks, for both good and not-so-good reasons.

First, the good: One of the most salient features of our time is the extraordinary wealth of scientific and biomedical knowledge that we now have at our disposal. Patients and doctors already benefit from recent technological advances, improved diagnostics, and new treatments. And it's abundantly clear that the potential for so much more is tantalizingly close, lying just beyond the horizon.

To make the most of this moment, we must combine these new capabilities with tried-and-true medical practice, sound clinical and translational science, and the will to extend health care to all those who need it.

That brings us to the flip side of all this newfound potential. Medicine is a humanistic enterprise, but one has to wonder if humanism will overcome tribalism in this population of more than 7 billion human beings. We may find out in the next century. We already face serious medical and public health challenges brought on by global climate change, and it's safe to assume those challenges will intensify.

For that reason, I challenge my colleagues every day to make the best use of this extraordinary moment in history and to seize the opportunity while we can. No previous generation has received a biomedical and scientific inheritance such as we have. Our job as clinicians and scientists is to proceed urgently and courageously, to probe the boundaries of current medical knowledge in the belief that we can learn much more to improve the human condition. To that end, we invest strategically and take action entrepreneurially; this high-risk, high-reward approach is rooted not in blind optimism, but in confidence and humanism.

At the University of Pittsburgh School of Medicine, we're striving to construct a compelling vision of the future today—to think and act in the future tense. I invite you to discover for yourself, on the pages of this report, evidence of our recent progress.

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

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News & Achievements

Pitt and UPMC Move Side by Side Into the Future

Every day, significant health sciences research and clinical medicine outcomes rest on the bedrock of the University of Pittsburgh and UPMC. The essential partnership of these two legally separate but interdependent entities continues to set the standard for academic medical centers in the advancement of knowledge, education, and training of new scientists and health care professionals in Pittsburgh and worldwide.

Pitt Research Funding

Funding from the National Institutes of Health (NIH) is a benchmark of overall stature among research-intensive academic health centers. Since 1998, the University of Pittsburgh has ranked among the top 10 recipients of NIH funding, driven by the School of Medicine. The University's faculty has been ranked fifth since 2010.

2017 NIH FUNDING
UNIVERSITY OF PITTSBURGH

2018 OVERALL RESEARCH SPENDING
UNIVERSITY OF PITTSBURGH

New Faces / Appointees

NEW CHAIR OF ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE

Aman Mahajan, MD, PhD, MBA, has been appointed chair of the newly renamed Department of Anesthesiology and Perioperative Medicine. Mahajan, Peter and Eva Safar Professor of Anesthesiology, is also director of perioperative services for the University of Pittsburgh Physicians and UPMC.

He previously served as chair of the Department of Anesthesiology and Perioperative Medicine at the UCLA David Geffen School of Medicine. His clinical expertise includes cardiothoracic anesthesiology, cardiac electrophysiology, and echocardiography. His research interests focus on spinal neural modulation of cardiac electrophysiology and cardiac function assessment in heart failure.

Mahajan earned an MD at the University of Delhi, a PhD in physiology at UCLA, and an MBA at the University of Massachusetts. He holds seven patents and is a successful entrepreneur, having served as founder and chief technology officer for several startups. In addition, Mahajan is a diplomate of the American Board of Anesthesiology and a fellow of the American Heart Association.

CENTER FOR VACCINE RESEARCH DIRECTOR NAMED

W. Paul Duprex, PhD, a distinguished molecular virologist and vaccine designer, has been appointed director of the University of Pittsburgh's Center for Vaccine Research (CVR), which facilitates and conducts studies focused on the development of diagnostics, therapeutics, and vaccines for infectious diseases that pose risks to global public health and security. Duprex is an expert in measles and mumps viruses, and he studies barriers that stop animal viruses from jumping to humans. He officially joins the faculty in December 2018 and will hold the UPMC Jonas Salk Chair in Vaccine Research at Pitt. Duprex will also direct Pitt's Regional Biocontainment Laboratory, a facility that allows scientists to safely contain and examine potentially dangerous pathogens.

Duprex comes to Pitt from the Boston University School of Medicine, where he served as professor of microbiology and director of bioimaging at the university's National Emerging Infectious Diseases Laboratories.

In March 2018, Duprex was awarded a grant from the Human Frontiers Science Program—an international organization that funds pioneering biological research—to study the interactions of a newly discovered measles-like virus with its vampire bat host. His research team is relocating to Pittsburgh with him.

Goals for the CVR go beyond infectious disease studies, says Duprex. "The vast majority of vaccines are still given by injection, but Pitt has exciting, ongoing research to change that and deliver them in ways that don't involve large needles. This offers tremendous opportunities to develop temperature-stable vaccines, something that motivates me greatly since this could have a major impact on delivery in the developing world. New pathogens continually emerge, and keeping one step ahead is critical."

WOMEN'S CANCER EXPERT RECRUITED

Ronald Buckanovich, MD, PhD, a renowned physician-scientist and expert in gynecologic cancers, has been recruited to colead the Women's Cancer Research Center at the Magee-Womens Research Institute, the UPMC Ovarian Cancer Center of Excellence, and the Hillman Breast and Ovarian Cancer Program. He has been appointed professor of medicine and of obstetrics, gynecology, and reproductive sciences at the School of Medicine and will also join the **Comprehensive Ovarian Biology Research Center** (see page 31).

Buckanovich was recruited from the University of Michigan, where he was associate professor of internal medicine in the Divisions of Hematology and Oncology and Gynecological Oncology. He earned a PhD at Rockefeller University and an MD at Weill Medical College at Cornell University. He completed an internal medicine residency and hematology/oncology fellowship at the University of Pennsylvania.

Along with his team, Buckanovich recently developed a novel tumor model to study the role of human cancer stem cells, which are thought to drive cancer recurrence. The laboratory model mimics the human tumor environment closely and allows scientists to test new cancer therapies. His team has identified two novel compounds that directly target cancer stem cells and are being developed for first-in-human clinical trials.

In addition, the team has determined novel diagnostic serum biomarkers to potentially screen for ovarian cancer at its earliest stages.

Pitt Faculty Make the AAP, ASCI Grade

When it comes to Pitt faculty membership in two of medicine's most elite professional societies, 2018 could be the year of the Magnificent Six.

ASCI is a medical honor society celebrating scholarly achievement among up-and-coming biomedical researchers, who must be 50 or younger at the time of election. Each year, 60 physicians are chosen to join AAP in recognition of outstanding achievements in basic and clinical science and their application to clinical medicine.

From top, left: Ahmari, Dombrovski, Kaplan, Rosengart, Buysse, Sahel

Elected to the American Society for Clinical Investigation (ASCI) were:

Susanne Ahmari, MD, PhD, assistant professor of psychiatry. Ahmari earned her MD and PhD in molecular and cellular physiology at Stanford University and completed residency and postdoctoral training in anxiety and affective disorders at Columbia University. Her research interests focus on neural circuits underlying repetitive thoughts, the intersection of compulsive behaviors and anxiety, and the use of novel tools like optogenetics for circuit dissection.

Alexandre Dombrovski, MD, associate professor of psychiatry. Dombrovski earned his MD at Sechenov Moscow Medical Academy and completed residency and postdoctoral training in geriatric psychiatry at UPMC Western Psychiatric Hospital. His research interests include reinforcement learning, decision-making in suicidal behavior, and borderline personality disorder.

Daniel Kaplan, MD, PhD, professor of dermatology and of immunology. Kaplan received his MD and PhD degrees from Washington University in St. Louis, completed an internship at Beth Israel Hospital, Boston, a dermatology residency at Yale New Haven Hospital, and a postdoctoral fellowship at Yale University. His research interests focus on the function of skin-resident cells in determining the extent and character of skin inflammation, particularly the contributions of epidermal Langerhans cells and dermal dendritic cells in the development of adaptive T-cell immune responses, as well as local innate immune responses.

Matthew Rosengart, MD, MPH, professor of surgery, of critical care medicine, and of clinical and translational science. Rosengart earned his MD at the University of Alabama at Birmingham and his MPH at the University of Washington. He also finished general surgery residencies at both universities and fellowships in molecular biology, trauma, and critical care at the University of Washington. Rosengart has extensive experience examining the role of innate immunity in the systemic response to injury and infection, with particular expertise in phagocyte biology, calcium signaling, autophagy, mitochondrial function, and, recently, circadian biology, using clinically relevant models of sepsis and trauma.

Elected to the Association of American Physicians (AAP) were:

Daniel Buysse, MD, UPMC Professor of Sleep Medicine and professor of psychiatry and of clinical and translational science. Buysse's research focuses on the diagnosis, assessment, pathophysiology, and treatment of insomnia. He has published more than 350 peer-reviewed manuscripts and 100 book chapters or invited reviews. He is past president of the American Academy of Sleep Medicine, a current board member of the Sleep Research Society, and past deputy editor of *SLEEP* and the *Journal of Clinical Sleep Medicine*.

José-Alain Sahel, MD, Eye and Ear Foundation Professor and chair of ophthalmology. A member of the French Academy of Sciences, Sahel also leads the Vision Institute in Paris. He is a pioneer in the field of artificial retina and eye regenerative therapies. A major discovery by Sahel and colleagues is that the rod photoreceptors produce a trophic factor called RdCVF (rod-derived cone viability factor). This finding demonstrates the biological basis for paracrine interactions between rods and cones, which play a key role in maintaining photoreceptor viability. RdCVF, therefore, may preserve central vision in some blinding human diseases.

PEDIATRIC DIVISION HEADS NAMED

New Appointees in Gastroenterology and Newborn Medicine

An internationally recognized expert in liver disease, **Andrew Feranchak, MD**, has been appointed chief of the Pediatric Division of Gastroenterology, Hepatology, and Nutrition at UPMC Children's Hospital of Pittsburgh (CHP). He formerly served as professor of pediatrics and division director of pediatric gastroenterology at the University of Texas Southwestern Medical Center, Dallas.

A Pittsburgh native, Feranchak earned his medical degree at the University of Pittsburgh School of Medicine and completed a pediatrics residency at CHP. He completed a pediatric gastroenterology, hepatology, and nutrition fellowship at the University of Colorado. His research interests include the mechanisms of bile formation, biliary secretion, and liver cell volume regulation. These investigations will provide a foundation for new cholestatic liver disease therapies at CHP.

Thomas Diacovo, MD, has been appointed chief of the Division of Newborn Medicine and director of neonatal cardiovascular research at CHP's Heart Institute. Recognized as a leader in thrombosis research, he has made significant contributions to the development of pharmacological agents designed to treat neonatal intensive care patients with congenital heart disease, who are at high risk for forming blood clots.

Diacovo joined CHP from Columbia University Medical Center, where he was a professor of pediatrics, of pathology, and of cell biology. He received his MD from McGill University and completed postdoctoral training in cell biology and a fellowship in neonatology at Boston Children's Hospital and Harvard Medical School.

Gronenborn Joins Select Company

Angela Gronenborn, PhD, is among 213 individuals in a wide range of disciplines and professions who have been elected to the American Academy of Arts and Sciences in 2018. Gronenborn is Distinguished Professor, UPMC Rosalind Franklin Professor, and chair of structural biology in the School of Medicine. She is also professor of bioengineering, Swanson School of Engineering. Her research combines nuclear magnetic resonance spectroscopy with biophysics, biochemistry, and chemistry to investigate cellular processes at the molecular and atomic levels in relation to human disease. Her current interests focus on gene regulation and HIV pathogenesis.

Gronenborn was previously elected to the National Academy of Sciences (NAS), in 2007. In that elite group, she keeps company with fellow Pitt School of Medicine Distinguished Professors Yuan Chang, MD, Patrick S. Moore, MD, MPH, and Peter L. Strick, PhD. Also among School of Medicine faculty are 19 members of the National Academy of Medicine and four members of the National Academy of Inventors.

Pitt's Global Patent Ranking Rises to 21

University Also Sets New Record for Startups

Pitt innovators racked up **94 patents** for inventions in 2017. The University now ranks No. 21 worldwide, continuing a three-year ascent in position, according to a report compiled from United States Patent and Trademark Office data.

New patents ranged from a compound for diagnosing Alzheimer's disease to a system for measuring muscle motion to improve a baseball player's swing. Each year, the National Academy of Inventors and the Intellectual Property Owners Association ranks the top 100 universities named first on these documents, known as utility patents, to highlight the vital role patents play in university research and innovation.

The University also tracks its startups by fiscal year and set a new record of 22 such companies in fiscal year 2018. Among those companies founded by School of Medicine faculty are:

Globin Solutions Inc., a biotechnology startup formed in 2017 to develop a rapidly acting antidote to carbon monoxide poisoning. In April 2018, the company completed a Series A funding round of more than $5 million. Globin founders include **Mark T. Gladwin, MD**, Distinguished Professor of Medicine, Jack D. Myers Professor of Internal Medicine, and chair, Department of Medicine; **Jason J. Rose, MD, MBA**, assistant professor of medicine; and **Jesus Tejero Bravo, PhD**, associate professor of medicine.

LyGenesis Inc. is working to generate functional liver tissue—create mini-livers—using the body's own lymph nodes. Preclinical experiments have proven so successful that the concept became a featured subplot during the 2018 season of the ABC television series *Grey's Anatomy*. Company founders are **Eric Lagasse, PharmD, PhD**, associate professor of pathology, and **Paulo Fontes, MD**, who is affiliated with the Pitt-UPMC McGowan Institute for Regenerative Medicine.

Yealy Elected to National Academy

Donald M. Yealy, MD, professor and chair of emergency medicine, has been elected to the National Academy of Medicine (NAM), considered one of the highest honors in medicine.

Yealy earned his MD from the Medical College of Pennsylvania and completed an emergency medicine residency and clinical research fellowship at Pitt. He joined the Pitt faculty in 1993 as associate chief of what was then the Division of Emergency Medicine. He has been chair of the Department of Emergency Medicine since 2009.

Yealy serves as deputy editor of the *Annals of Emergency Medicine*. Yealy's research into prehospital airway management, acute care teamwork and fatigue, pneumonia, heart failure, pulmonary embolism, and sepsis has influenced clinical care in life-threatening situations, with his publications guiding national recommendations.

NAM was established in 1970 under the charter of the National Academy of Sciences to advise the nation's leadership on medical and health issues.

Cancer Organizations Honor Finn

Olivera J. Finn, PhD, Distinguished Professor of Immunology, received the 2017 Lloyd J. Old Award in Cancer Immunology from the American Association for Cancer Research and the Cancer Research Institute. The award, given yearly, recognizes an active cancer immunologist who has done pioneering, innovative, and influential research in cancer immunology.

Finn is credited with identifying the first tumor-associated T-cell target on human adenocarcinomas in 1989. Her research group also identified certain antibodies in cancers of the breast, pancreas, and colon, which led to the development of a cancer vaccine currently being tested in clinical trials.

Finn's research has been funded by the National Cancer Institute (NCI) continuously since 1984, and her current research is supported by an NCI Outstanding Investigator Award.

Andrew Schwartz, PhD, (left) touches a robotic hand manipulated by study participant Nathan Copeland (right), while members of the research team observe.

IN FOCUS: PITT'S BRAIN-COMPUTER INTERFACE RESEARCH TEAM

One October day in 2017, **Andrew Schwartz, PhD**, shared a table with Jan Scheuermann and journalist Raffi Khatchdourian at a University of Pittsburgh Brain Institute event.

Scheuermann, who has tetraplegia, is one of only three people to undergo a brain-computer interface (BCI) connection in the course of Pitt neuroscience research. A microelectrode array temporarily implanted in her motor cortex records neural activity associated with voluntary movements; those signals then direct the movement of a prosthetic arm and hand. The work is based, in part, on research by Schwartz, Distinguished Professor of Neurobiology.

Readers could learn more in the November 26, 2018, issue of *The New Yorker* in a feature written by Khatchdourian and narrated online by actor Julia Whelan. At nearly 13,000 words and 31 pages, "Degrees of Freedom" offers an in-depth look at the development of the brain-computer interface over decades—with particular focus on Schwartz, Scheuermann, and BCI research at Pitt.

The ultimate goal is to give people like Scheuermann access to a sophisticated, brain-powered prosthetic that responds like a natural arm and hand.

"As a scientist, you never expect anyone to care that much about your work," Schwartz says. "I don't think many people are lucky enough to get that kind of attention."

Although the positive feedback was nice ("that and $2 will get you a Coke," he quips), it's clear that he and the rest of the team are working hard to advance the work that Khatchdourian describes in such exquisite detail.

"What we've been good at doing is orienting the wrist and getting the [robotic] hand to move through space, but that's inconsequential unless you can also manipulate an object," says Schwartz. "And that's very challenging. We don't understand how the hand interacts with objects yet."

Currently, the BCI team is building additional computer algorithms based on measurements of neuronal output as nonhuman primates reach for and use a selection of objects in different ways and at variable speeds—what Schwartz calls "the science of object interaction."

In addition to Schwartz, **Jennifer Collinger, PhD**, and **Robert Gaunt, PhD**, both assistant professors of physical medicine and rehabilitation, are members of Pitt's human-related brain-computer prosthetics development team.

LEARN MORE AT: www.newyorker.com/magazine/2018/11/26/how-to-control-a-machine-with-your-brain.

Wanted: A Long and Healthy Life

Aging Institute Takes Aim at the Biology of Aging

The thing that interests **Toren Finkel, MD, PhD**, director of Pitt's Aging Institute and Beckwith Professor of Translational Medicine, is decoding the mechanics of aging—what happens when and why—and how we might be able to delay the process to stay healthier longer.

Finkel, who came to Pitt in late 2017 from the National Heart, Lung, and Blood Institute, has been busy recruiting new faculty in a variety of disciplines that converge on the challenges of aging and age-related diseases. The institute focuses on (1) basic science targeting the biology of aging, (2) drug discovery, and (3) clinical trials of therapies to slow aging and treat age-related illnesses.

"We've recruited 11 principal investigators—some of whom were at Pitt in other areas—who are interested in these questions," says Finkel.

Among them are **Yvonne S. Eisele, PhD**, and **Gang Li, PhD**, both assistant professors of medicine in the Division of Cardiology; and **Bokai Zhu, PhD**, assistant professor of medicine in the Division of Endocrinology and Metabolism.

Eisele's investigations focus on age-related neurodegenerative diseases—particularly those characterized by the misfolding and aggregation of specific proteins.

Li uses high-throughput approaches to identify and characterize functional single nucleotide polymorphisms relevant to risks for multiple sclerosis, rheumatoid arthritis, and Alzheimer's disease.

Zhu identified and continues to study the regulation and physiological function of the mammalian 12-hour circadian clock, with an emphasis on its roles in maintaining hepatic metabolic homeostasis and preventing age-associated disease.

Drug discovery at the institute is focused on developing compounds based on small-molecule biology to affect pathways leading to age-related diseases. For example, Department of Medicine faculty **Beibei "Bill" Chen, PhD**, **Yuan Liu, PhD**, and Finkel are forming a company to move some of their findings into the clinic with the assistance of UPMC Enterprises, says Finkel.

Finally, Pitt epidemiologist and geriatrician **Anne B. Newman, MD, MPH**, was appointed clinical director of the Aging Institute in May 2018. Newman is Katherine M. Detre Professor of Population Health Sciences and chair of epidemiology at the University of Pittsburgh Graduate School of Public Health.

"We have a unique and supportive environment at Pitt where almost every school has faculty members who are dedicated to improving the aging condition and who are working together to make our community the best place in the world to grow old," says Newman.

Pitt Faculty Rank among Most Highly Cited Scientists

Six School of Medicine faculty members were noted among the nation's most highly cited researchers for 2017—those whose papers ranked in the top 1 percent of articles published in the same year and field, according to the Web of Science. They are **Boris Birmaher, MD**, UPMC Professor of Early Onset Bipolar Disease and professor of psychiatry; **Thomas W. Kensler, PhD**, adjunct professor of pharmacology and chemical biology; **William E. Klunk, MD, PhD**, Distinguished Professor of Psychiatry, Levidow–Pittsburgh Foundation Professor of Alzheimer's Disease and Dementia Disorders, and professor of neurology; **David J. Kupfer, MD**, emeritus professor of psychiatry; **Chester A. Mathis, PhD**, Distinguished Professor of Radiology and Professor of Radiology PET Research; and **Dario A.A. Vignali, PhD**, Frank Dixon Professor of Cancer Immunology and vice chair of immunology.

A Visionary Future for Pittsburgh

Over the past two years, **José-Alain Sahel, MD**, has strengthened the School of Medicine's Department of Ophthalmology by recruiting new faculty and building on the school's existing culture of collaboration. A tangible building is also on the near horizon.

Groundbreaking for the nine-story, 410,000-square-foot **UPMC Vision and Rehabilitation Hospital** is scheduled for spring 2019 on the grounds of UPMC Mercy Hospital, with a projected opening in 2021.

The facility, dedicated to vision research and development of therapies to restore eye health, is designed to become a destination for patients seeking care from all over the world and an economic engine for its Uptown neighborhood.

"We have a good faculty aboard, several of whom are both clinicians and researchers, and we've expanded our capabilities in developmental biology, neuroscience, and stem cell biology," Sahel explained by phone after a November 2018 lecture at the Institut de la Vision in Paris, which he founded and still directs from abroad.

Sahel's vision is to create a hub in Pittsburgh similar to the Paris vision institute, which was established in 2008 as a site for translational research on treatments for currently untreatable inherited and age-related eye diseases. In just 10 years, the Paris institute has helped to reinvigorate its neighborhood and create more than 10 companies and 1,000 jobs.

"I'm quite happy with how things are going," says Sahel, who is Eye and Ear Foundation Professor and chair of ophthalmology, and director of the UPMC Eye Institute. He is working on another recruit to join 18 other scientists in Pittsburgh. Several already share time between the City of Lights and the "Paris of Appalachia."

"Together, the linked Paris and Pittsburgh hubs represent the largest academic study of ophthalmology anywhere in the world," George Fechter, chair of the Eye and Ear Foundation board, told the *Pittsburgh Business Times*.

Stem cell-based therapy developed by James Funderburgh, PhD, professor of ophthalmology, and Martha Funderburgh, lab manager at Pitt's Corneal Cell Biology Lab, has already shown success in treating corneal blindness in a clinical trial of 85 patients in India, Sahel said, adding that he wants to bring this option, which could reduce the necessity of corneal transplant, to Pittsburgh.

Other technological approaches Pitt scientists are investigating include gene and cell therapies, artificial retina stimulation, and new models to study the progression of degenerative eye diseases like retinopathies. Although the challenges are many, Sahel and his colleagues look ahead and see light.

