excellence

DEFINED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
You probably know excellence when you see it, or realize when you don’t, but what exactly is it? Even more to the point, how can excellence be defined in terms of educating tomorrow’s physicians and investigating today’s diseases? At the University of Pittsburgh School of Medicine, where excellence is an everyday pursuit (and a goal that is often attained), I believe that creativity and leadership are two of the characteristics of excellence that define it best.

Why? Our mission, first and foremost, is to educate the finest clinicians and investigators, and to be successful in either—or, in some cases, both—of these ventures requires nothing less than outstanding creativity and leadership.

One needs to be creative as a clinician because, despite all of the advances we have made in medicine, it is still quite often a mystery; and diagnoses are not always obvious. One needs to be creative as an
Amid life’s countless measures of success (or at least the 252 million Google hits on the phrase “top 10”), for research-intensive academic health centers, the ultimate metric is funding by the National Institutes of Health. Unlike reputational rankings, the NIH process is the only objective, nationally competitive, peer-reviewed standard available for measuring their multi-mission success.

According to this criterion, the University of Pittsburgh, driven mainly by the School of Medicine and its affiliates, has achieved a notable level of success not only by moving into the top 10 list of NIH funding recipients in 1997 but also by maintaining its position ever since—and steadily climbing within this enviable echelon as high as No. 7 among educational institutions and affiliates.

Such ranking shifts are rare. Although more than 3,400 U.S. institutions, including nearly all of the nation’s 126 accredited medical schools, vie for NIH dollars, the competition is fierce (perhaps now more than ever with the stagnation in federal appropriations to NIH). Furthermore, those in the top 10 tend to receive and retain a disproportionately large share of the funding awards each year because in biomedical research—as in the rest of life—success breeds success. Case in point: Pitt and its medical school have both more than doubled their NIH support since 1998.

However, to focus on this aspect of our performance to the exclusion of the others is unfair. There’s no such thing as a school that is strong in NIH support for its research program that doesn’t also have strength in its faculty, its clinical care program, and its students. They all go together, and, at the University of Pittsburgh, that composite is the true measure of our success.
Why, indeed. We posed the question to some of the many people who recently made the move to the School of Medicine from other places. Here’s what they had to say.
When Steven D. Shapiro, M.D., the new chair of medicine, informed his colleagues at Harvard Medical School that he was leaving for Pittsburgh, some of them said it seemed like a good idea, but others, like Jeffrey Drazen, M.D., editor-in-chief of the New England Journal of Medicine, asked why he would do such a thing. “Well,” Shapiro says, “I actually got a call from him recently basically saying what a good decision I’d made.” Not only does Shapiro agree (“It’s everything I expected—and more,” he says), but he, too, admits to being somewhat surprised—not that the move has worked out so well but that he made the move at all, leaving Harvard as the Parker B. Francis Professor of Medicine and chief of Pulmonary and Critical Care Medicine at Boston’s Brigham and Women’s Hospital. So, what was it that got his attention? In a word: opportunity. “Right now, we’re on the verge of understanding disease processes like never before and transforming that understanding into therapies that will improve patient outcomes. I think that going to a place that has the vision, the resources, and the critical mass to do that is what’s really appealing.” The more he looked at Pitt, the more he realized it offered him the best chance to make a difference. “I see Harvard as the present, but this place is the future,” Shapiro says. Now that he’s settling into his new role as head of the School of Medicine’s largest and most far-reaching department and as the Jack D. Myers Professor, he relishes the collaboration that he’s found among his new colleagues and their influence on his own acclaimed research, which has broadened in recent years from understanding the pathogenesis of chronic obstructive pulmonary disease and determining the proteases responsible for lung destruction in emphysema to include the biological functions of those proteases in lung cancer and infectious diseases. “I knew that people would be collaborative, but the quality of what they have to offer really makes my science stronger. It’s pretty amazing,” he says. “Of course, my own research is secondary to that of my faculty at this point, and I anticipate great things from them.”
In an office well above the constant caravan of cars inching through Pitt’s campus, J. Timothy Greenamyre, M.D., Ph.D., has found his niche. When he first joined the Department of Neurology as professor and chief of the Movement Disorders Division, he says, “I had a little office where I had to climb over boxes to get to my desk, and I had a lab about the same size.” In the last year, he has seen both his office and lab space grow and the Pittsburgh Institute for Neurodegenerative Diseases (PIND) come to life. The opportunity to direct PIND was one of the key reasons Greenamyre came to Pittsburgh (finding true love once he got here was an unexpected bonus), and he has assembled a dozen scientists from the Departments of Neurology, Structural Biology, and Pharmacology and the Division of Geriatric Medicine to join him in the institute’s work. In BST3, the University’s newest research building where PIND is based, research areas are without walls delineating each lab’s space, and Greenamyre, who holds the UPMC Chair in Movement Disorders in Neurology, likes that layout. Being able to see, literally, fellow researchers fosters collaboration, he says. “There’s a certain energy level here that’s really exciting.”