GROUNDBREAKING FOR THE NINE-STORY, 410,000-SQUARE-FOOT UPMC VISION AND REHABILITATION FACILITY IS SCHEDULED FOR SPRING 2019 ON THE GROUNDS OF UPMC MERCY HOSPITAL, WITH A PROJECTED OPENING IN 2021.

IT'S CALLED MAKING AN ENTRANCE

It's March 16, and from the convivial confines of Morning Grounds—the coffee shop that opened in January on Scaife Hall's fifth floor—three first-year Pitt Med students watch a stream of people hurry into the Petersen Events Center for the Match Day ceremony. Camila Ortiz, Lauren Auster, and Karen Olson plan to join in the ceremonies (for motivation and free food); they met here before heading across the street because they wanted coffee, obviously, and also because Morning Grounds has become Pitt Med's new meet-up spot.

"It has doubled the time I spend in Scaife," says Olson, a 25-year-old Arizona native.

"I used to go home [after class] and study, but now I study here," adds Auster, a Case Western Reserve University alum.

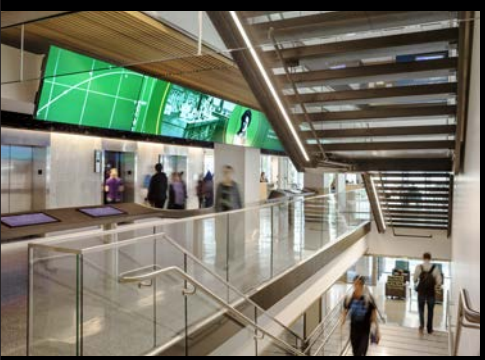
Ortiz, a 27-year-old Allegheny County native, likes the coffee shop's relaxed vibe. The space is warmly lit, with plenty of seating for those intent on getting acquainted with the Michaelis-Menten equation or fellow classmates. There's a pair of long tables for study groups, and a row of lounge chairs with adjustable desk arms faces floor-to-ceiling windows overlooking Terrace Street.

"You can have conversations with people and study," says Auster, 23. "And I like white noise when I study, so I like it here."

Morning Grounds was created as part of a Scaife Hall renovation project. The latest phase included replacing the escalators between the fourth and sixth floors with an open staircase, remodeling the lobbies on the fourth and fifth floors (including a glass "storefront" entrance), and adding a fifth-floor tribute to legendary Pitt Med physician-scientists (see story next page).

William Strober, a second-year Pitt Med student from Portola Valley, Calif., won the coffee shop's naming contest.

For his cleverness, Strober, 24, received a $100 gift card to Morning Grounds. He says he passed on puns involving an IV drip and bitter pills before landing on the winner. "I'm really happy that I'll be able to leave my mark on Pitt Med," Strober says.



DISPLAY FEATURES PITT PIONEERS OF MEDICINE

"They were guaranteed nothing, and they gave everything," Arthur S. Levine, MD, the John and Gertrude Petersen Dean of Medicine, said as he unveiled a digital and interactive tribute to five Pitt physician-scientists who changed the world. Those exiting the fifth floor elevators in Scaife Hall will now be reminded of the accomplishments of Bernard Fisher, MD, who transformed breast cancer treatment and our understanding of cancer; Peter Safar, MD, codeveloper of CPR who established the first modern ambulance service; Thomas Starzl, MD, PhD, giant of transplantation medicine; Maud Menten, MD, PhD, a biochemist whose work made drug development possible; and Jonas Salk, MD, of the killed-virus polio vaccine.

The doctors faced daunting challenges—Safar evaded the Nazi regime; Starzl dealt with medical residents who organized against his early attempts at liver transplantation; Menten, because she was a woman, was not allowed to be a university faculty member in her native Canada through most of her career.

"These are the people we want our students to think about as they confront their own obstacles and prepare to write the next chapters in American medicine," noted Levine.

The University will renovate the century-old former Ford Motor Company assembly plant and showroom to transform it into a world-class space for labs, offices, startup companies, and industry partners, aiming to attract the world's best scholars and students.

Centers Established To Focus on Immunotherapy and Genome Sequencing

The School of Medicine and UPMC made major commitments to advancing the biomedical and clinical sciences in 2018, announcing the establishment of new centers focusing on immunotherapy and the human genome.

The goal of the **UPMC Immune Transplant and Therapy Center** (ITTC) is to dramatically accelerate the translation of immunotherapy research findings from the laboratory to the clinic, where they can have immediate impact on the lives of patients.

With a $200 million investment by UPMC, the University will create a world-class space for labs, offices, startup companies, and industry partners. The property, adjacent to UPMC Hillman Cancer Center and UPMC Shadyside, represents Pitt's largest development project to date aimed at strengthening the city's innovation district. Building on Pitt and UPMC's longstanding record of success in patient care and research, ITTC investigators will seek ways to fine-tune the immune system to fight cancer cells, explore immune transplantation in conjunction with solid organ transplantation to reduce rejection and reliance on immunosuppressive medicines, and examine how immunotherapy can combat conditions like cardiovascular disease, obesity, and sickle cell anemia.

The goal of the **UPMC Genome Center** is to provide an advanced facility capable of large-scale genomic sequencing to support clinical diagnostics and research initiatives in precision medicine and immunotherapy.

Established with funding from the ITTC and the Institute for Precision Medicine at UPMC and Pitt, the center allows researchers and physicians to take advantage of rapid advances in genome sequencing, a process that reads the DNA molecules that make up the human genetic code. These advances have led to new ways of diagnosing diseases and created the emerging field of precision medicine, where treatments are tailored to each individual's genetic makeup.

In the future, the center also will leverage the extensive biobanking effort at Pitt, which includes more than half a million biological samples, and aims to work with industry partners to advance drug discovery and develop new therapies to help patients in the community and around the world.

THE GOAL OF THE UPMC IMMUNE TRANSPLANT AND THERAPY CENTER IS TO DRAMATICALLY ACCELERATE THE TRANSLATION OF IMMUNOTHERAPY RESEARCH FINDINGS FROM THE LABORATORY TO THE CLINIC, WHERE THEY CAN HAVE IMMEDIATE IMPACT ON THE LIVES OF PATIENTS.

PITT'S OWN WHO'S WHO

Each year, 12 Pitt scientists in the early stages of their careers are selected to present their work at a lunchtime lecture in Scaife Hall as part of the Senior Vice Chancellor's Research Seminar series. Most speakers are School of Medicine faculty, but 2018 also featured top young scientists from the Departments of Biological Sciences and Chemistry in the Dietrich School of Arts and Sciences, and a bioengineer from the Swanson School of Engineering. Whatever the topic, the speakers are invariably dynamic scientists who generate a great deal of interest and demonstrate the exciting, interdisciplinary nature of research at Pitt.

SPEAKERS FOR 2018 WERE:

JANUARY

Nara Lee, PhD
Assistant Professor of Microbiology and Molecular Genetics
Going Viral with New RNA Tools To Explore the Noncoding World

FEBRUARY

Yi Shi, PhD
Assistant Professor of Cell Biology
Structure of an Organelle-Sized Assembly

MARCH

Zachary Freyberg, MD, PhD
Assistant Professor of Psychiatry and of Cell Biology
Molecular Mechanisms of Dopamine Release

APRIL

Leah Byrne, PhD
Assistant Professor of Ophthalmology, of Neurobiology, and of Bioengineering
Viral Vector-Mediated Gene Therapy for Retinal Disease

MAY

Christopher Donnelly, PhD
Assistant Professor of Neurobiology
Optogenetic Modulation of Neurodegenerative Proteinopathies

JUNE

Brett A. Kaufman, PhD
Associate Professor of Medicine
Mitochondrial DNA at the Crossroads of Health and Disease

Anne-Ruxandra Carvunis, PhD
Assistant Professor of Computational and Systems Biology
Proto-Genes and De Novo *Gene Birth*

JULY

Prithu Sundd, PhD
Assistant Professor of Medicine and of Bioengineering
Innate Immune Mechanism of Pulmonary Pathophysiology in Sickle Cell Disease

SEPTEMBER

Scott W. Canna, MD
Assistant Professor of Pediatrics and of Immunology
In Natura Veritas*: Studying Rare Monogenic Disorders To Treat Sepsis*

OCTOBER

Kabirul Islam, PhD
Assistant Professor of Chemistry
Chemically Altered Epigenetic Landscape: Transcriptional Reprogramming at Precise Space and Time

NOVEMBER

Anne E. Carlson, PhD
Assistant Professor of Biological Sciences
A Chloride Channel Provides the First Defense against Abnormal Fertilization

DECEMBER

Hēth R. Turnquist, PhD
Associate Professor of Surgery and of Immunology
Sounding the Alarm, Fueling the Fire, and Controlling the Burn: Defining Functions of IL-33 in Transplantation

Carvunis Named Searle Scholar

Anne-Ruxandra Carvunis, PhD, assistant professor of computational and systems biology, will receive $300,000 over the next three years to support her research in evolutionary biology as part of the 2018 Searle Scholars Program.

The program names 15 scholars each year, funding exceptional young scientists who participate in high-risk, high-reward independent research and have recently become tenure-track assistant professors.

Carvunis studies how cells and organisms evolve, with a particular focus on the emergence of new genes, factors underlying how networks of interacting molecules form and change within cells, and how these networks differ across species.

She has received other honors, including a L'Oréal-UNESCO for Women in Science fellowship and a Pathway to Independence Award from the National Institutes of Health.

Reis Appointed Assistant Dean

Evelyn Cohen Reis, MD, has been appointed to the new position of assistant dean for the learning environment in the School of Medicine. She is also professor of pediatrics and of clinical and translational science and founding medical director of the Clinical and Translational Science Institute's Pediatric PittNet research network. In her new role, she will work closely with students and educators to enhance the learning environment by promoting professional behavior based on mutual dignity and respect and addressing specific reports of learner mistreatment.

Reis earned her MD at Harvard Medical School and completed a pediatric internship and residency at Boston Children's Hospital and a pediatric fellowship at Johns Hopkins University. She joined the Pitt faculty in 1994, where her career focused on professional development for students, residents, fellows, and faculty to enhance the doctor-patient relationship, build interpersonal communication skills, and preserve patient and physician well-being.

Jeremy Berg: A Voice for Science

For **Jeremy Berg, PhD**,editor-in-chief of the *Science* family of journals, the opportunity to advocate for science is part of a big job.

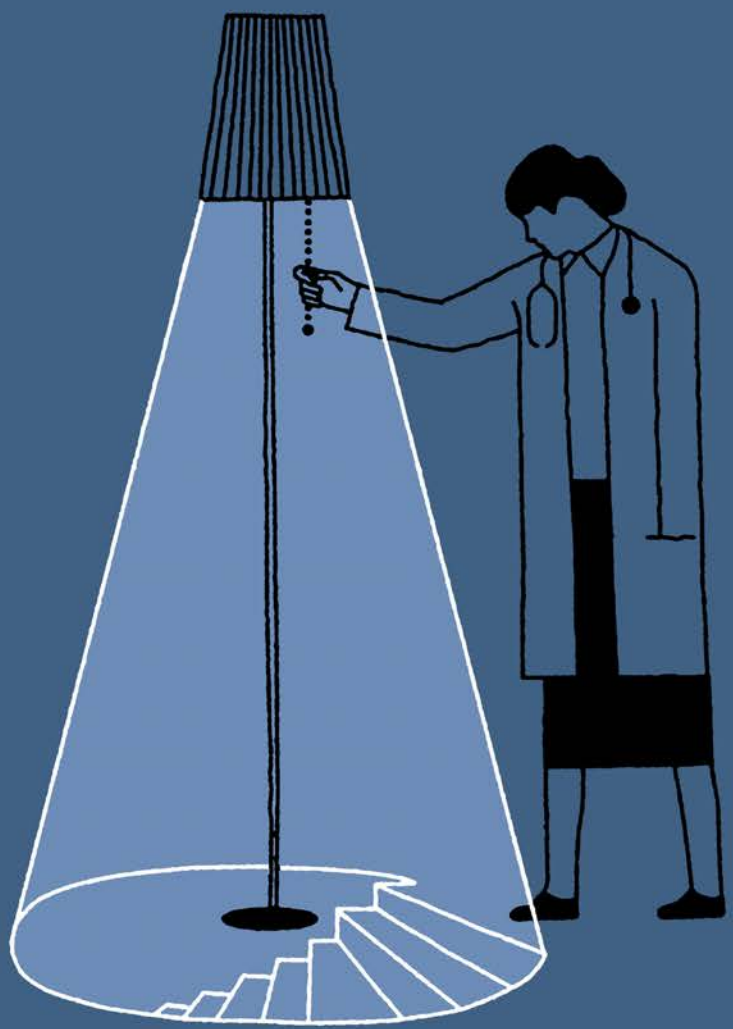
Fortunately, big jobs are nothing new for Berg, who continues to serve as Pitt's associate senior vice chancellor for science strategy and planning. Before that, he was director of the National Institute of General Medical Sciences of the National Institutes of Health.

In his first two years at Science, Berg has written commentaries on subjects as varied as data, taxes, gender issues, Environmental Protection Agency rules, improving scientific reproducibility, and government investment in science, pollution, and climate change, to name just a few.

"Imagine a world without facts," a recent editorial begins. "We are now living in a world where the reality of facts and the importance of scientific inquiry and responsible journalism are questioned with distressing frequency."

Current trends in public discourse, he continues, risk creating "a world of ignorance where many possibilities seem equally likely, causing subsequent discussions to proceed without much foundation and with outcomes determined by considerations other than facts."

In November 2018, Berg yielded editorial space to **José-Alain Sahel, MD**, Pitt's chair of ophthalmology, who urged scientists not to passively watch the worldwide rise of hatred, writing, "We are tasked with building a society of knowledge and care, where truth, integrity, and respect for all prevail."



Our mission is to educate science-based, skilled, and compassionate clinicians, as well as scientists whose biomedical research will better the human condition and advance our fundamental understanding of medical science.

Med Students Leap into Mentored Research

Pitt Med's Class of 2018 is the 11th cohort of graduating med students to complete the scholarly research requirement as a condition of graduation from the MD program. First introduced as an innovative (those less visionary called it "misguided") strategy to engage med students in mentored research throughout the course of their medical school experience, Pitt's Longitudinal Research Project has since become a model for other top medical schools attempting to incorporate a rigorous research component into the MD curriculum.

Arthur S. Levine, MD, dean of the medical school since 1998, recalls, "When I first suggested that every Pitt medical student should be required to do research, I was warned that, (1) applications to the medical school would plummet, (2) the quality of applicants would decline, and (3) I would not last long as dean. Well, none of those things has happened," says Levine, who celebrated 20 years as dean in 2018. He notes that admission to the medical school has become increasingly competitive. "And the fact that other top medical schools have followed our lead tells me we're doing something right."

The best medical students, it turns out, see the value of engaging in biomedical research. In fact, they increasingly recognize that their medical education would be incomplete without it.

THE BEST MEDICAL STUDENTS, IT TURNS OUT, SEE THE VALUE OF ENGAGING IN BIOMEDICAL RESEARCH. IN FACT, THEY INCREASINGLY RECOGNIZE THAT THEIR MEDICAL EDUCATION WOULD BE INCOMPLETE WITHOUT IT.

LONGITUDINAL RESEARCH PROJECT BY THE NUMBERS / CLASS OF 2018

Beginning in year one of medical school, students in the Class of 2018 embraced the opportunity to engage in research through the Longitudinal Research Project. As of graduation day, the fruits of their labor include:

117
med students completed a research project
78 percent (of the class) participated in summer research between their first and second years of med school

258
peer-reviewed publications
plus an additional 54 submitted and/or under review

360
presentations at national and international meetings

49
national or state awards

80
local awards

2018 O'MALLEY AWARD WINNERS

At Scholars Day 2018, four graduating MD students were individually honored with a Bert and Sally O'Malley Award for Outstanding Medical Student Research.

The best of the best from the Class of 2018:

4-Year
Basic Science Research

NETANYA POLLOCK, MD
c-Fes Kinase and MALT1 Protease Cooperation in AGTR1+ Breast Carcinoma

Residency Match:
Pediatrics, Children's Hospital Boston

Mentor:
Linda McAllister-Lucas, MD, PhD, Associate Professor of Pediatrics and of Microbiology and Molecular Genetics

4-Year
Clinical Science Research

ARPAN PRABHU, MD
Radiation Oncology and YouTube: Assessing Informed Consent in Brachytherapy Patient Education Videos

Residency Match:
Radiation Oncology, University of Arkansas College of Medicine, Little Rock

Mentor:
Sushil Beriwal, MD, Professor of Radiation Oncology

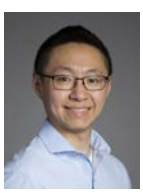
5-Year
Clinical Science Research

JAMES DOLEZAL, MD
Machine Learning Reveals Patterns of Ribosomal Protein Expression in Human Cancers

Residency Match:
Internal Medicine, University of Chicago Medical Center

Mentor:
Edward Prochownik, MD, PhD, Professor of Pediatrics and of Clinical and Translational Science

5-Year
Basic Science Research



XIAO ZHU, MD
Role of the Receptor for Activated C Kinase 1 in Angiotensin-II Induced Contractions of Preglomerular Vascular Smooth Muscle Cells

Residency Match:
Plastic Surgery, UPMC Medical Education Program, University of Pittsburgh

Mentor:
Edwin Jackson, PhD, Professor of Pharmacology and Chemical Biology and of Medicine, Division of Renal-Electrolyte

MED SCHOOL DEMOGRAPHICS

6,874 students applied and **737 were interviewed** for the **162 available positions** in the medical school **Class of 2022**.

As of the **2018–19** academic year, **579 MD students** are registered in the School of Medicine, including **315 women (54 percent)** and **264 (46 percent) men**. Of these, **187 (32 percent) are Pennsylvania residents**; **approximately 17 percent** of Pitt medical students **are from groups that are underrepresented within the medical profession**.

There are **308 registrants in PhD programs** (including those in the Medical Scientist Training Program), **134 students in MS programs**, and **29 students in certificate programs**.

The School of Medicine has **2,350 regular** and **1,664 volunteer faculty members**. Of these, **70 are current members of the Academy of Master Educators**, an organization that recognizes and rewards excellence in medical education.

Educator Spotlight

SCOTT MAURER ON EMOTIONAL INTEL

Overheard

For pediatrician **Scott Maurer, MD**, work is a practice in empathy. Maurer, associate professor of pediatrics and chief of the Division of Palliative Medicine and Supportive Care at UPMC Children's Hospital of Pittsburgh, serves families experiencing the pain of having a child with a chronic or terminal illness. His leadership in the classroom and in the hospital goes beyond teaching the nuts and bolts of patient care; he strives to model and teach emotional intelligence, which he says is necessary to the health of both patients and staff.

How do you and your colleagues maintain the stamina to witness and hold grief every day at work?

Sometimes I offer a kind word, or I pull someone aside when I know they have had a stressful day. I am a firm believer that the human experience is a shared experience. If something happens to you, it is helpful and cathartic if you can tell somebody about it. My colleagues and I are a family, and one person's experience affects the rest of [us]. I rely on my colleagues as they rely on me.

Is emotional intelligence something that can be learned?

Often people think of communication skills as something that is just part of one's natural ability, but communication is a teachable skill. I have the honor to be mentored by Bob Arnold, who is head of palliative medicine at Pitt and a cofounder of VitalTalk, a nonprofit dedicated to supporting emotional skills in medical professionals. I teach students that when dealing with patients and their families, the first step is to expect an emotional response, and then to identify the present emotion, and lastly to follow that observation with an expression of support and understanding.

Why is emotional intelligence crucial to being a successful doctor?

Study after study shows that parents take your medical knowledge for granted, and the way they are going to judge your skills as a physician is how compassionate you are and how well you communicate with them. Medicine is one of those strange things in that you have to rapidly build rapport with somebody. I know if someone trusts me. I have become very good at reading body language and reading nonverbal cues.

Next Gen

Postdoctoral fellow **Akash Verma, PhD**, earned the cover story in a November 2017 issue of *Science Immunology* (see page 34) when he identified how the human immune system responds to an oral fungus by the name of *Candida albicans*. Verma works in the Gaffen Lab, where the team identified the protein responsible for sounding the alarm when *C. albicans* invades the mouth. The research could lead to better treatment options for those suffering from a condition called oral thrush. Verma's advisor, Sarah Gaffen, PhD, is the Gerald P. Rodnan Professor of Rheumatology in the Department of Immunology.

Filip Istvanic knows about bubble bursting. A student in the Physician Scientist Training Program, Istvanic developed a method using microbubbles, stimulated by ultrasound, to break apart tiny blood clots in blood vessels. Istvanic gave a talk on the subject at the European Symposium on Ultrasound Contrast Imaging in Rotterdam in January 2018. The Howard Hughes Medical Institute's Medical Research Fellows Program supported his efforts. Istvanic began this work under his advisor, John Pacella, MD, associate professor of medicine, and Flordeliza Villanueva, MD, professor of medicine and vice chair for preclinical research.

Postdoctoral scholar in the Department of Biomedical Informatics **Sarah Aboutalib, PhD**, won a Radiological Society of North America Trainee Research Prize for her abstract on a computerized method aimed at classifying mammogram images in breast cancer patients. She worked with Shandong Wu, PhD, assistant professor of radiology and biomedical informatics.

Mehret Birru Talabi, MD, PhD, a 2011 graduate of Pitt's Medical Scientist Training Program, was named one of 10 Distinguished Fellows by the American College of Rheumatology in 2017 for her focus on women's health in rheumatic diseases. Birru Talabi, now an assistant professor of medicine, says she'd like to see a larger focus on women's health in her field. "We need to figure out how to train providers — gynecologists, primary care physicians, rheumatologists — to make sure that issues related to contraception, reproductive health, and pregnancy planning are part of the ongoing conversation with patients."

Pitt Med student **Stephen Canton** claimed the title Future City 2018 Alumnus of the Year in January 2018, landing him a spot as a judge at the 2018 Future City competition. In both 2004 and 2005, Canton participated in the competition, which exposes middle school students to the principles of engineering. "It's the reason I went into engineering," says Canton, who got his degree in bioengineering from Pitt in 2013. Canton is now developing a virtual reality training program that simulates how to scrub in.

A MATCH MADE IN PITTSBURGH

Match Day 2018 at the University of Pittsburgh was a lively celebration of the hard work and accomplishments of our graduating med students. Held in the bright and airy confines of the Petersen Events Center lobby, Pitt's Match Day festivities included dance music on full blast and a wall map of the United States, which students decorated with pushpins after they learned where in the world they would begin their residency training.

More than 18,000 graduating med students participated in the match across the nation. One hundred and forty Pitt students learned their residency assignments on Match Day. The Class of 2018 posted a record number of matches in two highly competitive specialties—10 in psychiatry and 10 in orthopaedic surgery. The programs attracting the most Pitt grads (after UPMC, which welcomes 37 new Pitt Med graduates to its training programs in 2018) include Johns Hopkins University, the University of Washington, and the University of Michigan.

Numerous Pitt Med students reported that research experience gained at Pitt paid off when it was time to select and interview for residency programs. While conducting mentored research as students, many feel that they got to "test drive" a specialty and a research area, giving them greater confidence in choosing a career path. Others added that they were glad they could speak about research with confidence and from experience in residency interviews.

GRADUATION KEYNOTE STRESSES MEDICINE AND MEANING

The 2018 School of Medicine Diploma Ceremony took place on May 21, in the historic Soldiers and Sailors Memorial Hall. The keynote speaker was **Dayna Bowen Matthew, JD, PhD**, William L. Matheson and Robert M. Morgenthau Distinguished Professor of Law and F. Palmer Weber Research Professor of Civil Liberties and Human Rights at the University of Virginia School of Law. Matthew is a long-standing advocate for health care equality and author of the book *Just Medicine: A Cure for Racial Inequality in American Health Care.* Matthew cofounded the Colorado Health Equity Project to help low-income people access better health care and, in 2015, worked for the U.S. Environmental Protection Agency's Office of Civil Rights to assist historically vulnerable communities besieged by pollution.

MED STUDENT MINGLES WITH NOBEL LAUREATES AT LINDAU

Tolani Olonisakin attended the 68th Lindau Nobel Laureate Meeting in June 2018. At this prestigious annual gathering, Nobel laureates mingle and share scientific inspiration with hundreds of students and postdoctoral fellows.

The 2018 meeting not only featured geographic diversity (with 43 Nobel laureates and students from 84 countries), but also, for the first time, women made up half of all student attendees. Eighteen University of Pittsburgh students have attended Lindau since 2004, when the organizers began tracking representation. Olonisakin, an MD/PhD student in Pitt's Medical Scientist Training Program, was the only Pitt student selected for 2018.

Olonisakin described the experience as a unique opportunity to meet some of the top scientists in the world and to network with other young scientists from around the world. She appreciated the open exchange with her peers from Turkey, South Africa, Spain, and many other countries. She aims to keep in touch with many. "Lindau fosters collaboration among participants, even beyond the meeting," Olonisakin told *Pitt Med* magazine. "Alumni are closely followed, and their continued scientific success is paramount."

Olonisakin's research in the lab of Janet Lee, MD, professor of medicine, focuses on bacteria like *Klebsiella pneumonia*, which have caused a growing number of deadly outbreaks in recent years due to multiple antibiotic resistant strains. She hopes to contribute to development of new tools to fight such infections.

While studying infections and immunity, Olonisakin is trying to forge her own career path as a physician-scientist, although her exact focus is yet to be determined. As she moves forward, she appreciates having the words of 2003 Nobel Laureate Peter Agre, MD, to help guide her decisions.

"He said to ask important questions that are beneficial to mankind," Olonisakin said. "As I go further along my career, that will always be in the back of my head—not to go where the money is but to ask the important questions that will benefit mankind."

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 or the Physician Scientist Training Program.

CSTP

The Clinical Scientist Training Program (CSTP) offers a leg up for medical students who show an interest in and a talent for clinical research. Select students whose 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.

Four members of the Class of 2018 are products of Pitt's CSTP, having previously completed the research year.

CSTP GRADUATES AND THEIR RESIDENCY PROGRAMS:

GABRIELA ALGARROBA, MD

Residency Match:
Obstetrics/Gynecology, New York University, Winthrop Hospital, Mineola, N.Y.

Mentor:
Debra Bogen, MD, Professor of Pediatrics, of Psychiatry, and of Clinical and Translational Science

JAMES DOLEZAL, MD

Residency Match:
Internal Medicine, University of Chicago Medical Center

Mentor:
Edward Prochownik, MD, PhD, Professor of Pediatrics and of Clinical and Translational Science

MAULIN SHAH, MD

Residency Match:
Internal Medicine, Cedars-Sinai Medical Center, University of California, Los Angeles

Mentor:
Jon Davison, MD, Associate Professor of Pathology and of Clinical and Translational Science

SHANTAL VILLALOBOS, MD

Residency Match:
Family Medicine, UPMC Medical Education Program, University of Pittsburgh

Mentor:
Evan Waxman, MD, PhD, Associate Professor of Ophthalmology

PSTP

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 2018 included seven graduating PSTP students who matched to top residency programs in highly competitive medical specialties.

PSTP GRADUATES AND THEIR RESIDENCY PROGRAMS:

BERKCAN AKPINAR, MD

"I chose PSTP because I enjoy and value pursuing research in the setting of improving patient care."

Residency Match:
Orthopaedic Surgery, New York University, New York City

Mentor:
L. Dade Lunsford, MD, Distinguished Professor and Lars Leksell Professor of Neurological Surgery

KASSANDRA ALLBRIGHT, MD

"I knew I wanted to pursue a career with research as a component, but I didn't want to complete a full MD/PhD program or lose track of the clinical pieces of my career and training."

Residency Match:
Internal Medicine, Johns Hopkins Hospital, Baltimore

Mentor:
Kacey G. Marra, PhD, Associate Professor of Plastic Surgery and of Bioengineering

RAFEY FEROZE, MD

"It gave me the unique opportunity to meet fellow medical students with a passion for laboratory research and allowed me to pursue cutting-edge biomedical science."

Residency Match:
Internal Medicine, University of Michigan, Ann Arbor

Mentor:
Flordeliza Villanueva, MD, Professor of Medicine, Division of Cardiology

NAOMI GUNAWARDENA, MD

"I wanted to have the opportunity to dedicate more time to my research project than is typically available in medical school."

Residency Match:
Pediatrics, UPMC Medical Education Program, University of Pittsburgh

Mentor:
Grant Bullock, MD, PhD, Assistant Professor of Pathology

MARSHALL HUANG, MD

"The program offers a unique opportunity to spend a full year on basic science research without concurrent clinical responsibilities. This experience, combined with the didactic curriculum and regular discussion sessions, allowed me to develop skills essential for success in an academic career."

Residency Match:
Ophthalmology, University of Utah, Salt Lake City

Mentor:
Robert Friedlander, MD, Walter E. Dandy Professor and Chair of Neurological Surgery

THOMAS WOZNY, MD

"I had a passion for basic science and translational research that I knew I wanted to translate into a career in academic medicine. The program's emphasis on longitudinal development through an individualized, trainee-driven curriculum was evident from the outset and has already proven to be invaluable in my own scientific and clinical pursuits."

Residency Match:
Neurological Surgery, UPMC Medical Education Program, University of Pittsburgh

Mentor:
R. Mark Richardson, MD, PhD, Associate Professor of Neurological Surgery

XIAO ZHU, MD

"I wanted to be among peers with like-minded goals of becoming the next generation of physician-scientists, innovating, and contributing to a brighter future for patients."

Residency Match:
Plastic Surgery, UPMC Medical Education Program, University of Pittsburgh

Mentor:
Edwin K. Jackson, PhD, Professor of Pharmacology and Chemical Biology, Professor of Medicine, Division of Renal-Electrolyte

PSTP Students Win Prestigious HHMI Fellowships for 2018–19

Two Pitt PSTP students were awarded highly coveted research training fellowships through the Howard Hughes Medical Institute (HHMI) Medical Research Fellows Program in 2018. The students will be supported through a one-year leave of absence, during which they'll dedicate themselves to their research projects and associated training.

HHMI selected 66 top medical and veterinary students from around the nation to conduct full-time biomedical research in its Medical Research Fellows Program. The $3 million annual initiative is designed to develop the next generation of physician-scientists by giving the students a full year of mentored research training. HHMI fellows each receive $43,000 in grant support as they immerse themselves in their basic, translational, or applied biomedical research.

As an HHMI fellow, Aneta Kowalski hopes to build on what she learned in her first two years of med school. "I found our cardiology course to be the most fascinating, so during my research year, I'm excited to be learning about cardiology from a basic science point of view. I hope to not only refine my technical skills and produce sound data, but more importantly, I want to become the mini 'expert' on my project."

Pitt students have a strong track record in HHMI's fellowship program; successful students often credit the specialized grant writing course they take between their 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.

In addition to financial support and the protected research time, HHMI provides fellows with extensive networking opportunities and a good deal of social support. Successful research fellows have the option of requesting a second year of funding.

"I've met distinguished physician-scientists as well as research-minded medical students from across the country," said Audrey Kindsfather, who earned her second consecutive year of HHMI support. "I hope to use my second year in the program to continue to learn how to effectively communicate my research to physicians, scientists, and the general public. By studying how maternal age and fertility treatments affect embryos both individually and together, I hope to contribute to the growing knowledge base used by clinicians to select the best embryos for transfer to the mother."

PITT'S HHMI MEDICAL RESEARCH FELLOWS AND THEIR PROJECTS:

ANETA KOWALSKI (1ST-YEAR HHMI FELLOW)

Research Title/Topic:
Role of CREBRF and Its Metabolic-Risk Variant in Cardiac Metabolism and Function

Mentor:
Erin Kershaw, MD, Professor of Diabetes and Obesity Research, Associate Professor of Medicine, and Chief, Division of Endocrinology and Metabolism

AUDREY KINDSFATHER (2ND-YEAR HHMI FELLOW)

Research Title/Topic:
Investigating the Combined Effects of Advanced Maternal Age and Assisted Reproductive Technologies on Mitochondria and Genomic Imprinting in Mouse Embryos

Mentor:
Melissa Mann, PhD, Associate Professor of Obstetrics, Gynecology, and Reproductive Sciences

83 Med Students Pursue Dual MD/PhD Degrees

The Medical Scientist Training Program (MSTP) provides an opportunity for medical students interested in a biomedical research career to undertake doctoral work at either the University of Pittsburgh or Carnegie Mellon University in basic science, engineering, or public health. After two years of medical school, students complete PhD work before returning to medical training. Both degrees are completed in an average of seven to eight years. The program, funded by a grant from NIH with support from the Office of the Dean, offers full tuition and a yearly stipend.

In 2018, Pitt said farewell to 11 of these budding physician-scientists, who have matched to some of the most prestigious residency programs in the nation.

Including the 14 new students beginning their first year of medical school in 2018, Pitt's MSTP has 83 students currently—big enough to maintain a lively and diverse group dynamic. In the 2018–19 academic year, MSTP maintains its highest level of NIH support since its founding 30 years ago, with 20 Pitt MD/PhD students funded by NIH per year.

MSTP GRADUATE IS ON MIT'S TOP INNOVATORS LIST

As she prepared for her final year in Pitt's Medical Scientist Training Program in summer 2017, Shinjini Kundu made some Internet waves with a well-received TEDx talk called "Artificial Intelligence Can Change the Future of Medical Diagnosis." In the video, Kundu explores a medical future in which machine learning and artificial intelligence allow physicians to glean knowledge from medical images and thereby predict and prevent disease to an extent previously unimaginable. Kundu summarizes the research, including her own innovations, that indicate this is indeed possible.

Kundu has been working to make that future a reality. During her time in the MSTP, she earned a PhD in biomedical engineering at Carnegie Mellon University and created an artificial intelligence system that analyzes biomedical images to find patterns undetectable to the naked eye. In 2018, her innovations caught the attention of *MIT Technology Review*, which named her to its prestigious annual list of 35 Innovators Under 35.

Kundu's technique, transport-based morphometry (TBM), is based on the mathematics of optimal mass transport and enables fully automated, data-driven analysis and statistical results that are easily interpreted biologically. She and her colleagues have used TBM in a variety of clinical applications, including osteoarthritis, which traditionally can't be diagnosed until symptoms manifest and irreversible damage is visible on X-ray. According to their results, TBM enables detection of osteoarthritis three years in advance of symptoms with 86 percent accuracy based on the appearance of cartilage on knee MRIs.

As a graduate student, Kundu was inspired by the powerful effect that engineers could have on patient care. Now an MD/PhD Pitt graduate and a resident in diagnostic radiology at Johns Hopkins Hospital in Baltimore, she aims to become a leading expert in biomedical imaging technology by combining patient care with her passion for imaging technology and signal processing research.

PITT'S 2018 MSTP GRADUATES AND THEIR RESIDENCY MATCHES:

D. WONJAE CHUNG, MD, PHD
Residency Match:
Psychiatry, UPMC Medical Education, University of Pittsburgh
Mentor:
David Lewis, MD, Distinguished Professor, Thomas Detre Professor, and Chair of Psychiatry

XUAN DING, MD, PHD
Residency Match:
Internal Medicine, Vanderbilt University Medical Center, Nashville, Tenn.
Mentor:
Kang Kim, PhD, Associate Professor of Medicine, Division of Cardiology; Associate Professor of Bioengineering

TAYLOR J. EDDENS, MD, PHD
Residency Match:
Pediatrics, UPMC Medical Education, University of Pittsburgh
Mentor:
Jay Kolls, MD, Adjunct Professor of Medicine; Professor of Medicine and of Pediatrics, Tulane University School of Medicine

MATTHEW A. GERAMITA, MD, PHD
Residency Match:
Psychiatry, UPMC Medical Education, University of Pittsburgh
Mentor:
Nathan Urban, PhD, Professor of Neurobiology

SHINJINI KUNDU, MD, PHD
Residency Match:
Diagnostic Radiology, Johns Hopkins Hospital, Baltimore
Mentor:
Gustavo Rohde, PhD, Professor of Electrical and Computer Engineering, Carnegie Mellon University

JOHANNES C. KUTTEN, MD, PHD
Residency Match:
Anesthesiology, University of Massachusetts Medical School, Worcester
Mentor:
Jeffrey Isenberg, MD, MPH, Associate Professor of Medicine and of Pharmacology and Chemical Biology; Associate Professor of Bioengineering

JARED L. MOREINES, MD, PHD
Residency Match:
Internal Medicine, Yale New Haven Hospital, New Haven, Conn.
Mentor:
Anthony Grace, PhD, Distinguished Professor of Neuroscience; Professor of Psychiatry and of Psychology

JOSIAH E. RADDER, MD, PHD
Residency Match:
Internal Medicine, UPMC Medical Education, University of Pittsburgh
Mentor:
Steven Shapiro, MD, Distinguished Professor of Medicine and Professor of Clinical and Translational Science

EMILY M. ROSENBERGER, MD, PHD
Residency Match:
Internal Medicine, UPMC Medical Education, University of Pittsburgh
Mentor:
Mary Amanda Dew, PhD, Professor of Psychiatry, of Epidemiology, of Biostatistics, of Psychology, and of Clinical and Translational Science

BENJAMIN B. ROTHRAUFF, MD, PHD
Residency Match:
Postdoctoral Fellow, University of Pittsburgh
Mentor:
Rocky Tuan, PhD, Distinguished Professor of Orthopaedic Surgery

BO WANG, MD, PHD
Residency Match:
Ophthalmology, Johns Hopkins Wilmer Eye Institute, Baltimore
Mentor:
Joel Schuman, MD, Adjunct Professor of Ophthalmology; Chair, Department of Ophthalmology, New York University

Award-Winning MSTP Research Projects

On average over the past six years, Pitt 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:

HEATHER ACUFF
Structural-Functioning Relationships: a Multimodal Neuroimaging Approach to the Study of Children and Adolescents Genetically at Risk for Bipolar Disorder
National Institute of Mental Health

Mentor:
Mary L. Phillips, MD, Pittsburgh Foundation–Emmerling Professor of Psychotic Disorders, Department of Psychiatry

MIRANDA CULLEY
Frataxin Loss Induces Endothelial Dysfunction To Promote Pulmonary Hypertension
National Heart, Lung, and Blood Institute

Mentor:
Stephen Chan, MD, PhD, Associate Professor of Medicine, Division of Cardiology

JARED KOPELMAN
Examining the Role of EAAT3 in OCD-like Behavior
National Institute of Mental Health

Mentor:
Susanne E. Ahmari, MD, PhD, Assistant Professor of Psychiatry

ANDREW LAMADE
Targeting Mitochondrial PARP1 in Neuronal Ischemia-Reperfusion Injury
National Heart, Lung, and Blood Institute

Mentor:
Hülya Bayır, MD, Professor of Critical Care Pediatric Research and Professor of Critical Care Medicine

OTHER NOTABLE AWARDS TO MSTP STUDENTS:

ATINUKE DOSUNMU-OGUNBI
2018 Minority Medical Student Award, American Society of Hematology

Mentor:
Enrico Novelli, MD, MS, Associate Professor of Medicine, Division of Hematology/Oncology

MARIA LY
American Association for Geriatric Psychiatry Scholar Award

Mentor:
Howard Aizenstein, MD, PhD, Charles F. Reynolds III and Ellen G. Detlefsen Professor of Geriatric Psychiatry; Professor of Bioengineering; Professor of Clinical and Translational Science

TOLANI OLONISAKIN
American Heart Association Predoctoral Fellowship
Role of Thrombospondin-1 in Platelet-Mediated Protection during *Pseudomonas aeruginosa*-Induced Injury

Mentor:
Janet Lee, MD, Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine

RESEARCH FELLOWSHIPS SEND MSTP STUDENTS TO TOP FRENCH LABS

Thanks to fellowships from the Embassy of France, two Pitt MSTP students will pursue unique research experiences in France in 2018-19. The Chateaubriand Fellowship allows outstanding PhD students from American universities to conduct research in France for up to nine months.

MD/PhD students Gaelen Dwyer and Laura Molina began their PhD studies in 2017, after completing the first two years of medical school. Before embarking upon the final two years of medical school, each will spend four years in the laboratory completing PhD thesis research. Dwyer is a microbiology and immunology student in the laboratory of Hēth Turnquist, PhD, associate professor of surgery and of immunology. In France, she'll work with cytokine signaling expert Jean-Philippe Girard, PhD, director of the Institute of Pharmacology and Structural Biology at the University of Toulouse and senior research director at France's Institute of Health and Medical Research (Inserm). Dwyer will explore proteomic techniques and apply them to her own research on cytokine signaling networks in graft-versus-host disease.

Molina's graduate work is in the med school's cellular and molecular pathology program. She works in the lab of Satdarshan (Paul) Monga, MD, who holds an endowed chair as Professor of Experimental Pathology and has a secondary appointment as professor of medicine. Molina is studying how developmental signaling pathways contribute to pediatric liver disease. With the support of the Chateaubriand Fellowship, she'll work in France with Jessica Zucman-Rossi, MD, PhD, a world-renowned expert in the study of liver tumors and leader of Inserm's research team exploring the functional genomics of solid tumors. Molina will gain valuable experience with computational biology techniques and apply them to the study of liver cancer.

Chateaubriand fellows are selected through a merit-based competition involving expert evaluators in both countries. Between 40 and 50 students in science, technology, and health fields are accepted annually, plus several more in the humanities and social sciences. The program allows top American doctoral students to initiate or reinforce collaborations, partnerships, or joint projects between French and American research teams. This fellowship is offered by the Office for Science and Technology of the Embassy of France in partnership with American universities, the National Science Foundation, and French research organizations.

WHITE COAT PHOTO BOOTH

Since 1998, the School of Medicine has celebrated its incoming class with a ceremony marking their entrance into the medical profession. In what has become a rite of passage, the students are bestowed a crisp white coat (donated by the Medical Alumni Association) and lots of congratulations. This year, the August ceremony, held at Carnegie Music Hall of Pittsburgh, was positively resplendent.

Seen at the affair: members of the Pittsburgh Ballet Theatre, the Pittsburgh Symphony Orchestra, and Pittsburgh Opera companies (all of whom performed); Dean Arthur S. Levine and other Pitt Med luminaries; KDKA-TV news anchor Susan Koeppen (who relayed the story of how two Pitt medical students helped save her life in 2011—lifesavers Vanessa Franco and Ranmal Samarasinghe, both MD/PhD Class of 2012, joined her at the event); and ceremony hosts and main sponsors orthopaedic surgery chair Freddie Fu, MD, and Hilda Pang Fu.

But the real stars of the show were the 162 matriculating students. We invited them to take turns posing as *Pitt Med* cover models at our pop-up photo booth. We're only able to show a few shots here. But as you'll see on these pages, the docs-to-be didn't want to leave out the people who helped them get this far. Among our most popular tag lines: "Hi Mom!"

Allied With Patients, Med Students Discover a New Perspective

In 2012, med school dean Arthur S. Levine, MD, proposed a new program to 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 such experience is the mandatory Longitudinal Research Project—the four-year research endeavor Pitt med students undertake. This was like adding another, very different pillar to support the curriculum.

Directed by Robin Maier, MD, MA, assistant professor of family medicine, and codirector Lisa Podgurksi, MD, clinical assistant professor of medicine, the Longitudinal Alliance Project (LAP) allows students to see the medical system from the patient's perspective.

Med students report that the experience completely changes the tone of a clinical experience, because after medical appointments, students debrief with patients instead of medical professionals. They might discuss what information was conveyed by a physician, whether it was clearly communicated, and whether patients and family members feel that their concerns are being addressed.

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 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.

A great deal of learning happens in student group sessions, where students give presentations on the medical science behind their patients' health concerns and also reflect on the patient experience. The variety of medical conditions and individual patient circumstances that each student encounters make for dynamic discussion.

"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 imagine what kind of doctors they want to be.

Interprofessional Care

All health professionals—physicians, surgeons, scientists, dental specialists, nurses, pharmacists, and many others—share the fundamental and sacred duty to care for and heal the patient. With so much expertise spread across so many individuals, it's become clear that patients are served best by interprofessional teams working in multidisciplinary collaboration

That's why interprofessionalism is fundamental to all health sciences education at the University of Pittsburgh. First-year medical students learn this in their first months on campus when they participate in the Interprofessional Forum with their peers from the Schools of Nursing, Dental Medicine, Pharmacy, Public Health, and Health and Rehabilitation Sciences.

Throughout their med school experience, students learn that faculty clinicians and students move easily among all six Schools of the Health Sciences, frequently coming together to care for patients in the clinical facilities of UPMC.

MEDICAL SCHOOL ISN'T JUST FOR MDS

In addition to nearly 600 students in the MD program, more than 300 students are pursuing PhD degrees in programs like neuroscience, biomedical informatics, computational biology, molecular biophysics and structural biology, and clinical and translational science.

The **Interdisciplinary Biomedical Graduate Program** (PhD) combines a core curriculum with research and a dissertation focused on a choice of cell biology and molecular physiology, cellular and molecular pathology, molecular genetics and developmental biology, or molecular pharmacology.

The cross-campus **Center for Neuroscience Graduate Training Program** (PhD) introduces students to the fundamental issues and experimental approaches in neuroscience and trains them in the theory and practice of laboratory research.