The decision to leave Emory University after 10 years was an easy one, he says. “There were all the markings of putting together something great here.”

As an associate professor of medicine and immunology at Yale School of Medicine, Fadi G. Lakkis, M.D., found that his research on the roles of memory T cells and cytokines in allograft acceptance was rapidly distinguishing him as a leading thinker in the area of transplantation tolerance. However, when he was offered the opportunity to come to Pittsburgh as scientific director of the Thomas E. Starzl Transplantation Institute, he didn’t hesitate. “Everyone knows this is a good place,” says Lakkis, who also serves as professor of surgery and immunology as well as the Frank and Athena Sarris Professor of Transplantation Biology. “It has already achieved great things. But more importantly, I get the impression that, no matter how much success there is here, there will always be a greater vision, a drive to do even better. It’s clear that Pittsburgh is committed to providing the resources and intellectual freedom that are needed to produce high-quality science. That’s why I’m here.”

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“The vitality that comes from the adjustments and new learning that a move induces have been wonderful,” says Bruce Freeman, Ph.D., who, after 20 years, left the University of Alabama, Birmingham, as vice chair for research in anesthesiology to become UPMC Irwin Fridovich Professor and chair of pharmacology at Pitt. Part of the excitement was the kind of science being done here. “People in leadership roles at Pitt display a clear-cut vision of the future and an exquisite taste in science in terms of being able to identify what’s hot and what might be a little mundane or old hat,” he says. “There’s a nice synergy between my interests in inflammatory mechanisms—and how to control them—with both basic science and clinical activities at Pitt; here, there’s a significant interest in the future to aging (heart, joint, neurodegenerative disorders) and organ transplantation, and my work meshes nicely with those endeavors.” Other influences were less tangible. “It was just that amorphous spirit that you sense with people here,” he says. “There are indefinable energies that you see in a place where things are working well; people display optimism and a high level of energy, and those traits can’t help but also promote additional creativity.”
Angela Gronenborn, Ph.D., has achieved one of the highest honors to which an American scientist can aspire. She is one of the 72 newest members of the prestigious National Academy of Sciences, all of whom were elected in recognition of distinguished and continuing achievements in original research. Pitt is now home to four of the academy’s 2,025 active members.

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“Pittsburgh? Oh, it was all Art’s doing,” says Angela M. Gronenborn, Ph.D., who had achieved what most researchers only dream about—a tenured berth at the National Institutes of Health. Since NIH scientists aren’t obligated to look for funding or teach, Gronenborn was able to focus completely on her role as chief of the Structural Biology Section in the Laboratory of Chemical Physics at the National Institute of Diabetes and Digestive and Kidney Diseases. Along with most of her colleagues, she assumed it would be a lifelong position; a common joke was that anyone in his or her right mind would only leave the Bethesda campus feet first. “Leaving,” says Gronenborn, “is certainly not regarded as normal. People there were genuinely shocked. It takes someone either very crazy or very adventurous to do such a thing, and I’m not sure which category they thought I was in.”