The **Biomedical Informatics Training Program** (PhD, MS, or certificate) applies modern information technology to health care, education, and biomedical research.

Offered by the University of Pittsburgh and Carnegie Mellon University, the **Joint Program in Computational Biology** (PhD) is designed to develop expertise in the use of computational methods to identify and solve complex biological problems.

The interdisciplinary **Molecular Biophysics and Structural Biology Graduate Program** (PhD) trains students in a broad range of cutting-edge technologies used to study the function of biological macromolecules in physical terms and covers a diversity of research topics in molecular biophysics and structural biology.

The goal of the **Integrative Systems Biology Program** (PhD) is to train students in emerging transformative methodologies that emphasize genomics, proteomics, complex cellular pathways, and the dynamics of cellular and organismal function. Students in this program operate at the exciting interface between basic bench-top biology, computational analysis of large data sets, and the emergence of 21st century clinical translation.

The **Program in Microbiology and Immunology** (PhD) aims to train highly motivated graduate students as self-reliant scholars in an environment with ready access to the breadth of expertise, approaches, and sub-disciplines that constitute the diverse fields of microbiology and immunology.

The **Biomedical Master's Program** (MS) is designed for students who desire additional training, mentoring, and advising to strengthen their academic and professional credentials for admission to health professional schools or for entry into the biomedical workforce.

Among offerings from Pitt's Institute for **Clinical Research Education** (ICRE) are programs in Clinical and Translational Science (PhD), Clinical Research (MS), and Medical Education (MS).

Pitt Med Global

The School of Medicine operates on a global stage, with active collaborations connecting Pittsburgh with China, Colombia, France, Ghana, Honduras, India, Italy, Kazakhstan, Malawi, the Philippines, Vietnam, and many other nations.

On Pitt's campus, 2018–19 is the Year of PittGlobal, as declared by the Office of the Provost. As we celebrate the University being at home in the world and highlight its position as a global convening point, the School of Medicine is happy to provide a few global updates of its own (in addition to those on pages 7, 21, and 29).

In 2012, Pitt's School of Medicine was selected to guide the Republic of Kazakhstan's Nazarbayev University (NU) as it established its own medical school. The Nazarbayev University School of Medicine now approaches a major milestone as the very first class of physicians is set to graduate in the spring of 2019.

The school's mission is to educate physician-scientists to become this Central Asian nation's next leaders in health care, medical education, and biomedical research. Pitt has worked 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. The NU School of Medicine welcomed its first class in 2015 and began accepting international students in 2017.

A partnership that includes UPMC, Pitt, and the Italian government brought solid-organ transplantation to Sicily in 1999. That project got a permanent home in 2004, when a 70-bed hospital opened in Palermo.

Since 2008, a similar public-private partnership known as Ri.MED (*Ricerca Mediterranea* or Mediterranean Research) has provided an innovative approach to advanced research training of highly talented early-stage investigators from Italy at the University of Pittsburgh, initially through a postdoctoral fellowship program and, later, as Pitt research associates and research faculty.

Under the guidance of scientific director **Dario A.A. Vignali, PhD**, Frank Dixon Professor of Cancer Immunology and vice chair of immunology, Ri.MED held its most recent annual symposium in Palermo, on the theme of cancer immunotherapy.

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Scholars from Shanghai Jiao Tong University participate in the Excellence in Clinical Research Training program in 2018.

Expanding Collaborations with Chinese Institutions

In response to requests from several Chinese partner universities regarding opportunities for Chinese learners—ranging from students to faculty—to advance their knowledge and skills in clinical and translational research, Pitt's School of Medicine and its renowned Institute for Clinical Research Education (ICRE) adapted a highly successful clinical research training program to create a customized certificate program for international scholars, with an initial focus on Chinese learners. The Excellence in Clinical Research Training (Excel-CRT) program emphasizes the multidisciplinary nature of clinical and translational research and engages adult learners by focusing on applied approaches and practical skill building. The program initiated a pilot of the model in July 2018 with a cohort of seven scholars from Shanghai Jiao Tong University, all of them medical students in the final years of an eight-year program. (Read more about Pitt's successful collaborations with China's prestigious Tsinghua University and Central South University Xiangya School of Medicine on page 29.)

The core curriculum provides trainees with the basic set of skills required for clinical investigators in all fields of interest. These skills include an understanding of research design, epidemiologic methods, biostatistics, and measurement of outcomes for research involving human participants. Scholars spend six months at Pitt. For four months, the scholars shadow clinical investigators and their lab teams. They observe research assistants and coordinators in daily activities, take part in research team meetings, and interact with research participants. Their final project is to prepare a clinical study proposal, allowing them to review and apply what they have learned in the program.

Pivots

Shivdev Rao, MD, Class of 2007

While an undergrad at Carnegie Mellon University, Shivdev Rao was a skateboarder and social history major, interested in philosophy and headed toward an academic career in the humanities.

Then he went to a lecture by architect William McDonough.

McDonough told the story of Govindappa Venkataswamy, an Indian eye doctor who founded one of the largest ophthalmology hospital networks in the world and restored more than 2 million people's sight for free. Venkataswamy achieved this by designing a swiveling surgical room resembling an assembly line, where he and his team could perform a cataract operation in 10 to 20 minutes, then quickly move to the next prepped patient.

McDonough's philosophy, that "design is the first signal of human intention," spoke deeply to Rao. "He inspired me to think about how I want to impact people," says Rao, who then "pivoted" toward medicine. Rao (MD '07) is now a clinical instructor in medicine at Pitt and executive vice president for UPMC Enterprises, the commercialization arm of the medical center.

Rao carries his ethos of influencing the world through design to his work at UPMC Enterprises. The unit invests in and builds technologies that do what Rao calls the "three As": assist, augment, or automate aspects of health care delivery, with an immediate focus on UPMC's $16 billion health care system.

This mission is newly evolved, says Rao. Enterprises—which has its colorful open-concept offices in Bakery Square—was originally called the Technology Development Center and focused largely on software-centered solutions for UPMC and elsewhere. The vision has broadened in recent years to include solutions based on everything from basic science to advanced analytics.

Rao says Enterprises' "secret sauce" is access to UPMC's 40 hospitals, 600 doctor offices, and 4,800 physicians, as well as its insurance plan; UPMC's massive system constantly generates data and can function as a real-time feedback mechanism.

Still a practicing cardiologist, Rao takes weekly appointments at UPMC Magee-Womens Hospital and performs rounds at UPMC Presbyterian.

"Seeing patients always…informs me about some new nuance that I can bring here [to Enterprises]," he says.

At Enterprises, Rao focuses on solutions that "work backward" from patient care. Rao says the goal is to embrace higher-level ideas that would affect patient and provider experiences. These include artificial intelligence and its subsets like deep learning (wherein networks, with designs inspired by the structure of the brain, are capable of learning and sometimes making decisions from large datasets).

"Deep learning really sings in the imaging space, more than any other domain. Radiology, pathology, aspects of ophthalmology, and cardiology" will all benefit, says Rao.

RAO CARRIES HIS ETHOS OF INFLUENCING THE WORLD THROUGH DESIGN TO HIS WORK AT UPMC ENTERPRISES. THE UNIT INVESTS IN AND BUILDS TECHNOLOGIES THAT DO WHAT RAO CALLS THE "THREE As": ASSIST, AUGMENT, OR AUTOMATE ASPECTS OF HEALTH CARE DELIVERY, WITH AN IMMEDIATE FOCUS ON UPMC'S $16 BILLION HEALTH CARE SYSTEM.

For instance, a pathology system might filter for images with abnormalities and even make diagnostic suggestions based on the data to create an entirely new workflow. For perpetually overworked clinicians, Rao believes such technology would improve efficiency and help with decision-making. He emphasizes he doesn't believe in "push-button" technology for diagnosis in the near future. Instead, he believes that "we can help doctors do better." Through a partnership with Microsoft's artificial intelligence labs, he envisions leveraging "technology to transform clinicians from overwhelmed and time scarce, to nearly omniscient and omnipresent healers."

He says Enterprises is walking a path toward wholly person-centered health care, where every patient controls his or her own data over vastly interconnected systems.

"We're far from that," says Rao. "But we have all the ingredients."

Door to Door

Raul Ruiz, MD

Trained in Emergency Medicine at Pitt, Raul Ruiz returned to his roots in California and now serves in the U.S. House of Representatives.

Raul Ruiz was 17 when he banged out a contract on a manual typewriter, polished his dress shoes, borrowed a briefcase, and bought an itchy navy suit two sizes too big. "I wanted one to grow into as an investment for medical school interviews," he explains.

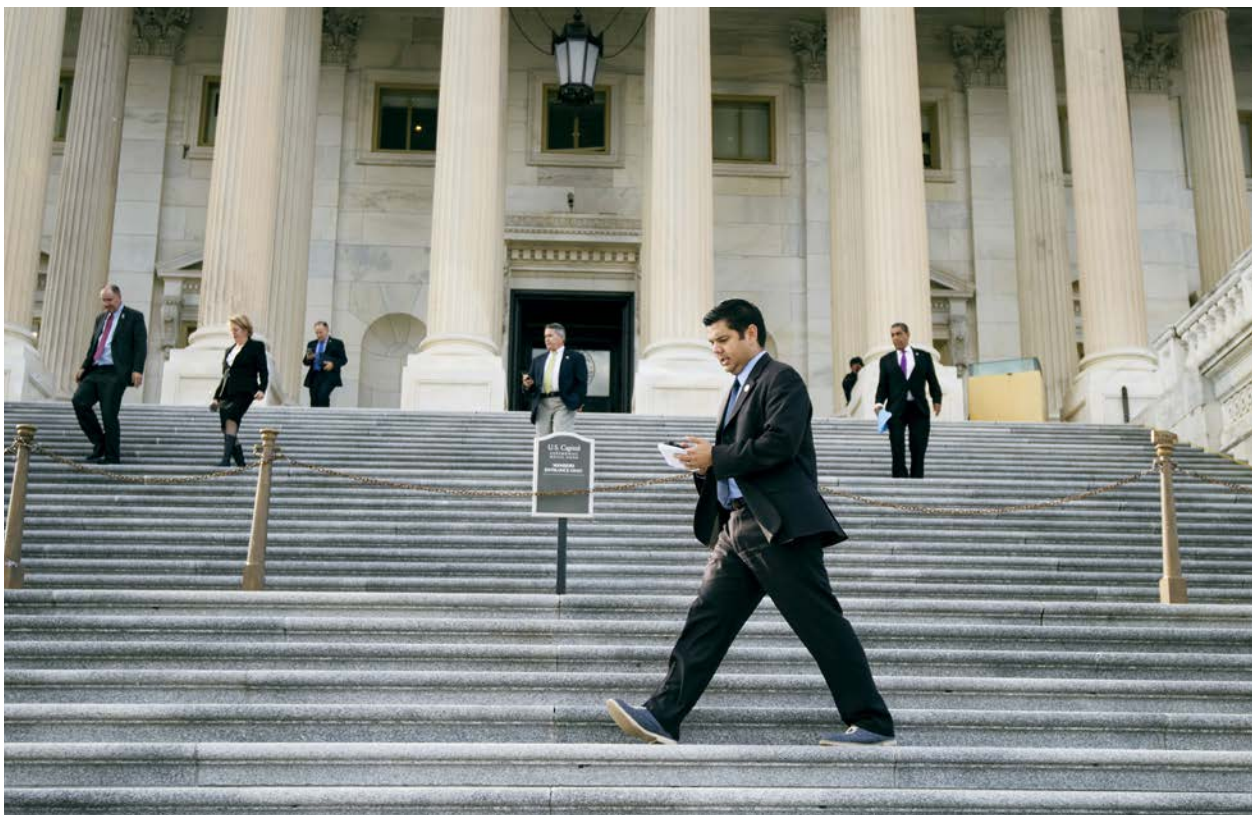
Then he proceeded to walk door-to-door in the hot desert sun, talking to business owners and store clerks alike. In exchange for his neighbors' financial support, Ruiz stipulated that he would earn an MD and return to his underserved Southern California community. "This was my life goal and mission," says Ruiz. "I was inviting people to invest in their future."

Ruiz never aspired to elected office, but for a kid raised in a trailer and coached to offer solutions, not complaints, the trajectory seems inevitable. Born in Mexico, Ruiz was reared by an aunt and uncle, migrant farm laborers who worked the fields of California's Coachella Valley. The family couldn't afford health insurance, yet that wasn't the biggest obstacle to accessing medical care. The region had just one doctor for every 9,000 residents. No matter where Ruiz turned, it was hard to miss the desperate medical needs of his neighbors in the low-income, predominantly agricultural, and increasingly Latino community.

With pledges of support from his neighbors plus $2,000 in hand, Ruiz attended UCLA, graduated *magna cum laude*, and earned three graduate degrees from Harvard (an MD, as well as master's degrees in public policy and public health). He did a few stints abroad as a public health worker in Mexico, El Salvador, and Serbia; completed his emergency medicine residency at Pitt; and returned home in 2007. Ruiz was elected to the U.S. House of Representatives in 2012 and reelected in 2014, 2016, and 2018.

"My heart and soul were in the community," he says, "with my patients, with the people in the greatest need for health care and facing the greatest barriers. When we live in a society that is healthy and productive, we all benefit. The bottom line of a health care system is to produce a healthy population. That's how we should measure our success in health care."

"MY HEART AND SOUL WERE IN THE COMMUNITY, WITH MY PATIENTS, WITH THE PEOPLE IN THE GREATEST NEED FOR HEALTH CARE AND FACING THE GREATEST BARRIERS. WHEN WE LIVE IN A SOCIETY THAT IS HEALTHY AND PRODUCTIVE, WE ALL BENEFIT. THE BOTTOM LINE OF A HEALTH CARE SYSTEM IS TO PRODUCE A HEALTHY POPULATION. THAT'S HOW WE SHOULD MEASURE OUR SUCCESS IN HEALTH CARE."—RAUL RUIZ, MD



Alumnae Address Race, Bias, and Otherness in Medicine

The School of Medicine diversity office—over the decades led by William Wallace, Carolyn Carter, Nancy Washington, Paula Davis (who is now assistant vice chancellor for diversity), and, for the past several years, Chenits Pettigrew—has been home base for generations of students seeking friendship, guidance, and assurance that they belong. In April, Pitt Med hosted a dialogue with Pitt alumnae who are now diversity and inclusion officers at schools and hospitals around the country. Current med student Nia James, who is president of Pitt's Student National Medical Association, moderated the conversation that touched on the stakes of unconscious bias, student dilemmas, and what's working well at their institutions.

Sherri-Ann Burnett-Bowie (MD '97) Associate Director, Center for Diversity and Inclusion, Massachusetts General Hospital Faculty Assistant Dean, Student Affairs, Assistant Director, Office of Recruitment and Multicultural Affairs, Harvard Medical School

Nia James (Class of '21), President, Student National Medical Association, University of Pittsburgh

Margaret Larkins-Pettigrew (MD '94, Res '98) Director and Endowed Professor, Center for Clinical Excellence and Diversity, University Hospitals Cleveland Medical Center

Mia Mallory (MD '94) Associate Dean of Diversity and Inclusion, University of Cincinnati College of Medicine

Stephanie White (MD '08) Diversity Liaison for Student/Resident Advising, Geisel School of Medicine at Dartmouth College

From top: Burnett-Bowie (*SBB*), James (*NJ*), Larkins-Pettigrew (*MLP*), Mallory (*MM*), White (*SW*)

A DIALOGUE ON DIVERSITY AND INCLUSION

NJ: **Is there a part of your job that surprises you?**

MLP: I need to continue to check myself about where my bias lies.

SW: Lots of schools have made it pretty far being well intentioned. To really continue to push issues forward, there need to be standardized ways of accomplishing things—and metrics for evaluation.

MM: I am often surprised that not everyone believes in the importance of diversity in the health care workforce, especially given that the population of the patients that we are caring for is becoming increasingly diverse.

NJ: **What is trending in the world of diversity and inclusion offices?**

SBB: There is a significant conversation that's ongoing around supporting learners and faculty with disabilities. The idea that you have to be perfect is a real barrier to both seeking wellness and seeking accommodation.

SW: Students are coming in with more experience dealing with social justice. Think about the key events that took place in their formative years with Trayvon Martin and the inappropriate deaths of black males. This has been in their lives for as long as they remember, and it's really hard as faculty to keep in mind that they do think about things differently. We're going to have to bridge that gap, because they're going to continue to want to talk about it.

MM: We've been seeing an uptick in patients who display biases against our students and physicians for a variety of reasons, whether it's because they belong to a certain racial group, ethnic group, gender group, or sexual identity group. Now we are working to develop standards to educate and empower our students to combat the biases they are facing.

MLP: We just recently changed our patient bill of rights because we had so many cases where our patients refused to have people who are of the Jewish faith or African American take care of them. We have decided to have a no-tolerance response. We say to a patient that we are all diverse, and this is a training institution, but if you are uncomfortable here we will transfer you at cost to another institution.

SW: **If faculty members hear their students encountering something, they need to speak up for them at the time and not just ignore it, because that can be very demeaning. Students are in a difficult place because, in most situations, their grades and evaluations depend on their actions, and they don't necessarily know what the attending would think if they verbalized their concerns.**

NJ: **Are there challenges that may be more significant than what you already listed?**

MLP: **I still feel that we can talk about all the "isms" that exist in our world today—as it relates to our LGBT population, our women—but at the end of the day, the people who are dying in my field [obstetrics and gynecology] are black women and black babies. Part of our responsibility is to recognize that unconscious bias does kill, and it can kill at the bedside.**

SBB: **Physicians and health care providers—not just physicians—sometimes need convincing that we have bias because there's such empathy that's inherent in the choice to provide relief of suffering. Sometimes people make the mistake of thinking, I can't be biased because I'm in this pursuit... There is so much upheaval in our geopolitical context that it's a hard time to be a student who is concerned about social justice. I have sent out e-mails about what I think are really heartbreaking national tragedies—after Charleston [church massacre], after Orlando [gay nightclub massacre]—where I share that I'm struggling with what has transpired, and that I would anticipate that they would be struggling as well, and that there are resources here to help them.**

SW: **Students really want change, like, yesterday. They are much more social-justice minded, and they're pushing academic medicine educators to think about how we're doing everything within the classroom, clinics, and medical school environment.**

Pitt's Tsinghua Scholars, Class of 2018

Pitt–China Collaborations Reach New Heights

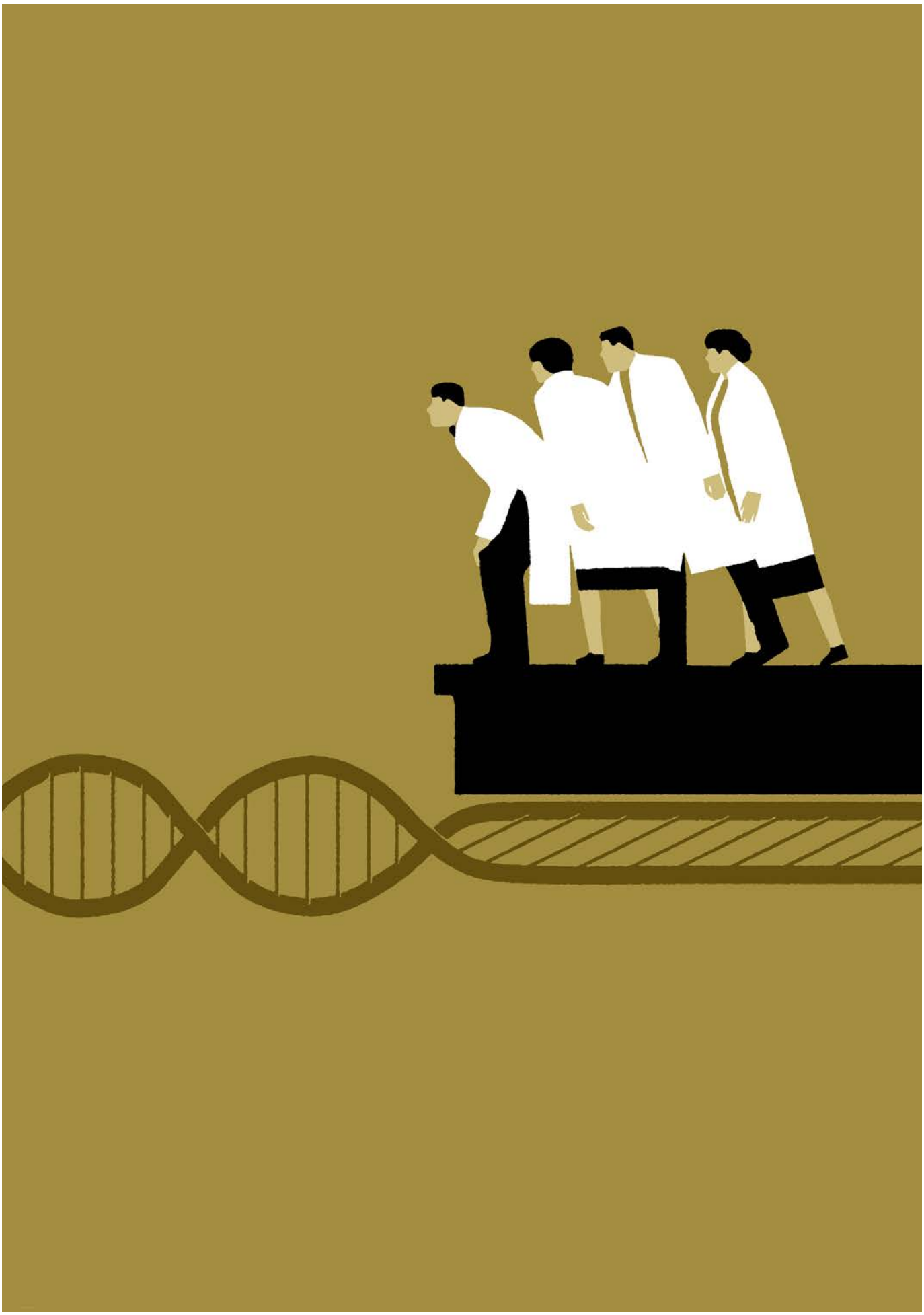
A highly innovative global partnership connecting the University of Pittsburgh School of Medicine with the top science and technology university in all of China reached an important milestone in 2017. That summer, 13 Chinese medical students who previously spent two years in Pittsburgh as part of Pitt's Tsinghua Scholars Program graduated from the Tsinghua University School of Medicine and became the first Pitt–Tsinghua Scholars to earn their medical degrees. Initiated in 2012 to elevate the training of Chinese physician-scientists, the Tsinghua Scholars Program allows medical students at this most prestigious of Chinese universities to undergo a rigorous, two-year biomedical research training program in Pittsburgh.

Yigong Shi, PhD, the vice president of Tsinghua University who left an endowed professorship at Princeton University to return to his native China in 2008, explained the rationale for the program: "The traditional teaching method in China emphasizes passive listening and memorization. Students seldom raise critical questions and comments. I have been advocating for active learning in the classroom ever since I returned to China .... The strength of the Chinese educational system is clear: Students receive comprehensive and sound knowledge in mathematics and natural sciences. The weakness is also evident: The system does not encourage innovation!"

The historic agreement between Pitt and Tsinghua University has been renewed for a second five-year term. The Tsinghua Scholars program currently has 92 alumni and 41 active scholars on Pitt's campus, where they work in the laboratories of some of Pitt's most accomplished biomedical researchers.

Also in 2012, the School of Medicine began a collaboration with China's prestigious Central South University Xiangya School of Medicine. Under the 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 November 2018, 25 of these medical students are on campus, and 11 have recently returned to Changsha to graduate from medical school after their two years in Pittsburgh. In 2014, Xiangya Hospital formed a partnership with UPMC to establish an international medical center, which has improved access to high-quality care for patients in the region since opening in 2015.

Building on the successful collaboration, Pitt and Tsinghua are considering the formation of a combined MD/PhD program, which would be modeled after the highly successful Medical Scientist Training Program at Pitt and other U.S. medical schools. If implemented, it would be China's first such dual-degree program.



We aim to bring about transformational changes in American medicine by exploring the most fundamental and important areas in biological science and clinical care.

Grants of Note

NEW PHYSICIAN-SCIENTIST PROGRAM FUNDED

Funding of more than **$5.2 million** from the Burroughs Wellcome Fund (BWF), UPMC, and the University of Pittsburgh will support the development of an elite training program designed to set new physicians on a career path integrating scientific research with clinical care. BWF launched the initiative in response to a 2017 *Chronicle of Higher Education* report that only 1.5 percent of physicians in the United States today also conduct research. **The University of Pittsburgh Physician-Scientist Incubator Program** is one of only five such programs BWF selected from 92 submissions. The incubator program will build on the School of Medicine's curriculum for medical students to earn both MD and PhD degrees to include interns, residents, fellows, and other specialists who have completed medical degrees. Twenty-one physicians will be enrolled during the program's first five years, but hundreds more will benefit from the workshops, online materials, and lectures that the program funds.

CANCER RESEARCH GETS HILLMAN-SIZED BOOST

The Henry L. Hillman Foundation has committed **$30 million** over 10 years to support Pitt and UPMC's **Hillman Fellows for Innovative Cancer Research Program**, which provides seed funding to scientists and encourages partnerships with young researchers to cultivate novel anticancer approaches that improve treatment, detection, and prevention of cancer worldwide. Since the program's inception in 2004, the Hillman Fellows Program has directly supported more than 100 scientists. New funds will also be used to accelerate high-priority research like linking cancer genomics and immunology to precision patient care.

CENTER ESTABLISHED TO STUDY OVARIAN BIOLOGY

The Magee-Womens Research Institute (MWRI) has received **$3 million** from the Eden Hall Foundation to establish the **Comprehensive Ovarian Biology Research Center** at MWRI and the School of Medicine, which will bring biology and oncology researchers together to study the molecular and physiological factors that shape ovarian development. Including a matching grant from UPMC, funding for the new center totals **$6 million**. Researchers will also study hormone production, fertility, and menopausal changes to generate critically needed data on ovarian biology across the lifespan. In addition, investigators will study how other factors, such as the immune response, microbiome, diet, and environmental influences, may shape disease risk.

FUNDING SPURS RESEARCH ON BRAIN'S KEY FUNCTIONS

The National Institutes of Health and National Science Foundation (NSF) awarded Pitt researchers more than **$6 million** to study how the brain performs mathematics, perceives the world, and governs social interaction, among other key functions.

With a **$3.8 million** National Institute of Mental Health grant, **Tobias Teichert, PhD**, assistant professor of psychiatry, **Dean Salisbury, PhD**, professor of psychiatry, and **Brent Doiron, PhD**, associate professor of mathematics, are using electrophysiological, pharmacological, and computational methods to explore how noninvasive tests like electroencephalography (EEG) and magnetoencephalography (MEG) could reveal underlying neural and synaptic activity.

Associate professor of ophthalmology **Matt Smith, PhD**, and Carnegie Mellon University's **Byron Yu, PhD**, associate professor of electrical and computer engineering, received a **$1 million** NSF grant to investigate how our perception and interpretation of the surrounding world derive from a combination of our sensory environment and state of mind.

To better understand brain circuits in real-world settings, **Avniel Singh Ghuman, PhD**, associate professor of neurological surgery, and **R. Mark Richardson, MD, PhD**, associate professor of neurological surgery, will collaborate with Carnegie Mellon University researchers **Max G'Sell, PhD**, assistant professor of statistics, and **Louis-Philippe Morency, PhD**, assistant professor of computer science. With a **$1 million** NSF grant, the team will examine brain activity in patients who are undergoing neurosurgical treatment for epilepsy as they interact socially. They hope to shed light on neural processes that misalign in brain disorders like autism and post-traumatic stress disorder.

SUPPORT TOOL TO AID PREGNANCY DECISION-MAKING

Helping women make informed decisions about surgical procedures that permanently prevent pregnancy is the goal of principal investigator **Sonya Borrero, MD, MS**, associate professor of medicine, and other researchers who received a **$3.5 million** National Institute on Minority Health and Health Disparities grant. The team is developing a Web-based decision-support tool to help women—particularly low-income and minority women—better understand female sterilization and birth control options that can fit their future plans and goals.

DEFENSE FUNDING BOLSTERS PHYSICAL REHABILITATION RESEARCH FOR MILITARY PERSONNEL

Funding from the U.S. Department of Defense will support a variety of collaborative research projects intended to benefit military personnel and veterans. Each project represents a robust collaboration between Pitt's School of Medicine and School of Health and Rehabilitation Sciences. **Anne Germain, PhD**, professor of psychiatry, and **Bradley Nindl, PhD**, professor of sports medicine and nutrition, will receive **$2.5 million** to study the mental resiliency and readiness of military service members. They aim to develop metrics to evaluate and encourage preparedness for military service. **Volker Musahl, MD**, associate professor and chief of sports medicine in the Department of Orthopaedic Surgery, and **James Irrgang, PhD**, professor and chair of physical therapy, were awarded **$4.5 million** to investigate how timing of surgery and postoperative rehabilitation affect recovery after multiple-ligament knee injuries, which can complicate healing and prolong the return to physically demanding military activities and similar pursuits.

SUPPORTING BRAIN TUMOR IMMUNOTHERAPY FOR CHILDREN

The St. Baldrick's Foundation, which raises money for childhood cancer research, awarded a scholar grant of **$298,000** to **Gary Kohanbash, PhD**, assistant professor of neurological surgery and a researcher at UPMC Children's Hospital of Pittsburgh. The award supports Kohanbash and his colleagues' work to improve immunotherapy for ependymomas, the third most common form of brain tumor in children.

Publications of Note

AGING CELL

AGING OF THE EXTRACELLULAR MATRIX DISRUPTS MUSCLE STEM CELLS' REGENERATIVE ABILITIES

JUN 2017 \ VOL 16 \ ISSUE 3

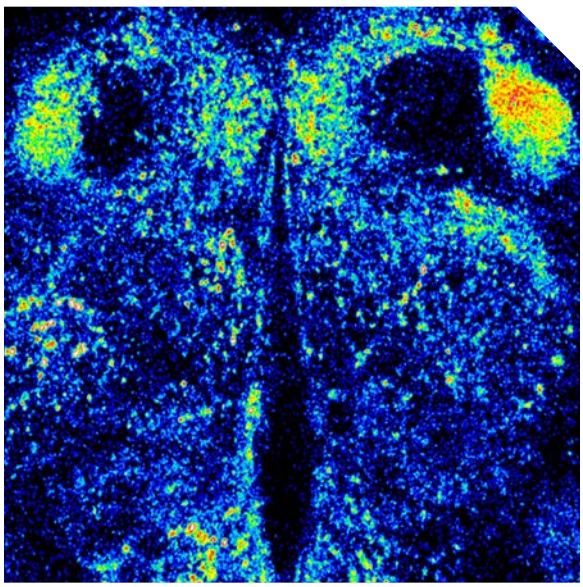
Age-related decline in skeletal muscle regenerative ability is often attributed to muscle stem cell (MuSC) dysfunction. However, aging of the extracellular matrix (ECM) also affects stem cell behavior and hampers MuSC responses, a study found. As age increases, collagen tortuosity decreases and muscle stiffening increases. These biophysical changes affect stem cell function, and MuSCs planted *ex vivo* onto ECM constructs from aged muscles showed increased fibrogenesis and decreased formation of muscle tissue compared to MuSCs exposed to young ECM. The research team, including **Fabrisia Ambrosio, PhD, MPT**, associate professor of physical medicine and rehabilitation, found that, *in vitro*, fibroblasts from aged muscle exuded certain molecules and agents that promoted a fibrogenic conversion of MuSCs. Therefore, an age-related increase in muscle stiffness underlies pathogenic expression of matricellular proteins by fibroblasts, which may disrupt MuSCs' abilities to heal muscle after injury. This paper was selected for the 2017 *Aging Cell* Best Paper Prize.

NATURE COMMUNICATIONS

ALTERNATIVE DNA REPAIR PATHWAY PROTECTS THE TRANSCRIBED GENOME

OCT 2018

Actively transcribed regions of the genome are protected by transcription-coupled DNA repair mechanisms, including transcription-coupled homologous recombination (TC-HR). After using reactive oxygen species (ROS) to cause chromosomal damage at a transcribed locus in human cells and induce TC-HR, researchers including **Arthur S. Levine, MD**, Petersen Dean of Medicine and professor of medicine and molecular genetics; **Yaqun Teng**, Tsinghua University scholar; and **Li Lan, MD, PhD**, assistant professor of radiation oncology at Harvard University, made the surprising observation that TC-HR did not require the involvement of BRCA1 and BRCA2 proteins, as scientists had long believed. In fact, the research team established the existence of a BRCA1/2-independent alternative HR pathway protecting the transcribed genome — one that involves Cockayne Syndrome Protein B (CSB). CSB is recruited by R loops, nucleic acid structures strongly induced by ROS in transcribed regions; thus, TC-HR is triggered by R loops, initiated by CSB, and carried out by the CSB-RAD51-RAD52 axis.



NEURON

DOPAMINE RELEASE LEVELS ARE SUBJECT TO CHANGE

AUG 2017 \ VOL 95 \ ISSUE 5

A team of researchers found that neurons in fruit flies and mice can alter the amount of dopamine they release depending on overall neuronal activity. A neuronal communicative agent, dopamine is carried in sacs called synaptic vesicles and released into the synapse in supposedly fixed amounts. But the researchers, including senior author **Zachary Freyberg, MD, PhD**, assistant professor of psychiatry, found that increased levels of acidity within the synaptic vesicles — driven by an influx of negatively charged glutamate ions — led to additional dopamine being loaded into and subsequently released from these vesicles. These findings oppose existing beliefs that a definite amount of chemical signal is loaded into a vesicle and that acidity is fixed. Exploring abnormal dopamine neuron signaling and altered levels of the neurotransmitter could advance treatments for Parkinson's disease, schizophrenia, addiction, and other dopamine-related diseases.

Neurons in fruit flies and mice can alter the amount of dopamine they release depending on overall neuronal activity.

SCIENCE TRANSLATIONAL MEDICINE

TICK SALIVA MECHANISM COULD DETER HEART DISEASE IN INDIVIDUALS WITH HIV

AUG 2017 \ VOL 9 \ ISSUE 405

HIV-positive individuals live longer, healthier lives today thanks to antiviral treatments, but they still experience double the likelihood of developing heart disease. Why? Researchers from Pitt's Center for Vaccine Research, including cosenior author **Ivona Pandrea, MD, PhD**, professor of pathology, found that people with HIV, even when medication keeps their disease under control, harbor a greater number of monocytes that express "tissue factor," a protein linked to blood clotting and inflammation, driving heart disease. The team also found that in nonhuman primates infected with SIV — the HIV primate equivalent — Ixolaris, an experimental drug derived from tick saliva, effectively blocked the tissue factor activity. The drug, which requires further testing, could potentially reduce the incidence of heart disease in individuals with HIV.

SCIENCE ADVANCES

MXB PROTEIN STRUCTURE REVEALS HIV RESTRICTION INTERFACE

SEP 2017 \ VOL 3 \ ISSUE 9

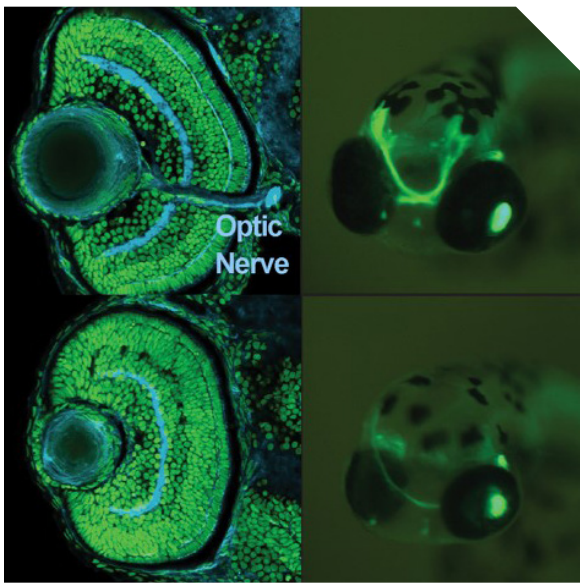
The interferon-inducible myxovirus resistance 2 (MxB) protein is a potent HIV-1 inhibitor, but determination of its structural assembly is key to its effectiveness. Pitt researchers, including **Peijun Zhang, PhD**, associate professor of structural biology, School of Medicine, and professor of structural biology, University of Oxford, used cryo-electron microscopy to determine MxB assembly structure at 4.6 Å resolution, revealing the first near-atomic resolution structure in the mammalian dynamin super-family. They found that full-length wild-type MxB oligomers contain a novel MxB assembly interface that is critical for HIV restriction. Further, the high resolution structure provides insight into the diverse functions of dynamin family GTPases, enzymes that regulate many cellular processes.

SCIENCE IMMUNOLOGY

MECHANISM ENABLING ORAL THRUSH ONSET IDENTIFIED

NOV 2017 \ VOL 2 \ ISSUE 17

The wall of oral epithelial cells that lines the inside of the mouth isn't usually troubled by the common *Candida albicans* fungus. But, when the immune system is suppressed, the fungal cells can elongate and become invasive, triggering oral candidiasis, or thrush. The condition, which is common in babies, HIV/AIDS patients, and immunosuppressed patients, can cause painful difficulty eating and swallowing. In a recent study, an international team led by Pitt researchers, including **Sarah Gaffen, PhD**, Gerald P. Rodnan Professor of Rheumatology in the Department of Medicine, and postdoctoral fellow **Akash Verma, PhD**, found that *Candida* emits a toxin called Candidalysin that punctures the oral epithelial cell wall and triggers immune system defenses. By identifying Candidalysin's key role, the research offers clues to understanding the immune defense network at barrier sites of the body, Gaffen says, knowledge that could be harnessed to develop antifungal vaccines, of which none are currently commercially available.



PLOS GENETICS

EPIGENETIC REGULATION AND RETINAL NEUROGENESIS

SEP 2017 \ VOL 13 \ ISSUE 9

Little is known about how DNA hydroxymethylation, an epigenetic mechanism, may affect eye development. The process plays a role in gene expression and in a variety of developmental contexts. While studying retinal neurogenesis in zebrafish, researchers observed Tet protein activity and found that Tet function may be required for terminal morphogenesis of differentiated retinal neurons. During retinal ganglion cell differentiation and morphogenesis, the investigators, including **Jeffrey Gross, PhD**, the E. Ronald Salvitti Professor of Ophthalmology Research, found that tet2 and tet3 regulate the Notch and Wnt signaling pathways. Transcriptome analyses revealed abnormal expression of non-retinal genes in tet2 and tet3 double mutant retinae, which correlated with DNA demethylation. As the first detailed analysis of Tet function during ocular development, the study sheds light on the retinal progenitor cell's progression to a differentiated retinal neuron and highlights a new component of epigenetic regulation and retinal neurogenesis.

The study highlights a new component of epigenetic regulation and retinal neurogenesis.

NATURE COMMUNICATIONS

MOLECULAR CHAPERONE USED TO TREAT RETINITIS PIGMENTOSA

MAY 2018

Protein misfolding diseases are associated with many visual disorders, but many inherited retinal diseases lack effective treatments. Mutations that cause misfolding in the photoreceptor protein rhodopsin can lead to autosomal dominant retinitis pigmentosa (adRP). While this progressive form of retinal degeneration remains untreatable, assistant professor of ophthalmology **Yuanyuan Chen, PhD**, and researchers from Case Western Reserve University have identified a novel pharmacological molecular chaperone, YC-001, capable of stabilizing the P23H rod opsin mutant that causes most cases of adRP in North America. Underscoring YC-001's chaperone activity is its ability to rescue the transport of multiple rod opsin mutants in mammalian cells. The molecule has also demonstrated strong micromolar potency and efficacy and lower toxicity in mice. Further, YC-001 has demonstrated therapeutic potential, successfully protecting mice subjected to bright light-induced retinal degeneration.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

EVALUATING CURRENT (AND FUTURE) NNRTI-BASED HIV THERAPIES

JAN 2018 \ VOL 115 \ ISSUE 4

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) have long been a key agent in combination antiretroviral therapies against HIV-1. **Nicolas Sluis-Cremer, PhD**, professor of medicine in the Division of Infectious Diseases, says, however, that NNRTI molecules may be increasingly ineffective. NNRTIs bind to the same site in HIV-1 reverse transcriptase and are prone to mutation, potentially diminishing their clinical efficacy. The growing problem of resistance and cross-resistance, particularly in lower-income countries, stems from the majority of NNRTI resistance mutations occurring in or near the NNRTI-binding pocket, the molecule's key reaction site. As described in the commentary, a new class of catechol diether-based NNRTIs have shown promising synergistic antiviral activity in HIV-1–infected mice and may be key to future NNRTI-based therapies.

SCIENCE SIGNALING

STUDY REVEALS NEW MOLECULAR TARGETS OF SENESCENCE

OCT 2017 \ VOL 10 \ ISSUE 501

Senescent cells do not proliferate, so their presence is associated with aging and organ homeostasis impairment. After studying senescence in human cells and aged tissue, research instructors **Sanghamitra Sahoo, PhD**, and **Eugenia Cifuentes-Pagano, PhD**, and professor and vice chair **Patrick J. Pagano, PhD**, all of the Department of Pharmacology and Chemical Biology, linked the matricellular protein thrombospondin1 (TSP1) and its receptor to NADPH oxidase 1 (Nox1) activation, which underlies senescence. TSP1 attenuated normal parenchymal cell cycle progression and proliferation by inducing a DNA damage response stemming from increased transcription factor p53, which resulted from reactive oxygen species (ROS) generated by TSP1. Mouse models of senescence that lacked TSP1 exhibited decreased ROS production, p53 activity, and $p21^{cip}$ expression, all of which inhibit normal cell cycle processes. Lung tissue from aging humans showed increased levels of all of these agents.

NATURE CELL BIOLOGY

CASTING LIGHT ON GENETIC PATHWAYS BEHIND GERM CELL DEVELOPMENT

JUN 2018 \ VOL 20 \ ISSUE 6

To further understand why dysregulation of genetic pathways during germ cell development leads to infertility, an investigative team that included professor of obstetrics, gynecology, and reproductive sciences **Kyle Orwig, PhD**, studied the developmental genetics behind human germ cell specification and differentiation in human primordial germ cells (hPGCs). By comparing levels of the transcription factor protein OCT4 in hPGCs to levels in human embryonic stem cells (hESCs), the study revealed that while OCT4 partners with the SOX2 transcription factor to maintain pluripotency in hESCs, it switches to partner with the PAX5 and PRDM1 transcription factors to maintain germ cells in the developing embryo and prevent their differentiation to somatic lineages. These findings demonstrate the power of combining genome editing with stem cell differentiation and transplantation to unravel the molecular programs that direct embryonic development.

ELIFE

RESEARCHERS EXPLORE SYNAPTIC ZINC'S ROLE IN DISTINGUISHING SOUND VOLUME

SEP 2017

To better understand how synaptic zinc affects neuronal processing *in vivo*, Pitt researchers, including **Thanos Tzounopoulos, PhD**, Professor of Auditory Physiology and vice chair for research in the Department of Otolaryngology, explored in mice how zinc influences neurons' responses to sounds at different volumes. After reducing the number of zinc ions present in neuronal synapses, excitatory neurons (which activate neighboring cells) showed increased response, while inhibitory neurons (which reduce neighboring cells' activity) showed decreased response. These zinc-governed response variations may help explain the brain's ability to process and distinguish sounds in settings with varying volumes. By establishing a new link between synaptic zinc and auditory cortical processing, the study provides insight into the role of the auditory cortex in sound processing. The findings may also shed light on disorders such as tinnitus and auditory neuropathies that involve the brain's reaction to volume changes.

ELIFE

EPIDERMAL GROWTH FACTOR RECEPTORS DRIVE TUMORIGENESIS

DEC 2017

Though epidermal growth factor receptor (EGFR) plays a well-documented role in tumorigenesis, its endocytosis and signaling haven't been studied *in vivo* in tumors. **Alexander Sorkin, PhD**, Richard Beatty Mellon Professor of Physiology and chair of cell biology, and other Pitt researchers used gene-edited mouse tumor xenografts and a variety of imaging and biochemical techniques to analyze EGFR endocytosis, phosphorylation, ubiquitination, and signaling in tumors *in vivo*. The observed EGFR activities resembled those activities in tumor cells treated with extremely low concentrations of EGF *in vitro*. The observations together suggest that even a small number of active EGFR can drive tumorigenesis primarily through the Ras-MAP kinase signaling pathway.

NEW ENGLAND JOURNAL OF MEDICINE

PRECISION THERAPY TREATS COPD PATIENT SUBGROUP

OCT 2017 \ VOLUME 377 \ ISSUE 17

Chronic obstructive pulmonary disease (COPD), which is marked by airway obstruction and chronic lung inflammation, affects 30 million Americans. As many as 40 percent of COPD patients have eosinophilic predominant COPD, which is characterized by elevated levels of white blood cells known as eosinophils. Recently, two phase III clinical trials evaluated the drug mepolizumab — an antibody treatment that reduces the number of eosinophils in the blood by blocking interleukin-5's inflammatory effects — in moderate to severe treatment-resistant eosinophilic COPD patients. In both trials, nearly 20 percent of patients receiving the drug experienced a reduced rate of flare-ups associated with the condition, which can decrease lung function, decrease quality of life, and increase mortality rates. The findings provide the first demonstration of an effective precision therapy in a subgroup of treatment-resistant COPD patients, says lead author **Frank Sciurba, MD**, professor in the Department of Medicine's Division of Pulmonary, Allergy, and Critical Care Medicine.