However, she knew someone who’d made a similar move: Arthur S. Levine, M.D., a former colleague who’s now senior vice chancellor for the health sciences and dean of the School of Medicine. After leaving NIH in 1998, Levine stayed in contact with Gronenborn. “We talked about building things here,” she says. He was particularly interested in her input on plans for the new Biomedical Science Tower, BST3. Gronenborn freely offered her opinions on the concepts behind the building and how they might be executed. She thought she was simply taking part in an invigorating discussion about basic research in medical education. Art Levine had a better idea. “I wasn’t planning on going anywhere,” she says, “but he made me an offer I couldn’t refuse.” That offer was the chance to create and chair the new Department of Structural Biology. Now, as the UPMC Rosalind Franklin Professor, Gronenborn is based in the very building she helped plan. “I can interact with so many different types of people now,” she says, “I can talk to clinicians and see firsthand how basic science supports and influences clinical care. I have graduate students to keep me on my toes. There is a wonderful energy here.”
In many ways, says Hans-Christoph Pape, M.D., Pittsburgh reminds him of Hannover, the German city from which he moved to become associate professor and chief of orthopaedic trauma surgery in the Department of Orthopaedic Surgery. “The cities are about the same size, you don’t have to spend hours in the car commuting, and there are many cultural options,” he says. “I’ve found the environment to be excellent.” Pape is known for his expertise in damage control orthopaedics, an approach adopted by trauma centers around the world in which a critically injured patient’s major organs and systems are stabilized before orthopaedic repairs are made. The reaction of colleagues at Hannover Medical School to his departure ran the gamut. “Some were proud of me, some thought I was crazy, and some were even a little jealous,” Pape says. He thinks it was a great move. “The research opportunities here are excellent. This is one of the top orthopaedic centers in the world, and every graduate should be proud to have trained here.”

HANS-CHRISTOPH PAPE, M.D.

GEORGE K. GITTES, M.D.

“The academic environment here was the strongest and had the greatest potential for me. I’m surrounded by colleagues who operate at a very high level.”

When George K. Gittes, M.D., was considering his most recent career move, he had several opportunities before him—five to be exact. Universities across the country, including Pitt, wanted to hire him as chief of pediatric surgery. Pittsburgh won out, and Gittes is now surgeon-in-chief and director of pediatric surgical research at Children’s Hospital of Pittsburgh of UPMC as well as the Benjamin R. Fisher Professor of Pediatric Surgery and professor of surgery at the School of Medicine. “The academic environment here was the strongest and had the greatest potential for me. I’m surrounded by colleagues who operate at a very high level, and I have the ability to recruit and develop top-notch faculty,” says Gittes. “It was clear to me that Pitt, by far, was the best choice.”

MARY PHILLIPS, M.B.B.CH.

“There’s a terrific science community, from researchers to clinicians, at all levels, and I’m able to collaborate with so many people.”

“Pittsburgh is second to none in neuroimaging and mood disorders,” says Mary Phillips, M.B.B.Ch. “It was a huge opportunity to come here and do this unique kind of research.” As professor of psychiatry and director of functional neuroimaging in emotional disorders, Phillips uses functional magnetic resonance imaging to examine the brain as a basis of emotion and the extent to which neural mechanisms underlying emotions are normal in people with mood and anxiety disorders. She is pleased with how well her research is going since coming to Pitt from London’s Institute of Psychiatry. “There’s a terrific science community, from researchers to clinicians, at all levels, and I’m able to collaborate with so many people,” she says.
Donald S. Burke, M.D., readily admits he wasn’t looking for a job when his new jobs—at Johns Hopkins Bloomberg School of Public Health in 1997 after 23 years in the U.S. Army Medical Corps—found him. “I was happy doing what I was doing,” says the internationally recognized expert in global health and infectious diseases who joined the faculty at Johns Hopkins. Yet, he was intrigued when Pitt began recruiting for a director of its Center for Vaccine Research, a major new initiative at the School of Medicine. As the story played out in 2006, he ended up with not only that job but two others as well: associate vice chancellor for global health and dean of the Graduate School of Public Health; and professor of anesthesiology and director of PCPR, which is engaging the collaborative efforts of pain investigators from the Departments of Anesthesiology and Neurosurgery and the Department of Medicine’s Division of Gastroenterology, Hepatology, and Nutrition. “It was clear there were resources and opportunities here at few other institutions.”

Leading the School of Medicine’s new Pittsburgh Center for Pain Research (PCPR) is a leading expert in the subject, Gerald F. Gebhart, Ph.D., who left the University of Iowa’s College of Medicine as professor and head of pharmacology because he sees the potential for PCPR to become a world-class pain research program. “That’s clearly why I came here,” says Gebhart, professor of anesthesiology and director of PCPR, which is engaging the collaborative efforts of pain investigators from the Departments of Anesthesiology and Neurosurgery and the Department of Medicine’s Division of Gastroenterology, Hepatology, and Nutrition. “It was clear there were resources and opportunities here at few other institutions.”

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Dyeing to See How Hearts Beat

What if cardiologists could one day identify more precisely who is at risk for a fatal heart arrhythmia, know why they are at risk today more than they were last week, and take steps to reduce that risk? Few scientists really understand the electrical system that keeps our hearts ticking reliably, but bioengineer Guy Salama, Ph.D., probes why fatal arrhythmias occur by mapping cardiac voltage and calcium changes. The professor of cell biology and physiology has pioneered the development and use of voltage-sensitive dyes and optical imaging systems to observe the basic electrophysiology of the heart, including the movement of calcium ions, which control force generation and change the polarity of heart cells as they move in and out of the cell. By capturing the changing concentration of calcium ions (a strong indicator of voltage) and overall voltage changes in precise environments, Salama is able to show an electrical signal moving across the heart as a wave. Using this technology, he has demonstrated how a myocardial infarction creates a barrier to this wave, potentially setting off an arrhythmia or even a chain reaction of uncontrolled and uncoordinated heart beats called fibrillation. Still to come, Salama hopes to determine the difference between an irregular beat that the heart can handle and one that is life-threatening. With new dyes and the right technology, he also hopes to someday achieve a first: 3-D imaging of voltage changes deep within the heart as well as on its surface.

A Doorbell to the Immune System

What insights can a primitive relative of the jellyfish provide to better understand the complexities of tolerance for transplanted human organs? Fadi G. Lakkis, M.D., who became scientific director of the Thomas E. Starzl Transplantation Institute in 2005, hopes that the tiny sea creatures known as Hydractinia (sometimes called “snail fur” because of their affinity for growing on the backs of hermit crabs) might allow him to explore the mysteries of the innate immune system. The ability of these tiny invertebrates to recognize and even fuse with one another—or, conversely, to reject dissimilar organisms—is thought to hold some clues to what triggers antibodies and other components of the more sophisticated adaptive immune system that plays such a critical role in organ transplantation. Lakkis likens the innate immune system to a giant doorbell that can awaken the adaptive immune system. By studying Hydractinia, he hopes to answer some of the fundamental questions—like what are the mechanisms that turn the innate immune system on and off—that could apply to humans as well.

Two New Members of an Elite Cadre

A mong the newest members of the Institute of Medicine, an elite cadre of individuals recognized for professional achievement and contributions to the medical sciences, health care, and public health, are Timothy R. Billiar, M.D., and David A. Brent, M.D. Their shared distinction honors individual areas of medical expertise. Billiar, a distinguished trauma and general surgeon, is the George V. Foster Professor and chair of surgery; he is well known for his research on the body’s response to injury and infection. Brent, a leading figure in the study of the risk factors and prevention of adolescent suicide, holds an endowed chair in suicide studies in the Department of Psychiatry and serves as academic chief of the Division of Child and Adolescent Psychiatry at Western Psychiatric Institute and Clinic. Since the Institute of Medicine was established in 1970 by the National Academy of Sciences, only 1,649 people have been admitted to membership, including 15 others from the University of Pittsburgh.

Starzl Awarded National Medal of Science

O n the words ever linked to Thomas E. Starzl, M.D., Ph.D., and his august career on the frontier of organ transplantation, probably his most cherished appear on a simple, round medalion that says “National Medal of Science.” When news came that he would receive the nation’s highest scientific honor, Starzl responded in typical Starzl style: “I don’t think the medal is being given to me; it’s being given to Pittsburgh and the University.” Yes, both are widely identified with Starzl’s work as a surgeon and a scientist in pioneering the field of transplant medicine, but it was his own successes here over a span of decades that secured his legacy. In fact, it was Starzl’s achievements that opened a new vision of the city and its namesake facility that includes an elite cadre of individuals recognized for professional achievement and contributions to the medical sciences, health care, and public health. The building’s strict security, he says, “There’s a guard who sits there, and I still have to show my ID.”

David A. Brent, M.D., left, and Timothy R. Billiar, M.D.
A Novel Approach to Brain Surgery

The best way to the heart is through the stomach, then the best way to the brain is through... the nose? For the past few years, Pitt physicians have been working on an innovative brain surgery technique involving none of the usual incisions and facial disassembly. Using telescopic tools in a procedure called endoscopic transnasal brain surgery, they are able to extract tumors and treat other conditions through the nostrils without manipulating the brain, critical arteries, or cranial nerves. “The technology allows us to navigate deep inside the brain in ways that were once thought impossible and operate with greater confidence to ensure the best possible outcome for the patient,” says Amin B. Kassam, M.D., professor and chair of neurological surgery. Kassam and Carl H. Snyderman, M.D., professor of otolaryngology, are co-directors of the UPMC Center for Minimally Invasive and Cranial Base Neurosurgery and pioneers of the endonasal approach, along with Ricardo L. Carras, M.D., professor of otolaryngology. After the endonasal procedure, patients usually are discharged from the hospital much sooner and with fewer lingering effects than if they had undergone traditional brain surgery. The technique has most recently been successfully expanded from the treatment of adults to pediatric patients.