NATURE STRUCTURAL & MOLECULAR BIOLOGY

TARGETING RECEPTOR ANTAGONISTS FOR ANTI-INFLAMMATORY THERAPIES

JUN 2018 \ VOL 25 \ ISSUE 6

A strong inflammatory response occurs when the G-protein-coupled receptor (GPCR) C5aR encounters the anaphylatoxin C5a. Developing C5aR antagonist drugs to deliver anti-inflammatory therapies has been difficult, however. A team of investigators, including **Cheng Zhang, PhD**, assistant professor of pharmacology and chemical biology, studied two crystal structures of human C5aR complexes with the peptide antagonist PMX53 and two nonpeptide antagonists, including Avacopan, a drug candidate in phase III clinical trials. Signaling, biophysical, and computational data revealed that the orthosteric action of PMX53 stabilized the C5aR structure and the allosteric action of nonpeptide C5aR antagonists that had different binding poses. Further, other GPCRs may possess similar allosteric sites, based on comparative structural analysis. This enhanced understanding of GPCR binding sites and associated mechanisms could lead to development of novel C5aR-targeting drugs to control inflammatory disorders and conditions.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

ACOUSTOFLUIDIC TECHNIQUE SUCCESSFULLY ISOLATES EXOSOMES FOR FURTHER STUDY

OCT 2017 \ VOL 114 \ ISSUE 40

Using acoustofluidics, which integrate acoustics and microfluidics, a research team led by Duke University's Tony Huang, PhD, and including research assistant professor of obstetrics, gynecology, and reproductive sciences **Yingshi Ouyang, PhD**, and **Yoel Sadovsky, MD**, Distinguished Professor, Elsie Hilliard Hillman Professor of Women's and Infants' Health Research, vice chair of obstetrics, gynecology, and reproductive sciences, and director of Magee-Womens Research Institute, successfully isolated exosomes from whole blood. Exosomes are nanoscale extracellular vesicles involved with intercellular communication and molecular transport. Using the acoustofluidic technique, a microscale cell-removal module first removes larger blood components. Exosome isolation then occurs by extracellular vesicle subgroup separation. Integrating these two modules resulted in isolating exosomes and removing more than 99 percent of blood cells, delivering a high-purity yield. The technique, which is still in development, is label-free, contact-free, and rapid. The investigators believe it can be used to study exosomes' connection to human diseases, with applications to health monitoring, diagnosis, targeted drug delivery, and precision medicine.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

MELATONIN IS SYNTHESIZED IN NEURONAL MITOCHONDRIA AND BINDS TO A GPCR

SEP 2017 \ VOL 114 \ ISSUE 38

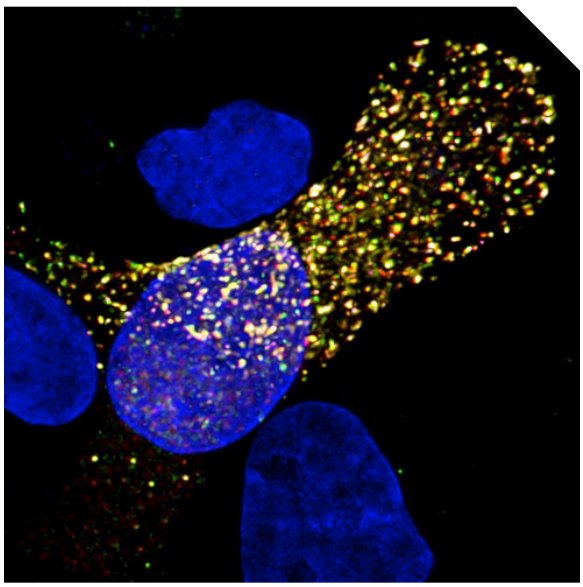
Researchers from Pitt's Departments of Neurological Surgery and of Pharmacology and Chemical Biology have found that G protein-coupled receptors (GPCRs), which transmit extracellular signals into cells, can be found on and within neuronal mitochondria. Within the mitochondria matrix, the ligand melatonin is produced and released, the study demonstrated. The mitochondrial melatonin type 1 receptors respond by activating heterotrimeric G proteins located in the intermembrane space and inhibit stress-mediated cytochrome c release. Combined, these findings by **Jean-Pierre Vilardaga, PhD**, professor of pharmacology and chemical biology, and **Robert M. Friedlander, MD**, Walter E. Dandy Professor and chair of neurological surgery, reveal that mitochondria both synthesize melatonin and harbor a specific receptor for this ligand. This "automitocrine" intracellular organelle ligand–receptor pathway prevents neurodegeneration associated with mitochondrial cytochrome c release. Further understanding of this pathway will generate new insight — and questions — regarding mitochondrial GPCR biology.

NATURE COMMUNICATIONS

INTERFERING WITH HIV CAPSID MATURATION

NOV 2017 \ VOL 8 \ ISSUE 1

Using nuclear magnetic resonance, cryo-electron microscopy, and molecular dynamics simulations, researchers investigated a region of the Group-specific antigen (Gag) protein, comprising the capsid protein (CA) and the spacer peptide 1 (SP1), which is critical in HIV-1 virus maturation. The study revealed that in CA–SP1 tubes assembled *in vitro*, the SP1 peptide exists in a dynamic helix-coil equilibrium. By adding the maturation-inhibitors Bevirimat or DFH-055, the helical form of SP1 is stabilized. The team, which included **Angela Gronenborn, PhD**, Distinguished Professor, UPMC Rosalind Franklin Professor, and chair of structural biology, also observed that a mutant amino acid in SP1 stabilizes SP1's helical structure, as well as causing further global dynamical and conformational changes to the capsid protein. These findings demonstrate that structural and dynamics characteristics in the capsid protein and SP1 are critical for HIV capsid maturation and that molecular agents, which disturb motional behavior, can inhibit formation of the mature HIV-1 capsid shell.



NUCLEIC ACIDS RESEARCH

INFLUENZA GENOME MODEL GETS KEY UPDATE

SEP 2017 \ VOL 45 \ ISSUE 15

The traditional influenza genome model depicts a uniform random binding of proteins along the length of each of its eight RNA segments, resembling uniformly spaced beads on a string — but, as Pitt researchers recently found, it's wrong. Using an advanced sequencing technique, the research team, which included Department of Microbiology and Molecular Genetics assistant professors **Seema S. Lakdawala, PhD**, and **Nara Lee, PhD**, and professor **Vaughn Cooper, PhD**, found several areas where the RNA was not bound by the nucleoprotein, leaving "naked" stretches of RNA. These exposed areas reveal non-uniform spacing and have been potentially binding to other viral RNA when one flu strain mingles with another, swapping genetic material and giving rise to new flu strains. Studying these interactions could allow scientists to better predict flu pandemics and further combat the virus.

These exposed areas have been potentially binding to other viral RNA when one flu strain mingles with another, giving rise to new flu strains.

NATURE MEDICINE

LEVERAGING GENE VARIANT COULD LEAD TO NEW THERAPIES FOR LOWERING CHOLESTEROL

SEP 2017 \ VOL 23 \ ISSUE 9

Investigation into newly identified gene coding variants in the triglyceride-rich lipoprotein (TRL) clearance pathway could lead to new therapies for lowering "bad" cholesterol. The gene APOC3 encodes a critical inhibitor of triglyceride breakdown and remnant TRL clearance. Researchers observed the mechanisms behind TRL reduction, specifically the activity of an APOC3 variant that lowers triglycerides and protects against coronary heart disease. In collaboration with Dan Rader, MD, of the University of Pennsylvania, Pitt researchers **Nathan Yates, PhD**, associate professor of cell biology, and **Xuemei Zeng, PhD,** director of proteomics in the Biomedical Mass Spectrometry Center, developed an ultra-sensitive blood test to measure the mutant protein in humans who carry the gene. With this test, researchers could confirm the molecular mechanism by which an APOC3 variant reduces circulating triglyceride levels and develop therapeutic antibodies that could lead to new approaches for lowering cholesterol.

ELIFE

STUDYING MAMMALIAN DEVELOPMENT BY COMPARING DNA AND RATES OF EVOLUTION

OCT 2017

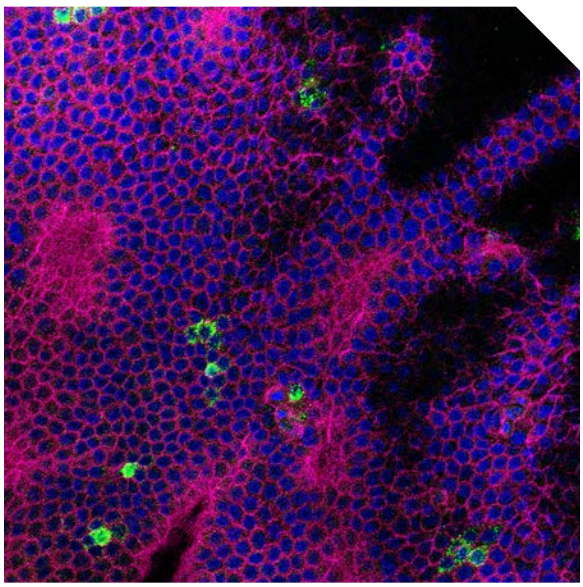
Over 100 million years, some mole rats have evolved to live underground and have completely lost their sense of sight. Thus, DNA mutations that can hinder or damage eye development are readily passed along, uninhibited by evolutionary weeding. While comparing the rodents' DNA to that of above-ground mammals, **Nathan L. Clark, PhD**, assistant professor of computational and systems biology, and colleagues homed in on DNA sections with high rates of sequence change to identify the parts of DNA controlling eye formation. The findings demonstrate how comparison of different species' rates of evolution can be used to pinpoint DNA sections that guide organismal development. Deeper understanding of how the eye forms may also help medical professionals diagnose and treat eye abnormalities and conditions.

NPJ SYSTEMS BIOLOGY AND APPLICATIONS

'COMPUTER CHIP' CELLULAR NETWORK SUBJECTED TO TGF-BETA TREATMENT

MAY 2018

By reconstructing the early response signal transduction network of human cells subjected to TGF-beta treatment, researchers explored the properties of extracellular signals. TGF-beta activates the network's transient and sustained signal response modules in a specific order, **Jianhua Xing, PhD**, associate professor of computational and systems biology, and colleagues observed. Further, cells use the network as checkpoints for signal duration and differential cellular responses, as variations in TGF-beta create varying temporal profiles of downstream gene expression. These observations prompt comparison of the network to a computer chip in its reliance on combinations of multiple units that enhance ability to code signal duration information.



SCIENCE TRANSLATIONAL MEDICINE

VIRUSES RELATED TO ZIKA CAPABLE OF TRANSPLACENTAL INFECTION OF FETUSES

JAN 2018 \ VOL 10 \ ISSUE 426

Despite the attention paid to Zika virus, similar viruses may be capable of inducing fetal damage. Pitt researchers, including **Carolyn Coyne, PhD**, associate professor of pediatrics, and investigators from Washington University School of Medicine in St. Louis infected pregnant mice with four viruses related to Zika virus: West Nile, Powassan, chikungunya, and Mayaro viruses. Interestingly, only the neurotropic flaviviruses — West Nile and Powassan — resulted in fetal demise. These two viruses also efficiently replicated in human maternal and fetal explant tissue isolated from mid-gestation pregnancies. In mice, West Nile virus infected the fetal central nervous system, injuring the developing brain; but the chikungunya and Mayaro viruses did not damage the placenta or fetus after infection. While the study looked at four viruses, its findings point to the possibility of other emerging neurotropic flaviviruses capable of congenital infections and fetal damage.

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CANCER RESEARCH

LEVERAGING SPATIAL INTRATUMORAL HETEROGENEITY TO ASSIST CANCER PROGNOSIS, DIAGNOSIS

NOV 2017 \ VOL 77 \ ISSUE 21

Knowing the number and variation of cell phenotypes and more deeply understanding the spatial relationships between cells and extracellular molecules in the tumor microenvironment — collectively known as spatial intratumoral heterogeneity — greatly aids cancer prognosis and diagnosis. To better quantify spatial intratumoral heterogeneity and to assist with interactive hypothesis testing, **Chakra Chennubhotla, PhD**, associate professor of computational and systems biology, and colleagues at Pitt's Drug Discovery Institute developed the open-source tool THRIVE (Tumor Heterogeneity Research Interactive Visualization Environment). The tool uses multiplexed fluorescence images to phenotype cells within tumor microenvironments, better distinguish tumor boundaries, and improve immune infiltration and epithelial/stromal separation evaluation, among other functions. The researchers hope to disseminate the data that the tool generates into mainstream cancer research.

MOLECULAR PSYCHIATRY

CELLULAR TRANSCRIPTOME ANALYSIS REVEALS POTENTIAL TARGETS FOR SCHIZOPHRENIA

JUL 2018 \ VOL 23 \ ISSUE 7

Using an immunohistochemical approach, laser microdissection, and microarray profiling, Pitt researchers, including **David A. Lewis, MD**, Distinguished Professor, Thomas Detre Professor of Academic Psychiatry, and chair of psychiatry, analyzed the transcriptome of a specific population of inhibitory neurons in the dorsolateral prefrontal cortex (DLPFC), dysfunction of which is associated with schizophrenia (SZ). In 36 matched pairs of SZ and human control subjects, more than 800 neuron transcripts were differentially expressed in SZ subjects, most of which have not previously been reported. Comparisons to the transcriptome of a population of excitatory neurons in the DLPFC from the same subjects revealed shared and also distinct disease-related effects on gene expression between cell types. The team further observed that gene pathway network structures were different across subject groups and cell types. The findings suggest cell type-specific molecular alterations that could be harnessed for future schizophrenia therapies.

NEW ENGLAND JOURNAL OF MEDICINE

EVEN BEYOND SIX-HOUR WINDOW, THROMBECTOMY BENEFICIAL TO STROKE VICTIMS

JAN 2018 \ VOL 378 \ ISSUE 1

Stroke victims who come to the emergency room beyond the standard six-hour treatment window for thrombectomy — a procedure that removes clots from blocked brain vessels accessed from inside the vascular system — can still benefit from the procedure. In a study sponsored by Stryker Neurovascular and led by UPMC and Emory University interventional neurologists, a research team randomly assigned stroke victims arriving beyond the six-hour window to receive thrombectomy or standard medical therapy, which typically provides aspirin.

(Clot-busting drugs are contraindicated beyond 4.5 hours.) Using brain imaging and clinical criteria — as opposed to time alone — the team, including coprincipal investigator **Tudor Jovin, MD**, professor of neurology and director, UPMC Stroke Institute, identified patients with small portions of irreversibly damaged brain tissue and larger brain tissue areas imminently threatened by blockage of a large vessel in the brain. Of the patients who underwent thrombectomy, 48.6 percent had a good outcome (defined as being independent in daily living activities) 90 days after treatment compared to only 13.1 percent of patients who received standard medical care. These positive results ended the trial early, having evaluated 206 patients instead of up to 500, as originally planned.

SCIENTIFIC REPORTS

EXPLORING PATHWAYS TO PROTECT NEURONAL CELLS FROM HUNTINGTON'S DISEASE

DEC 2017

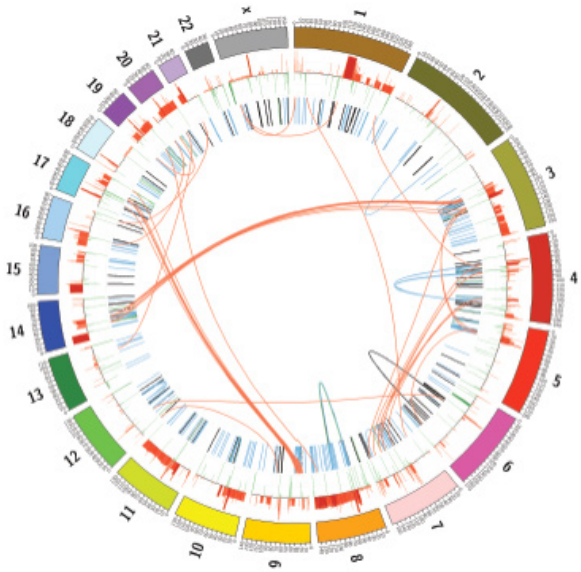
Using quantitative systems pharmacology, a drug discovery approach that iteratively integrates computational and experimental methods, **Mark Schurdak, PhD**, research associate professor of computational and systems biology, and other investigators at Pitt's Drug Discovery Institute sought to protect neuronal cells from mutant huntingtin-induced death associated with Huntington's disease (HD). Using the HD cell model ST*Hdh*^{Q111}, the researchers shed light on potential neuronal cell protection pathways by studying the protective effects of small molecule probes. Using combinations of mechanistically diverse protective probes enhanced the probes' protective abilities, and computational analysis of these probes revealed activation of the protein kinase A (PKA) enzyme network. The team then pharmacologically inhibited PKA activity, reducing protection and indicating that PKA may underlie the protective ability.

CLINICAL CANCER RESEARCH

ENHANCING CETUXIMAB THERAPY TO OVERCOME HEAD AND NECK CANCER IMMUNOSUPPRESSION

JAN 2018 \ VOL 24 \ ISSUE 1

Head and neck squamous cell carcinoma patients (HNSCC) have only a 15 to 20 percent response rate to cetuximab therapy, despite frequent epidermal growth factor receptor (EGFR) overexpression, which is linked to cancer. To overcome the immunosuppression common to HNSCC, investigators added a pro-inflammatory TLR8 agonist to cetuximab therapy to enhance immune response to the cancer by stimulating T lymphocytes and anti-EGFR-specific priming. *In vitro* testing successfully reversed suppression of T-cell proliferation; and, after applying this treatment to 14 previously untreated HNSCC patients in a phase Ib study, patients experienced similar results. Patients harbored fewer myeloid-derived suppressor cells (which suppress T cells) and showed increased M1 monocyte infiltration in their lymphocytes, the researchers, including **Robert L. Ferris, MD, PhD**, Hillman Professor of Oncology and director of the UPMC Hillman Cancer Center, found. Using motolimod plus cetuximab decreased Treg induction and further diminished suppressive mechanisms. The team also observed significantly more EGFR-specific T cells circulating and enhanced infiltration into tumors.



ANNALS OF ONCOLOGY

GENETIC ANALYSIS REVEALS MUTATION BEHIND BREAST CANCER TREATMENT RESISTANCE

APR 2018 \ VOLUME 29 \ ISSUE 4

Estrogen receptor (ER)-positive breast cancer, which afflicts two-thirds of breast cancer patients, can be treated with anti-estrogen therapy. However, ER-positive breast cancers often develop resistance to treatment and recur. Researchers from Magee-Womens Research Institute and UPMC Hillman Cancer Center recently found that ER gene fusion proteins present in treatment-resistant breast cancer can, according to senior author **Adrian Lee, PhD**, Pittsburgh Foundation Professor of Precision Medicine and professor of pharmacology and chemical biology, "outsmart" treatment methods by dividing in half and eliminating the anti-estrogen therapy binding sites. This genetic mutation, which was discovered during posthumous tissue genetic analysis, can be detected by a blood test. Further understanding of the mutation and continued genetic analysis will lead to improved treatments and outcomes for ER-positive breast cancer patients, says Lee, who directs Pitt's Institute for Precision Medicine.

Proteins present in treatment-resistant breast cancer can "outsmart" treatment methods by dividing in half and eliminating the anti-estrogen therapy binding sites.

JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

COMPUTER-ASSISTED MONITORING REDUCES ACUTE KIDNEY INJURY SEVERITY

FEB 2018 \ VOLUME 29 \ ISSUE 2

Standard in-hospital monitoring of kidney function can miss or delay detection of acute kidney injury, which affects one in eight patients and can lead to serious complications and death, says senior author **John Kellum, MD**, Professor of Critical Care Medicine Research and vice chair for research in the Department of Critical Care Medicine. In 2013, a School of Medicine research team launched a computer program within the electronic health record system across 14 UPMC hospitals to monitor and analyze blood creatinine levels, a kidney-health indicator. The program issued alerts if the creatinine levels rose too high or too quickly, indicating possible acute kidney injury. The team has since analyzed more than half a million patient records and found that, with the computer program in place, acute kidney injury patients had a 0.8 percent decrease in hospital mortality and a 2.7 percent decrease in dialysis rates. Magnifying these results across the patient population nationwide could translate to saving more than 17,000 lives and $1.2 billion per year.

JAMA PSYCHIATRY

ONLINE THERAPY MORE EFFECTIVE THAN STANDARD CARE FOR TREATING DEPRESSION, STUDY SHOWS

JAN 2018 \ VOL 75 \ ISSUE 1

Computerized cognitive behavioral therapy (CCBT) remains underused for treating mood and anxiety disorders, says **Bruce Rollman, MD, MPH**, professor of medicine and director of Pitt's Center for Behavioral Health and Smart Technology, who led a study showing that CCBT is more effective at treating anxiety and depression than doctors' standard primary care. For the study, UPMC physicians randomly assigned 704 depressed and anxious patients to participate in either an eight-session online CCBT program or the CCBT program plus a moderated Internet support group (ISG) or to receive only their primary physician's standard care. Over the six-month intervention, patients randomized to the CCBT study arms reported significantly greater improvements in mood and anxiety symptoms, and these benefits lasted for at least an additional six months following their intervention's conclusion. Further, the more CCBT sessions patients completed, the stronger the improvements in their symptoms. However, patients randomized to CCBT plus ISG reported no significant improvements in symptoms over exposure to CCBT alone.

SCIENTIFIC REPORTS

NEW FINDINGS BEHIND REGULATION OF GENE EXPRESSION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

NOV 2017

The calcium-activated chloride channel ANO1 is often overexpressed in head and neck squamous cell carcinoma (HNSCC) and is associated with poor survival rates in several cancers. More recently, the human papillomavirus (HPV) has been shown to act as a causative agent for head and neck squamous cell carcinoma. It remains unclear whether ANO1 expression is altered in HPV-associated cancers. To better understand the epigenetic regulation of ANO1, investigators looked at the mechanisms behind ANO1 expression. The team, which included Pitt assistant professor of otolaryngology **Umamaheswar Duvvuri, MD, PhD**, analyzed squamous cell carcinoma samples and used model systems, including E6 and E7 transfected normal oral keratinocytes (NOK), to stimulate hypermethylation of the ANO1 promoter. Two CpG islands — regions of DNA — positively correlated with AN01 expression; and hypermethylation of these positively correlated CpG islands induced ANO1 expression, which in turn correlated with patient survival. This insight into gene expression in HNSCC can potentially be harnessed for development of therapies to treat squamous cell carcinoma and other cancers.