New Departments Add Advanced Technology

Creating new academic departments at a medical school is like adding teams to the NFL; it just doesn’t happen every day. Yet, within one year, the School of Medicine added three new departments: Biomedical Informatics, Computational Biology, and Structural Biology, all of which reflect the school’s growing emphasis on the integration of advanced technology with basic science in some of the most rapidly developing and leading-edge fields of biomedical research. Biomedical informatics starts with data—complex life sciences data—and employs the principles of information science and technology to analyze and manage the data so as to solve specific problems or create useful models of information. Computational biology, on the other hand, starts with a hypothesis and applies mathematical modeling and computational simulation techniques to analyze and achieve better understanding of intricate biological processes like protein folding kinetics. Structural biology uses nuclear magnetic resonance imaging, X-ray crystallography, and other ultra-sophisticated techniques to study the shape, architecture, and dynamics of proteins, nucleic acids, and other macromolecules that are otherwise too small to be seen in detail so as to better understand their function and interactions. Not only do these disciplines complement one another, they also enhance the collaborative and interdisciplinary environment already established by the school’s other departments, which total 28—for now. Chances are, more are on the way.

I’ll Take Biodegradable Scaffolding Material for $500

On TV’s game show Jeopardy,” if the clue is “polyester urethane urea,” the correct answer would be: “What’s used to make a new, biodegradable scaffolding material that could one day serve as a tissue-engineered replacement for damaged pulmonary valves and other soft tissue?” Readers of Scientific American should get that one right. The journal’s editors chose this technology and the two Pitt bioengineers behind its development, William R. Wagner, Ph.D., and Michael S. Sacks, Ph.D., for the Scientific American 50 awards list for 2006. Thanks to the collaboration of these two researchers, both of whom are associated with the University’s McGowan Institute for Regenerative Medicine, the elastic, tissue-like scaffold, which is formed by using strong electrical fields to combine cells and polymer nanofibers, can be modeled to mimic even the complex workings of the human pulmonary valve. They’re now refining this technique to design tissues for other uses. “Although we may not be able to regrow limbs as salamanders do,” Scientific American notes, “the human body does have intrinsic regenerative power, and the discipline of tissue engineering has discovered ways to exploit it.”
Tucked away in a room of Pittsburgh’s Carnegie Museum of Natural History is a 3-year-old Egyptian who holds a secret. About 2,300 years ago, his organs were removed, his body treated with preservatives and laid to rest, wrapped in white linen and canvas, in a tiny cartonnage brushed with hieroglyphics. No one knows how he died.

The mystery of this mummified corpse was highlighted in the School of Medicine’s new Natural History of Medicine course, which is team-taught by leading scientists at the Carnegie Museum. One of the new mini-electives for first- and second-year students, the course is an outgrowth of the museum-medical school partnership called the Natural History Initiative, which is believed to be the first of its kind in the country.

The idea for this collaboration came about in conversations between two friends, K. Christopher Beard, Ph.D., curator and head of the museum’s vertebrate paleontology section, and John S. Lazo, Ph.D., Allegheny Foundation Professor of Pharmacology and museum board member. They share an interest in evolutionary biology and thought that a course about the history of disease and injury from an evolutionary perspective would enrich the medical school curriculum. The purpose of the course is to give students “insight into the interrelationships between medicine and natural science, which we believe will enhance their understanding of the scientific discovery process while getting them to think about medicine in new ways,” says Lazo.

“My hope is that students will gain a deeper understanding of human anatomy using an evolutionary perspective,” Beard says. Many contemporary medical issues stem from human origins. For example, the transition from walking on all fours to two hind legs contributed to modern orthopaedic issues (hip, knee, ankle, and lower back pain) and more difficult childbirth. Also, disease-causing microbes constantly evolve, and it’s important to comprehend how. HIV was initially a pathogen in primates that eventually mutated and crossed over to humans, so grasping basic principles of evolution can help students to better understand how mutations occur in diseases that are currently public health concerns (like avian flu).

Students taking the course can also observe a cancerous tumor in a 150 million-year-old Jurassic dinosaur bone and evidence of gout in one of the museum’s meat-eating dinosaur skeletons. Such observations can lead to fresh ideas about the origins, prevention, and treatment of human illnesses.

Medical students won’t be the only ones to benefit from the collaboration. Museum scientists can access Pitt’s computed tomography and magnetic resonance imaging scanners (rather than breaking apart a skeleton or fossil, a scanner allows researchers to peek inside it less destructively) and electron microscopes. They’ll also have beneficial interaction with the students themselves. “What strikes me most about these medical students is their overall quality. They have a strong background in the basic biological sciences and are swift to engage with new concepts. I’ve gotten several questions from students that have really made me think about things from a new perspective,” says Beard. He hopes that museum scientists and medical students will benefit from “reciprocal illumination.”

In the meantime, some additional planned research might provide a clearer idea as to what caused the young Egyptian’s death—without unfolding his death garments or disturbing his quiet sleep.
Potential Therapy for Rare Immunity Defect

Gene therapy might someday become a viable option for treating severe combined immune deficiency, a rare disease of the immune system; but unlocking that potential requires better understanding of B cells, the immune system’s antibody factories, and especially the process of recombination that creates those antibodies. Figuring out what drives and what stops antibody production is the focus of Lisa Borghesi, Ph.D., assistant professor of immunology, whose research has identified the stretch of B cell DNA where recombination begins. She also has learned that mice without a certain protein (transcription factor E47) show a 90 percent decrease in recombination activity, indicating that this protein plays an important role in the process. “Once we know the specific factors that turn recombination on and off in the mouse model, we’ll look in patients and see if they have those factors,” says Borghesi. “With gene therapy, there may be an opportunity to correct that defect if they don’t.”

Poetry and Medicine

When poet and physician William Carlos Williams was asked why he pursued his interests in poetry and medicine, he replied, “They amount for me to nearly the same thing.” Though the connection between the arts and medicine may not be obvious, many students in the School of Medicine also pursue each with a similar passion, judging by the number of submissions that editors receive for the student literary magazine Murmurs. Funded by the Medical Alumni Association and the Office of Admissions and Financial Aid, Murmurs is produced in the fall, and a CD of student music is created in the spring. When asked why poetry is so popular with physicians (JAMA has a regular column called “Poetry and Medicine,” and the New England Journal of Medicine sometimes prints poetry), one of the magazine’s current editors, Kevin Proctor, said, “Science is often seen as right or wrong, and there isn’t a lot of room for personal expression.” Poets and physicians are both expected to excel in observation, synthesis, and the creation of a whole from seemingly unrelated parts; many medical schools are incorporating the arts and humanities into their curricula. “Writing’s just a good distraction from school,” Proctor says. “People are looking for a creative outlet outside of studying.”

Obesity Researcher Looks to Leptin for Answers

In obesity research, a supposed panacea comes down the pike all the time, so Allan Zhao, Ph.D., associate professor of cell biology and physiology, is cautious when he talks about his work with leptin, a hormone produced by fat cells. Leptin causes people to limit food intake, expend more energy, and lose weight. It’s found in high levels in the blood of the obese, but for some reason, it has trouble in that population getting to the hypothalamus, where it works. Zhao decided to pass human serum through a leptin column, suspecting that whatever bound to leptin could be retarding its progress. Five major protein bands stuck. One of them—C-reactive protein (CRP)—has been found to be abundant in the blood of obese individuals and to suppress leptin’s functions. Zhao wonders whether an agent can be developed to disrupt the CRP/leptin interaction, but he doesn’t expect a quick fix. “Obesity is a complex problem,” he says.

Workings of the Teenage Brain

While no one may ever be able to explain why teenagers don’t clean their rooms, exploring the workings of the teenage brain—why adolescents sometimes put themselves in precarious situations or engage in impulsive behavior, for instance—has won Beatriz Luna, Ph.D., prestigious recognition. She was one of 56 young researchers who gathered at the White House in August 2006 to receive a Presidential Early Career Award for Scientists and Engineers. In addition, Luna received approximately $1 million to continue her research in adolescent brain development as associate professor of psychiatry and psychology and director of the Laboratory of Neurocognitive Development. Her current work, funded through the National Institute of Mental Health, aims to establish a template for “normal” cognitive maturation that can be used to identify impairments like schizophrenia or mood disorders that can emerge in adolescence.
Heart-Healthy Bacon? Maybe Someday