CELL

TARGETING PROTEIN AND PATHWAY COULD PREVENT CELL DEATH ONSET AND SPREAD

OCT 2017 \ VOLUME 171 \ ISSUE 3

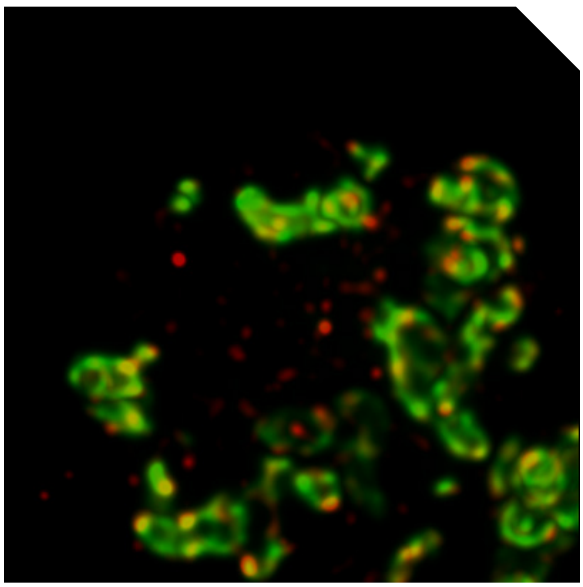
Ferroptosis, a highly regulated cell death process involving iron, is associated with many conditions, including asthma, kidney damage, and brain trauma. When a cell "decides" to initiate ferroptosis, a group of its enzymes known as 15-lipoxygenases (15LO) generates naturally occurring oxidized phospholipids called OOH-phosphatidylethanolamines (OOH-PEs). Pitt researchers, including **Valerian Kagan, PhD, DSc**, professor of environmental and occupational health, Graduate School of Public Health; **Hülya Bayır, MD**, Professor of Critical Care Pediatric Research; and **Sally E. Wenzel, MD**, UPMC Professor of Airway Biology and chair of Pitt Public Health's Department of Environmental and Occupational Health, found that a protein called PEBP1 controls whether the 15LO enzymes generate OOH-PEs or different non-deadly agents. Blocking PEBP1 from binding to 15LO enzymes and targeting the ferroptotic pathway could inhibit ferroptosis in kidney cells during renal failure, in neurons after brain trauma, in airway cells experiencing asthma, and in many other cells and conditions.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

COW'S MILK BABY FORMULA NOT LINKED TO TYPE 1 DIABETES

JAN 2018 \ VOL 319 \ ISSUE 1

Feeding cow's milk baby formula to infants does not increase their risk of developing type 1 diabetes during childhood, researchers from UPMC Children's Hospital of Pittsburgh, and other institutions, found. Previous studies indicated that early exposure to complex foreign proteins, like cow's milk, might increase type 1 diabetes onset in children with genetic risk for the condition. The current study involved weaning 1,081 infants to an extensively hydrolyzed casein formula with the cow's milk proteins split into small peptides closer in composition to breast milk. Another 1,078 infants were weaned to regular cow's milk-based formula. After 11.5 years, of the infants who received the hydrolyzed casein formula, 91 (8.4 percent) developed diabetes, and of those who received regular formula, 82 (7.6 percent) developed the condition. The study was not designed to assess the effect of breast feeding, although evaluation of the nutritional data collected did not reveal a breast feeding effect on the results. Based on this study, there is no need to revise dietary recommendations for infants at high risk of type 1 diabetes, says principal investigator **Dorothy Becker, MD**, professor of pediatrics.



JOURNAL OF EXPERIMENTAL MEDICINE

ACTIVATING PROTEIN FUELS T CELLS FOR BETTER COMBINED THERAPIES

APR 2018 \ VOLUME 215 \ ISSUE 4

Harsh conditions within the tumor microenvironment can quickly drain T cells of energy and impede their cancer-fighting abilities. While it has been known that activating the 41BB protein on T-cell surfaces helps the immune cells last longer in this microenvironment, researchers, including **Greg M. Delgoffe, PhD**, assistant professor of immunology, recently revealed that this activation alters T-cell metabolism, producing the energized effect. Drugs that activate 41BB have not been very successful in clinical trials, but the researchers paired 41BB activation with two existing immunotherapy approaches: a checkpoint inhibitor drug that blocks PD1 protein on T cells and a cellular therapy that uses engineered T cells to recognize tumor cells. Combining 41BB activation — effectively fixing the "fuel issue" — with the two immunotherapy approaches produced better outcomes when tested in melanoma mouse models and is being tested in human tumor models.

Combining protein activation with the two immunotherapy approaches produced better outcomes.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

EXPLORING MYOPIC PROTEIN'S KEY ROLE IN NEUROPEPTIDE RELEASE AND NEUROTRANSMISSION

FEB 2018 \ VOL 115 \ ISSUE 7

Research assistant professor **Dinara Bulgari, PhD**, and professor **Edwin S. Levitan, PhD**, both of the Department of Pharmacology and Chemical Biology, observed in fruit flies that increasing or decreasing expression of the protein Myopic, which is associated with neuronal development and neuropeptide gene expression, increases synaptic neuropeptide stores at the neuromuscular junction. This effect is produced by inhibiting synaptic neuropeptide release from dense core vesicles (DCVs). However, release by small synaptic vesicles (SSVs) is unaffected. This selectivity is surprising because DCVs and SSVs are thought to share the same secretory apparatus. Because neurotransmission involves releasing from both DCVs and SSVs, understanding how Myopic regulates synaptic neuropeptide release could help advance therapies for diseases and disorders involving neuropeptides, which control sleep, appetite, pain, and mood.

JOURNAL OF CLINICAL INVESTIGATION

MUCUS PLUGS LINKED TO AIRFLOW OBSTRUCTION IN SEVERE ASTHMA

MAR 2018 \ VOL 128 \ ISSUE 3

A team of researchers that included **Sally E. Wenzel, MD**, UPMC Professor of Airway Biology and chair of the Department of Environmental and Occupational Health, Graduate School of Public Health, found that mucus plugs, which block the bronchioles, are linked to chronic airflow obstruction in severe asthma and that eosinophils or their products may influence mucus plug formation. To determine this linkage, researchers used lung CT scans to quantify mucus plugs from 146 asthma patients and 22 controls. Patients with more mucus plugs also performed worse on pulmonary function tests. Understanding the relationship of eosinophils to mucus plugs could lead to development of new treatments to improve airflow in chronic severe asthma, the researchers believe.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

PUMA GENE INFLUENCES SIGNALING PROCESS BEHIND NECROPTOSIS

APR 2018 \ VOL 115 \ ISSUE 15

Understanding of the signaling process behind the regulated form of cell death necroptosis remains incomplete. While studying this process, researchers, including **Lin Zhang, PhD**, professor of pharmacology and chemical biology, showed that the gene *PUMA*, a pro-apoptotic BH3-only Bcl-2 protein family member, is transcriptionally activated and is linked to necroptosis. By driving mitochondrial DNA release and activation of cytosolic DNA sensors, *PUMA* boosts necroptotic signaling. In mouse models, genetic evidence points toward the functional role of *PUMA* in developmental defects due to necroptosis. The study is the first to show the ability of *PUMA* and cytosolic DNA sensors to govern necroptotic signaling amplification *in vitro* and *in vivo*.

VACCINE

OCT 2017 \ VOL 35 \ ISSUE 45

NEW ENGLAND JOURNAL OF MEDICINE

AUG 2017 \ VOL 377 \ ISSUE 6

EVALUATION OF VACCINE EFFECTIVENESS, UPTAKE FOR COMMON DISEASES

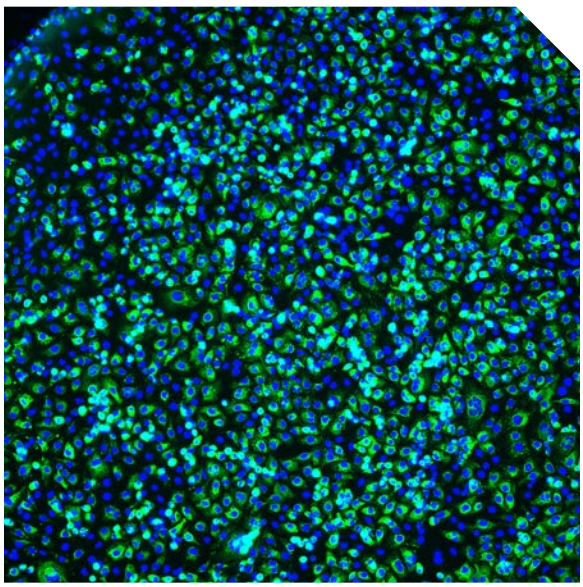
Professors of family medicine **Richard K. Zimmerman, MD, MPH**, and **Mary Patricia Nowalk, PhD, RD**, and other researchers recently contributed to two vaccine studies. One study reported the results of an intervention involving the 4 Pillars Practice Transformation Program, which seeks to guide physicians and medical providers on strategies to improve vaccine uptake in outpatient settings. The program sought to increase vaccination rates for human papillomavirus, influenza, meningococcus, and tetanus-pertussis-diphtheria at 11 pediatric and family medicine practices. Among 9,473 patients who ranged from ages 11 to 17, vaccination rates increased significantly post-intervention — by 17.1 percent for the HPV vaccine, 16.6 percent for meningococcal vaccine, and 14.6 percent for the Tdap vaccine. Influenza vaccine uptake did not increase significantly. In another study, researchers analyzed the effectiveness of the live attenuated influenza vaccine compared with the inactivated influenza vaccine for the 2015–16 flu season. After evaluating 6,879 participants age 6 months or older at various U.S. sites, the live attenuated vaccine was only 5 percent effective among children, compared to the inactivated influenza vaccine's 60 percent effectiveness. Therefore, the Advisory Committee on Immunization Practices recommended against using the live attenuated influenza vaccine for the 2016–17 season. For 2018–19, the live attenuated vaccine has been changed to remedy its ineffectiveness.

JOURNAL OF BIOLOGICAL CHEMISTRY

DEVISING NEW THERAPIES TO FIGHT TRIPLE NEGATIVE BREAST CANCER

JAN 2018 \ VOL 293 \ ISSUE 4

Triple negative breast cancer (TNBC) lacks the estrogen and progesterone receptors that are targeted by many breast cancer therapies. The TNBC phenotype is present in approximately 20 percent of all breast cancer patients; and because targeted therapies are ineffective, TNBC is the most aggressive cancer subtype with the lowest survival rate. Therefore, therapies that target TNBC via other pathways that promote cancer progression are greatly needed. Using preclinical models, investigators studied the effects of the electrophilic fatty acid nitroalkene derivative 10-nitro-octadec-9-enoic acid (NO2-OA) as an agent to combat TNBC. NO2-OA reduced TNBC cell growth *in vitro* and inhibited the growth of human TNBC cell xenografts in mice. NO2-OA also potently suppressed TNBC nuclear factor kappa ß (NF-kß) activity and expression in human TNBC cells, resulting in an inhibition of TNBC cell migration and proliferation. By studying NO2-OA's multifaceted inhibitive abilities, researchers from the Department of Pharmacology and Chemical Biology, including assistant professors **Yi Huang, PhD**, and **Stacy L. Wendell, PhD**; research instructor **Steven R. Woodcock, PhD**; and Distinguished Professor and UPMC Irwin Fridovich Professor and chair **Bruce Freeman, PhD**, found that electrophilic nitroalkenes react with alkylation-sensitive targets in TNBC cells to inhibit the growth and viability of TNBC.



NATURE MICROBIOLOGY

RESEARCHERS REVEAL REOVIRUS TAKEOVER OF PROTEIN-FOLDING MECHANISM

APR 2018 \ VOL 3 \ ISSUE 4

The mechanism by which viruses are assembled inside infected cells has been poorly understood. By studying this process using reovirus, Pitt researchers, including **Terence Dermody, MD**, Vira I. Heinz Professor and chair of pediatrics, revealed that the virus hijacks the TRiC protein, which folds proteins and is found in every cell. TRiC assembles a component of the protein shell that forms the outer coat of the virus, enabling the virus to exit the host cell and infect other cells. When TRiC is disrupted, the outer coat cannot form, disrupting viral replication. By shedding light on the protein-folding machinery inside cells, these findings could help explain protein-misfolding diseases like Alzheimer's and Huntington's, as well as how reovirus could be connected to celiac disease.

When TRiC is disrupted, the outer coat cannot form, disrupting viral replication.

PAIN

INVESTIGATING NEURAL CIRCUITRY BEHIND PAIN WIND-UP

AUG 2018 \ VOL 159 \ ISSUE 8

Wind-up is a phenomenon in which the intensity of a painful stimulus increases upon repeated stimulation, owing to increased activity in corresponding spinal cord neurons. While spinoparabrachial neurons likely contribute to the affective component of pain, whether they show wind-up is a question that Pitt researchers recently explored. After investigating the underlying neural circuitry, **Sarah E. Ross, PhD**, associate professor of neurobiology, and colleagues found that one-fifth of lamina I spinoparabrachial neurons undergo wind-up and that this amplification is governed partly by a spinal excitatory interneuron network that demonstrates reverberating activity. This insight into sensory augmentation circuitry may help explain pain wind-up occurrence and offer new approaches to manage it.

ELIFE

PHOSPHATASE SAC1'S ROLE EXPLORED IN LIVING CELLS

FEB 2018

Why would an enzyme be ensconced in an intracellular compartment where its substrate is rarely found? This was a central question in the biology of a lipid phosphatase, SAC1, which resides in the endoplasmic reticulum. Either the cell moves this membrane compartment close to other membranes to introduce SAC1 to its lipid substrate, or it uses other proteins to transport the lipid from its host membrane to SAC1 — setting up a chemical gradient in the process. Researchers, including **Gerald Hammond, PhD**, assistant professor of cell biology, found that blocking SAC1's activity in living cells led to accumulation of its lipid substrate in the same membrane compartment as the enzyme. Furthermore, they showed the enzyme does not localize in regions of proximity between membranes, and native SAC1 cannot act at the contact sites unless engineered to have a longer reach. Therefore, SAC1's surprising role appears to be in establishing lipid gradients between membranes.

MOLECULAR AND CELLULAR BIOLOGY

TRANSCRIPTIONAL REGULATION OF PLACENTAL DEVELOPMENT

MAY 2018 \ VOL 38 \ ISSUE 9

By examining regulation of the *Muc1* promoter, researchers from Pitt, Magee-Womens Research Institute, and other institutions gained insight into peroxisome proliferator-activated receptor gamma (PPAR gamma) signaling in the placenta. They found that, while the induction of *Muc1* by PPAR gamma requires, as expected, its obligate heterodimeric partner retinoid X receptor alpha (RXR alpha), it is inhibited, rather than activated, by RXR ligands (rexinoids), departing from the canonical mode of target gene activation by heterodimeric receptors. By more closely examining this unique regulation of *Muc1*, researchers, led by the team of **Yaacov Barak, PhD**, associate professor of obstetrics, gynecology, and reproductive sciences, demonstrated that the transcription cofactor ligand-dependent corepressor (LCoR) is required for *Muc1* activation by PPAR gamma–RXR alpha heterodimers. RXR alpha interacts with LCoR in its unliganded state; and its binding to rexinoids abolishes this interaction, resulting in *Muc1* inhibition. In addition, the investigators found that the transcription factor Krüppel-like factor 6, known previously for its roles in hematopoiesis and liver development, is also a key regulator of placental development and synergizes with PPAR gamma, RXR alpha, and LCoR in *Muc1* transcription. These findings unveil a novel combinatorial principle in nuclear receptor signaling and enhance our understanding of PPAR gamma signaling networks in placental development.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

ACCURATE ASSESSMENT OF PATHOGENICITY OF POINT MUTATIONS BY DYNAMICS-BASED COMPUTATIONS

APR 2018 \ VOL 115 \ ISSUE 16

Assessing how point mutations, or missense variants resulting in single amino acid substitutions, affect protein function can inform the prognosis and onset of many inherited diseases and cancers. Yet, computational predictions and methods to evaluate the effect of amino acid substitutions on protein activity usually rely on sequence-level analysis and some structural data. To improve pathogenicity predictions, researchers, led by **Ivet Bahar, PhD**, Distinguished Professor, John K. Vries Professor, and chair of computational and systems biology, developed a computational tool that evaluates changes in the structural dynamics of proteins stemming from point mutations. Their methodology used machine learning and protein topology coupled with amino acid conservation-based predictors. The new tool, benchmarked against more than 20,000 single amino acid human variants, outperforms existing tools for predicting the effect, deleterious or neutral, of mutations on protein function.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

PATIENTS WITH NON-ADVANCED POLYPS HAVE SIMILAR COLORECTAL CANCER RISK AS PATIENTS WITH NO POLYPS

MAY 2018 \ VOL 319 \ ISSUE 19

After undergoing colorectal cancer screenings, people found to have advanced polyps are more than 2.5 times as likely to develop colorectal cancer as those without polyps. However, people with non-advanced polyps have a similar colorectal cancer risk as those without any polyps. These findings come from a data analysis of 15,900 participants followed for up to 15 years. At baseline, 18 percent of patients had an advanced polyp; 32 percent had a non-advanced polyp; and 50 percent had no precancerous polyps. Advanced-polyp participants showed that cancer risk remained elevated throughout the 15 years, not just in the first years after polyp removal. The findings suggest that patients found to have non-advanced polyps may not need follow-up colonoscopies as frequently as guidelines recommend, says senior author **Robert E. Schoen, MD, MPH**, professor of medicine and chief of the Division of Gastroenterology, Hepatology, and Nutrition.

THE BMJ

NIGHT SHIFT VIDEO GAME IMPROVES PHYSICIAN TRIAGE DECISION-MAKING

DEC 2017 \ VOL 359 \ ISSUE 8134

Deepika Mohan, MD, MPH, associate professor of critical care medicine, and other Pitt researchers developed an educational video game aimed at improving physician decision-making in trauma triage. More than 350 emergency physicians working at non-trauma centers were randomly assigned either to play the adventure-based video game *Night Shift* or to use text-based educational apps for one hour, both on iPads. *Night Shift* is designed to recalibrate physicians' use of pattern recognition to recognize moderate to severe injuries through use of narrative engagement (storytelling). In a validated virtual simulation, physicians exposed to the game under-triaged fewer severely injured patients than physicians who received didactic education. At six months, physicians who played *Night Shift* remained less likely to under-triage patients. While real-world efficacy remains uncertain, the theoretically grounded video game improved the act of triage decision-making in a realistic virtual setting.

OTOLARYNGOLOGY—HEAD AND NECK SURGERY

OBSTRUCTIVE SLEEP APNEA TREATMENT PROCEDURE REVEALS POSITIVE 5-YEAR OUTCOMES

JUL 2018 \ VOL 159 \ ISSUE 1

A multicenter cohort of patients who failed to benefit from continuous positive airway pressure (CPAP) therapy received upper airway stimulation (UAS) non-anatomic surgery via a unilateral hypoglossal nerve implant. Enrolled participants met specific clinical and anatomic screening criteria. Five-year outcomes demonstrated clinically meaningful improvements in patient-reported measures of snoring, daytime sleepiness, and sleep-related quality of life. Of the patients completing the five-year sleep laboratory testing, significant and sustained improvements in objective measures of sleep apnea severity were also reported. Serious device-related adverse events were rare. Overall, the study, whose authors included **Ryan Soose, MD**, associate professor of otolaryngology, and **Patrick J. Strollo, MD**, professor and vice chair of medicine in the Division of Pulmonary, Allergy, and Critical Care Medicine, demonstrated that UAS can provide a safe and effective long-term treatment alternative for obstructive sleep apnea patients who are unable to use CPAP.

BIOLOGICAL PSYCHIATRY

MOLECULAR MECHANISMS OF MAJOR DEPRESSIVE DISORDER DIFFER BY SEX

JUL 2018 \ VOL 84 \ ISSUE 1

Reported sex differences in prevalence, symptomatology, and comorbidity in major depressive disorder (MDD) suggest that the molecular mechanisms of MDD may differ by sex. To test this hypothesis, investigators, including **Marianne Seney, PhD**, assistant professor of psychiatry, performed a gene expression analysis on three mood-related brain regions of 26 men and 24 women with MDD and compared them to control subjects. Surprisingly, only 9 percent of identified genes were differentially expressed in both men and women with MDD. Further, a majority of these shared genes were changed in opposite directions in depressed men and women. Gene ontology analysis revealed that men with MDD exhibited upregulation of genes in synapse-related pathways, while depressed women had downregulation of synapse-related genes. The researchers also observed an immune-related pathway (MHC protein complex) in which men with MDD had increased gene expression, but women with MDD had decreased expression. Further, cell type-specific analysis revealed that men exhibited increased expression in oligodendrocyte- and microglia-related genes, whereas women showed decreased expression of these markers. Together, these findings suggest that the transcriptional profile and molecular mechanisms of MDD differ greatly by sex.

NATURE IMMUNOLOGY

EVOLUTIONARY MEDICINE OFFERS NEW PERSPECTIVE ON ANIMAL MODELS AND HUMAN PHYSIOLOGY

MAY 2018 \ VOL 19 \ ISSUE 5

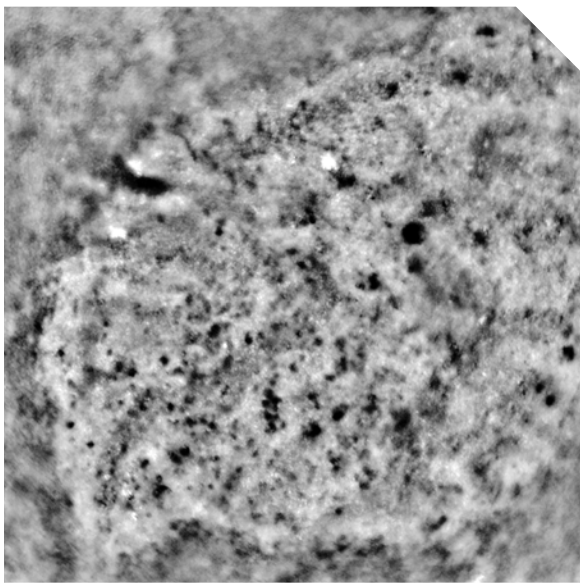
Research using animal models underlies countless new therapies and our understanding of human physiology. But animal models provide only an approximation of human physiology, one that can benefit from greater scrutiny. **Anne-Ruxandra Carvunis, PhD**, assistant professor of computational and systems biology, described the importance of genomic evolutionary history, epigenomes, and molecular networks shaped by animals' biospheres when evaluating animal models' suitability. Taking an evolutionary systems-biology approach, gene expression parallels between animals and humans can actually be quite different upon closer examination. Further, the immune systems of mice and humans evolve under very different and selective influences. By mapping the evolution of genetic interactome networks, researchers might better grasp the array of genetic similarities and differences between animal models and humans and benefit from an evolutionary medicine perspective.