You’ve heard of pork—the other source of heart-healthy omega-3 fatty acids, right? Until now, omega-3 fatty acids, which can improve heart function and reduce the risk of heart disease, have come primarily from dietary supplements or certain types of fish, especially salmon and tuna, which may also carry high mercury levels. A multi-institutional research team led by Yifan Dai, M.D., Ph.D., associate professor of surgery and a researcher at the School of Medicine’s Thomas E. Starzl Transplantation Institute, has cloned transgenic pigs engineered to produce omega-3 fatty acids, providing vast new opportunities for studying the substances’ influence on cardiovascular function, not only in pigs but in humans as well. The key to the development is the transfer of a gene known as fat-1, which creates an enzyme that converts less desirable but more abundant omega-6 fatty acids in the pigs into omega-3 fatty acids. Dai, whose collaborators on this project include transplant pioneer Thomas E. Starzl, M.D., Ph.D., and Rhobert Evans, Ph.D., from Pitt’s Graduate School of Public Health plus researchers from the University of Missouri-Columbia and Massachusetts General Hospital, says the pigs could also serve as a model for studying autoimmune disorders and diabetes. Although getting them into the food chain is not the current focus of the team’s research (and the Food and Drug Administration would certainly have something to say about that), the bonus might someday be the ability to make bacon that’s actually good for you.

Pitt’s Fogarty Fellows Around the World

Global health is an increasingly popular topic among Pitt medical students, as evidenced by their recent representation in the International Clinical Research Scholars Program sponsored by the National Institutes of Health’s Fogarty International Center.

Yetunde Olutunmbi, Pitt’s 2007 Fogarty fellow, is headed to Tanzania for a year of mentored clinical research at Muhimbili University College of Health Sciences. In 2006, Pitt had three Fogarty students. The program took Susan Wong to Nanjing, China, for work at the National Center for STD and Leprosy Control; Kate Dickman’s fellowship was at Makerere University in Kampala, Uganda; and Krista Pfaendler was in Lusaka, Zambia, at the Center for Infectious Disease Research-Zambia. All three students were able to acquire funding to extend their stays for another year. Dickman was awarded a Howard Hughes fellowship to continue her studies in Uganda. Pfaendler received additional support through one of her Fogarty mentors from the University of Alabama, which maintains a large-scale HIV treatment program in Zambia. Wong is now in Beijing as the first student at the Fogarty International Center-sponsored China Collaborative Suicide Research Training Program, with joint funding from the Dean’s Research Fellowship Program and the center.

Exosomes Grab Attention

Paul D. Robbins, Ph.D., got interested in exosomes by accident. These tiny vesicles, which are emitted from all kinds of cells, were originally thought to be responsible for nothing more than getting rid of cellular junk, but they’re now being studied for their role in cancer, immunosuppression, and as treatment for autoimmune diseases. Robbins, professor of molecular genetics and biochemistry, had been looking at modes of gene therapy for autoimmune diseases. After he injected a therapeutic dose into the paw of a mouse afflicted with rheumatoid arthritis, not only did the condition at the injection site improve, but the opposite paw got better too. The injected gene helped suppress the immune response that was causing rheumatoid arthritis, and the affected dendritic cells then emitted exosomes that traveled through the bloodstream and seemed to send the same signal to the other joint as well. Robbins is now working on generating exosomes from immune cells in vitro and injecting the resultant immunosuppressive exosomes into mice as a potentially viable treatment for all manner of autoimmune disease. But why use exosomes rather than cells? Whereas the immunosuppressive attributes of a cell can be reversed in the body, it seems that those of exosomes cannot. They’re a more stable and, Robbins believes, safer method of achieving immunosuppression.

Above right: Once ignored, exosomes are now seen as a potential treatment for autoimmune disease.
Enlisting Patients as Partners in Clinical Research

Flower than 4 percent of people with cancer generally participate in cancer-related studies, says Steven E. Reis, M.D., associate vice chancellor for clinical research. How does this fact affect cancer treatment? How can researchers make the study of health-related issues more attractive to patients who could benefit from the research? Having enough people willing to participate in clinical trials has always been a challenge.

Pitt, in collaboration with the University of Pittsburgh Medical Center (UPMC), is implementing a novel approach to combat the dearth of study participants by developing a clinical research registry—a database of people willing to participate in clinical research and an ongoing list of current studies being conducted through the University. The database will be embedded in UPMC’s electronic health record system (eRecord), giving researchers potential access to people who use UPMC’s 400 doctors’ offices/specialized outpatient clinics and 19 hospitals, which account for more than 3 million outpatient visits and more than 167,000 hospitalizations a year. The goals of the registry are to provide all UPMC network patients with educational materials about clinical research and to seek their permission to be contacted for study recruitment.