NEW ENGLAND JOURNAL OF MEDICINE

FAMILY-SUPPORT INTERVENTION IMPROVES COMMUNICATION, PATIENT-CENTEREDNESS IN ICU

JUN 2018 \ VOL 378 \ ISSUE 25

Critically ill patients' surrogate decision-makers often face psychological distress in their roles, affecting care decisions made on patients' behalf. At five ICUs involving 1,420 patients total, **Douglas B. White, MD, MAS**, Professor of Ethics in Critical Care Medicine, and other Pitt investigators compared a multicomponent family-support intervention delivered by an interprofessional ICU team to standard care. The randomized trial sought to investigate effects on surrogates' burden of psychological symptoms, quality of communication, and patient- and family-centeredness of care. The investigators found that while the interprofessional ICU team's intervention did not significantly affect or ameliorate surrogates' psychological burdens, overall communication quality and focus on the patients and families improved. Intervention-group patients' ICU length of stay was also shorter than with standard care.



NATURE

THE CHALLENGES, MODEL SYSTEMS, AND TRANSLATIONAL TECHNOLOGIES OF VISION RESTORATION

MAY 2018 \ VOL 557 \ ISSUE 7705

The current state of vision restoration involves new model systems and translational technologies aimed at retinal repair for the blind. As described by **José-Alain Sahel, MD**, Eye and Ear Foundation Professor and chair of ophthalmology and coauthor Botond Roska, MD, PhD, of the University of Basel, Switzerland, many challenges persist: Intrinsic regeneration of the mammalian retina is weak or nonexistent; and the retina has a very large surface area, comprising nearly 100 cell types with complex connections. Mice are a common but imperfect disease model, while primates' eyes have a thick membrane between the retina and inner eye, limiting efficacy of certain gene therapy vectors and other treatments. Despite these challenges, cutting-edge retina models stand to increase our understanding of retinal disease and drive new therapies. Retina-like neuronal structures, termed retinal organoids, can be derived from a skin biopsy and offer biologically realistic systems from which to derive treatments. Retinas from post-mortem human donors also provide an important model system in which to investigate retinal circuitry, a technique benefitting from recently improved methods to extend harvested cell longevity. Further, new technologies are enabling new therapies for repairing damaged retinas and restoring light sensitivity. They include: gene therapy via adeno-associated virus vectors, cell transplantation, artificial retinal stimulation from electronic implants and optogenetics, and others. Ultimately, retinal disease diagnosis and treatment should be cell-type focused and center on understanding the causes and mechanisms behind retinal cell disease and death.

NATURE COMMUNICATIONS

SPECIES-SPECIFIC HOST FACTORS MAY DRIVE HIV-1 VIRAL PATHOGENICITY

APR 2018 \ VOL 9 \ ISSUE 1

While HIV-1 causes AIDS and chronic inflammation in humans, the related simian immunodeficiency viruses (SIVs), which infect nonhuman primates, replicate in their hosts without causing disease or death. To explore potential virus-specific properties behind these two very different clinical outcomes, **Cristian Apetrei, MD, PhD**, professor of microbiology and molecular genetics and a researcher with Pitt's Center for Vaccine Research, collaborated with investigators in Europe and the United States. The team introduced two genes — *vpu*, which codes for a Vpu protein that blocks nuclear factor kappa ß activation and *nef*, which codes for a Nef protein that fails to suppress T-cell activation — into a non-pathogenic HIV-1-like SIVagm virus strain to evaluate their effect on viral replication, pathogenicity, and virulence in African green monkeys. While the SIVagm virus remained in the bloodstream for more than four years, immune activation and inflammation increased only moderately, and the virus did not cause immunodeficiency or any other disease. The findings indicate that species-specific host factors, and not viral virulence factors, determine primate lentivirus pathogenicity.

NATURE COMMUNICATIONS

ATYPICAL CENTRIOLE UNDERLIES HUMAN SPERM CENTROSOME FORMATION

JUN 2018

Fundamental events during fertilization remain mysterious, including the exact components that the sperm delivers into the egg. The centrosome, perhaps the last organelle to still be characterized, is vital for establishing the two spindle poles during cell divisions. Human sperm were known to have a proximal centriole, the barrel-shaped microtubule-organizing center. Using sophisticated light and correlative electron microscopy, a complementary research team, including **Gerald Schatten, PhD**, professor of obstetrics, gynecology, and reproductive sciences, and **Calvin Simerly, PhD**, research associate professor of obstetrics, gynecology, and reproductive sciences (both affiliated with Magee-Womens Research Institute) discovered an atypical distal centriole (DC). Made of splayed microtubules with rods of luminal proteins, it plays a distinct role during spermatogenesis and affects sperm centrosome functioning in the zygote and embryo. This atypical DC can recruit pericentriolar material to form a daughter centriole and to orient the spindle pole (which separates identical copies of chromosomes between daughter cells) during mitosis, resulting in the second centriole. Increased understanding of how the compositional and structural remodeling of the DC forms the atypical centriole could open the door for new diagnostic and therapeutic techniques to treat male infertility, pioneer novel male contraceptive strategies, and shed light on developmental defects that have consequences *in utero* and throughout life.

SCIENCE TRANSLATIONAL MEDICINE

STING PATHWAY INHIBITION MAY REDUCE SEPSIS LETHALITY

OCT 2017 \ VOL 9 \ ISSUE 412

With the overall goal of reducing the high mortality associated with sepsis, **Timothy Billiar, MD**, Distinguished Professor, George V. Foster Professor, and chair of surgery, and colleagues explored using kinase inhibitor drugs in mouse models to target the stimulator of interferon genes (STING) pathway. The pathway, which the team found is activated by anaplastic lymphoma kinase (ALK), is linked to sepsis's characteristic deadly inflammation. Pharmacologically or genetically disrupting ALK expression weakened STING-mediated immune responses and protected against lethal endotoxemia and sepsis in mice, suggesting that the ALK-STING pathway could be a target for novel sepsis therapies.

CELL STEM CELL

REPROGRAMMED PANCREATIC CELLS SUCCESSFULLY PRODUCE INSULIN, LIVE LONG IN MICE

JAN 2018 \ VOL 22 \ ISSUE 1

Using gene therapy, researchers from the School of Medicine and UPMC Children's Hospital of Pittsburgh reversed autoimmune diabetes in mice without the use of immunosuppressant drugs. By employing a method called pancreatic intraductal viral infusion, the research team, including **George K. Gittes, MD**, Benjamin R. Fisher Professor of Pediatric Surgery, delivered a therapeutic virus directly to the pancreas, where it reprogrammed non-insulin-producing pancreatic alpha cells into insulin-producing beta cells. In a subsequent mouse model of autoimmune type 1 diabetes, the therapy converted alpha cells to beta cells that successfully produced insulin and controlled blood sugar levels. These newly reprogrammed cells lasted approximately four months before being destroyed by an autoimmune reaction, a significantly longer time compared to other methods such as beta cell transplantation, in which the cells are killed immediately. The therapy, a step forward in developing a long-term therapeutic approach stimulating pancreatic cells to produce insulin, is being tested in a nonhuman primate model.

NEW ENGLAND JOURNAL OF MEDICINE

INFECTION BLOOD TEST OF LIMITED VALUE IN REDUCING ANTIBIOTIC USE

JUL 2018 \ VOL 379 \ ISSUE 3

Providing physicians with the results of biomarker tests from patients with suspected lower respiratory tract infections did not curb overall antibiotic use, according to findings from the Procalcitonin Antibiotic Consensus Trial (ProACT). Procalcitonin is a peptide whose levels typically increase during bacterial, but not viral, infections. While the interpretation of procalcitonin levels has been proposed to help inform antibiotic decision-making for respiratory infection, investigators led by **David T. Huang, MD, MPH**, associate professor of critical care medicine, sought to evaluate this concept. They randomly assigned 1,656 patients arriving at 14 U.S. hospitals with suspected lower respiratory tract infection to receive procalcitonin-guided treatment or usual care. In the guided-treatment group, physicians received patients' procalcitonin levels and antibiotic use guidelines based on these levels. In contrast to previous research, the ProACT trial found that the procalcitonin guideline had little overall impact on whether or not physicians prescribed antibiotics. Procalcitonin levels generally aligned with how visibly sick patients appeared and with their physicians' judgments of bacterial infection likelihood. Even when physicians did not know procalcitonin results, their decision to prescribe antibiotics was similar to when they did know the results. Thus, physicians likely already withheld antibiotics based on clinical signs and judgment, with procalcitonin offering limited incremental value.

PLOS MEDICINE

INTERLEUKIN 33 MAY PLAY KEY ROLE IN IMMUNE RESPONSE TO SEVERE INJURY

JUL 2017 \ VOL 14 \ ISSUE 7

The early type 2 immune responses associated with immunosuppression and immune dysregulation following severe injury may stem from release of a type of interleukin called IL33, a cytokine released from damaged stromal cells. To investigate this hypothesis, **Hēth Turnquist, PhD**, associate professor of surgery; **Yoram Vodovotz, PhD**, professor of surgery; **Timothy Billiar, MD**, Distinguished Professor, George V. Foster Professor, and chair of surgery; and other Pitt researchers evaluated IL33 changes in blood samples from blunt trauma patients. They found that severely injured patients had elevated IL33 levels over time that correlated positively with IL4, IL5, and IL13, which are linked with type 2 immune response. Mechanistic studies in a replicative mouse model of hemorrhagic shock and tissue trauma (HS/T) mirrored the early increase in IL33 and revealed a pathway used by IL33 to induce group 2 innate lymphoid cell (ILC2) activation in the lung within hours of HS/T. Altering ILC2's governing role in acute lung injury might lead to improved outcomes for trauma patients with lung dysfunction.

JAMA CARDIOLOGY

MARKERS OF PULMONARY HYPERTENSION IDENTIFIED, LINKED TO HEART FAILURE

APR 2018 \ VOL 3 \ ISSUE 4

Patients with heart failure with preserved ejection fraction (HFpEF), in which stiffening of the heart can cause difficulty breathing and exercise intolerance, commonly experience poor outcomes, and there are no approved therapies. While the development of pulmonary hypertension in HFpEF patients is associated with these outcomes, there is a dearth of sufficient hemodynamic data (characteristics of blood pressure and flow) needed to drive targeted therapies. To identify and assess hemodynamic characteristics and further evaluate outcomes, researchers, including **Marc A. Simon, MD**, associate professor of medicine in the Division of Cardiology, studied a cohort of 10,023 patients undergoing right heart catheterization (pulmonary hypertension and HFpEF are common in patients undergoing this procedure, occurring in 25 percent of all cases) at a single center from 2005–12. From the study, researchers analyzed mortality and hospitalization rates and found that transpulmonary gradient, pulmonary vascular resistance, and diastolic pulmonary gradient — hemodynamic markers of pulmonary hypertension — were predictive of mortality and cardiac hospitalization. The authors conclude that the pulmonary hypertension phenotype of HFpEF is common and should be the focus of developing targeted therapies.

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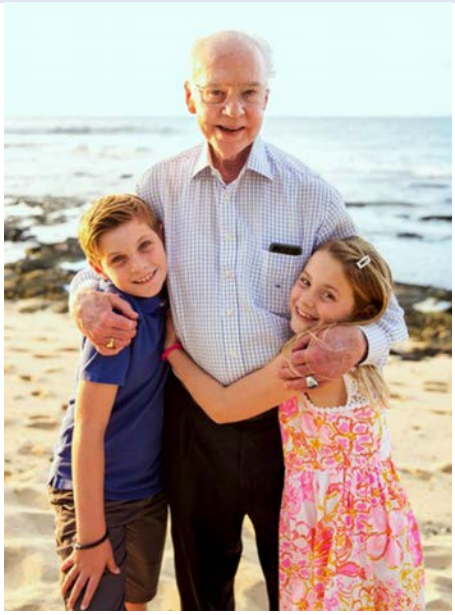

Tom W. Olofson

In the late 1950s, Tom Olofson was a high school student in West Palm Beach, Fla., with little to no expectation of going to college. By the time of his death in 2017, he had just retired as chair, chief executive officer, and founder of EPIQ Systems Inc., a global provider of technology and legal services, having recently sold it in a deal valued at $1 billion. His son, Scott Olofson, said his father credited the launch of his career to his basketball scholarship from the University of Pittsburgh.

"The Pitt scholarship was the only way my dad could've gone to college," says Scott Olofson. "It jump-started everything for him, and he never forgot that."

As a Pitt student, Mr. Olofson was president of student government, Omicron Delta Kappa's "Man of the Year," and a member of the Society for the Advancement of Management. He earned a bachelor's degree in business administration in 1963. After graduating, Mr. Olofson quickly ascended the management ranks while working for companies like Xerox Corporation and Marion Laboratories Inc.

In his late 30s, Mr. Olofson reached another turning point in his life. He was diagnosed with an aggressive form of cancer and was told that his odds of surviving were not good. However, with treatment that was experimental at the time, Mr. Olofson received immunotherapy that stimulated his immune system to attack the cancer cells. He survived and always believed that the innovative immunotherapy treatment had saved his life.

Mr. Olofson moved to Kansas City, Mo., bought the predecessor of EPIQ Systems Inc., and spent most of his remaining years turning it into a successful global company. But his loyalty to Pitt never waned, and he never forgot the cancer treatment that saved his life. So, he endowed the Tom W. Olofson Chair in Head and Neck Cancer Research in Pitt's School of Medicine and the Tom W. Olofson Chair in Entrepreneurial Studies in Pitt's Katz Graduate School of Business.

"He just adored Pitt," says Scott Olofson. "He always had a deep appreciation, respect, and acknowledgment that they believed in him and gave him a scholarship that he translated to a lot of success. He loved that his work allowed him to be active in philanthropy, which he saw as returning the favor to Pitt and giving other people opportunities they wouldn't have otherwise."

Robert L. Ferris, MD, PhD, Hillman Professor of Oncology, and director, UPMC Hillman Cancer Center, says that the endowment will allow the School of Medicine to maintain and extend Mr. Olofson's vision of helping others who face the same health issues he did.

"Mr. Olofson's generosity will permanently establish Hillman as one of the few places in the country to link immunotherapy and head and neck cancer," says Dr. Ferris, who is also professor of otolaryngology. "We feel very blessed that Mr. Olofson's allegiance to Pitt, his cancer survival, and Hillman's strengths in immunology, immunotherapy, and head and neck cancers are brought together by this endowment and will enable the person who holds the professorship to do some remarkable research and clinical work."

Pitt honored Mr. Olofson's achievements and his gifts by naming him a Distinguished Alumnus in 1997 and a Legacy Laureate in 2000. And though he thrived as an entrepreneur and philanthropist, his favorite role was that of grandfather to two grandchildren with whom he shared his love of traveling, especially to Hawai'i and Asia.

"He was just a cool guy—mellow and very humble," says Scott Olofson.

Tom Olofson with his grandchildren

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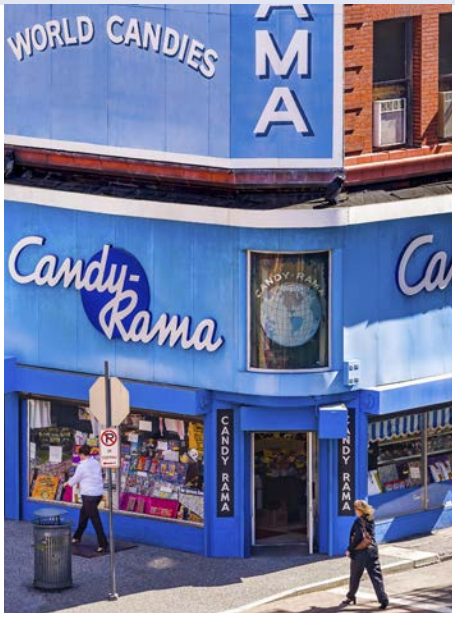

Ruth Gerber Estate

For more than a half-century, Candy-Rama was a Pittsburgh institution. The several Candy-Rama shops in downtown Pittsburgh were known for their friendly staff and for the array of penny and nostalgic candies, imported chocolate, and tchotchkes packed from floor to ceiling. Casual customers were probably unaware that Candy-Rama's founder and his wife, Isadore (Izzy) and Ruth Gerber, provided not only for their customers but also for family, friends, employees, and numerous others who needed help.

After serving in the Army Air Corps in World War II, Mr. Gerber returned to Pittsburgh and opened Gerber Super Fruit Store, a fresh produce market. He employed family members and people who would staff his future businesses for decades. According to his niece and eventual part-owner of Candy-Rama, Marian Pearson, Mr. Gerber would send out for lunches, coffee, and pastries to ensure staff members had a good meal. As his produce business grew, he built a kitchen onto the store, hired a cook, and made sure everyone had a chance to eat during the work day. On Saturday nights, Mr. Gerber would distribute produce to families in need through churches on Pittsburgh's North Side.

Mr. Gerber began selling imported candy at the market and eventually closed it to focus full-time on Candy-Rama, bringing his longtime employees with him. As the candy business grew, he continued to care for his employees and held yearly family picnics and formal dinners for them and their spouses. He regularly donated candy and cash to senior citizens at the Jewish Home for Aging and to children around the city.

"Many people don't know that, after holidays, Izzy had specialty candy and chocolate left over, and he wouldn't just sell it the next day at a discounted price," says Rich Kitay, Mrs. Gerber's friend, accountant, and executor of her estate. "He would take it up to the Lions Club on the North Side and give it to children there."

Ruth and Izzy Gerber married in 1963 and were active in their Adath Jeshurun Congregation. Mrs. Gerber worked in the produce market and Candy-Rama during holidays and other busy seasons but otherwise worked inside the home. Mr. Gerber retired in 1976, and family members, including Mrs. Pearson, took over the business, with Mr. Gerber contributing as a consultant. The Gerbers lived a quiet life, sometimes taking friends to dinner and to the Pittsburgh Civic Light Opera, which Mr. Gerber especially enjoyed, recalls Mr. Kitay. In 1982, the Lions Club of the North Side honored him with their Distinguished Service Award, and in 1995, the Lions Club International Foundation presented him with an award for dedicated humanitarian services. In 1996, Mr. Gerber died after a six-year battle with Alzheimer's disease.

According to Mr. Kitay, Mrs. Gerber was a private woman who wanted no publicity. Before she died at age 93 in 2016, however, she arranged for significant gifts to the School of Medicine — a Ruth Gerber Cancer Research Fund for UPMC Hillman Cancer Center and a fund supporting the Alzheimer's Disease Research Center in memory of Mr. Gerber and her late sister and brother-in-law, Belle and Meir Weiner. After her death, Mrs. Gerber was inducted into Pitt's Brackenridge Circle and Cathedral of Learning Society.

"They were good people," says Mr. Kitay. "Mrs. Gerber was always worried about other people, especially family. She was a quiet and loving person."

Candy-Rama in downtown Pittsburgh

Sean Logan

Nearly every day over the past two years, Sean Logan has taken a three- to four-mile walk at a park near his home. The weather has to be awful for him to miss his walk. In fact, he can count those occasions on one hand. He committed himself to daily exercise after he was diagnosed with Parkinson's disease at age 46 and found that exercise helped with muscle stiffness, helped him sleep well, and "cleared the fog in his brain." Parkinson's disease is a neurodegenerative disorder in which nerve cells in the brain that produce the transmitter dopamine are damaged. The lack of dopamine causes the symptoms of the disease, including body tremors, slowed movement, and balance problems.

After his diagnosis, Mr. Logan's first thoughts were of his two children. He wanted to use his talents and connections — as a former Pennsylvania state senator, former mayor of Monroeville, Pa., and current board chair for UPMC East and UPMC McKeesport — to raise awareness of Parkinson's, as he says, "for my kids and for everyone else's kids who are affected by neurodegenerative diseases." Specifically, Mr. Logan has focused on raising money for the Pittsburgh Institute for Neurodegenerative Diseases (PIND). Affiliated with the University of Pittsburgh, PIND's focus is studying the mechanisms of neurodegenerative diseases like Parkinson's and Alzheimer's to find better treatments.

"My wife and I knew we wanted to do something for PIND the first time we walked through," he says, adding that they were impressed by both the researchers and the environment. "There are no walls — someone may be working on Alzheimer's over here, on Parkinson's there, and someone else is working on Huntington's disease over there, and they discuss and collaborate on their research. I just wanted to pay for the lights or coffee for these amazing people."

Mr. Logan has done more than just raise money for PIND's operating costs or caffeine needs. To help fund the institute's research, he and supporters created the PIND 5K Run/Walk, which is now entering its third year. He wants the money raised through the 5K to allow PIND researchers to "go crazy, to do something they normally wouldn't do, to be creative." To honor Mr. Logan's fundraising achievements, PIND created the Sean Logan Distinguished Lecture Series on Neurodegeneration, which brings in renowned scientists to discuss their research and establish collaborations with PIND researchers.

Mr. Logan has found that many people want to help him support PIND because almost everyone knows someone affected by neurodegenerative disease. He recalls giving an interview and receiving a handwritten note in the mail a few days later.

"One of the sinister symptoms of Parkinson's is that your handwriting goes," he says. "I still force myself to hand-write my checks, but I have to take a nap afterward. So, I get this envelope from a woman who has Parkinson's, and inside was a note and a check for $15 for PIND. The handwriting was shaky, and I knew what a struggle it had been; probably about a week's worth of energy went into writing the note and check. That $15 was like $1 million to me."

Though he admits that raising awareness sometimes means sacrificing some privacy, Mr. Logan says, "As long as I'm able to call people and ask them for money, hold races, and lobby for PIND in state budget appropriations, I'll do it. I really do believe that a cure will come from PIND."

Sean Logan and family in Boyce Park

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Special production assistance was provided by Sandra Honick, Barbara Good, and Linda Riner, Office of Faculty Affairs, School of Medicine, University of Pittsburgh; Beth Ann Conway, Medical and Health Sciences Foundation, University of Pittsburgh and UPMC; and Gayle L. Tissue Kaloyeropoulou, UPMC Hillman Cancer Center.

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Designed by Landesberg Design, Pittsburgh, Pa.

The report is printed on environmentally responsible, FSC-certified Domtar Cougar opaque paper.

Printing by RR Donnelley Printing, Pittsburgh, Pa.

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