“We see development of the research registry as a natural step toward our vision of extending eRecord to areas such as clinical trials enrollment and epidemiological research,” says G. Daniel Martich, M.D., UPMC’s chief medical information officer. “UPMC has spent more than half a billion dollars building a truly interoperable, long-term electronic health record not only to enhance clinical care and improve quality but also to pave the way for research.”

The registry is just one component of Pitt’s new Clinical and Translational Science Institute (CTSI), established with an $83.5 million grant from the National Institutes of Health. Pitt is one of the first institutions selected to receive this award, joining 11 other academic medical centers in aiming to transform how clinical and translational research is done. The purpose of CTSI is to quicken the time it takes for biomedical advances to reach the medical consumer. Other goals are to promote initiatives that ensure patients—especially minority patients and those from underserved populations—greater access to clinical trials; to encourage collaborations that can facilitate the adoption of new medical therapies in clinical practice; to foster the launch of novel technologies; and to promote the training of a new generation of clinical scientists.

Creating the clinical research registry is an important part of the translation process. The critical first step is to introduce people to the registry when they check in at a UPMC point-of-service office. They’ll receive educational materials about clinical research and the potential benefits of becoming a research participant. They’ll also be asked to provide written permission to participate in the registry. “We think that asking for consent at first contact—rather than an unsolicited mailing, for example, or waiting for responses to posted requests—is crucial,” says Reis, the grant’s principal investigator and head of CTSI. If patients sign up, their medical records will be matched with inclusion criteria for more than 5,600 Institutional Review Board-approved studies currently going on at Pitt. They’ll receive regular mailings about studies or medical issues that might be pertinent to them and be offered the chance to participate in specific studies. At the same time, safeguards will be established to protect the confidentiality of patient records and to prevent their use outside the registry’s carefully prescribed parameters.

Reis hopes the registry helps to create a “research-informed patient.” Many people distrust or have no interest in clinical research, don’t know what its benefits or risks are, or have no idea how it can affect their health care. By removing such barriers, the expectation is that people will develop a vested interest in clinical research because they’ll see how it can translate into better health care. For example, he says, “We don’t have polio in our nation today because of the polio vaccine, which was developed through clinical research.”
When they first met, David H. Perlmutter, M.D., Vira I. Heinz Professor and chair of pediatrics, and Jeffrey Brodsky, Ph.D., Avinoff Professor of Biological Sciences, saw each other as potential rivals because both studied a similar area of cellular protein degradation. After realizing that their research and experience would be complementary, however, Perlmutter and Brodsky began working together on ways to keep proteins from aggregating, a process linked to diseases like Alzheimer’s, amyotrophic lateral sclerosis (Lou Gehrig’s disease), and various liver dysfunctions. Before they began collaborating, Perlmutter and Brodsky independently showed that autophagy degrades the enzyme inhibitor alpha-1-antitrypsin (A1AT), the deficiency of which can lead to abnormal protein aggregates. They also found that when cells don’t have a normal autophagic response, they are susceptible to greater aggregation when exposed to too much of the mutated protein. They believe that defects in autophagic response could be part of the cause of liver damage in 10 percent of patients with A1AT deficiency. Therefore, Brodsky and Perlmutter are now looking for compounds that trigger the autophagic response or prevent protein aggregation in A1AT deficiency and other protein aggregate diseases. They are searching for such compounds with baker’s yeast and with the small roundworm Caenorhabditis elegans; colleagues are helping them create a worm model of A1AT deficiency with protein aggregates and testing compounds to see if any degrade the aggregates without hurting the worm. “We’re cautiously optimistic about our chances of finding some interesting compounds that will have application to a number of protein aggregate diseases,” says Perlmutter.

Diversity in Medicine

Numbers tell the story: 25 percent of the U.S. population today is composed of African Americans, Hispanic Americans, and Native Americans, yet only 6 percent of the nation’s practicing physicians come from these minority groups. To bolster diversity in medicine, especially among the physician workforce, the Association of American Medical Colleges (AAMC) has initiated a campaign called Aspiring Docs and selected the University of Pittsburgh as one of the program’s four pilot schools, at which particular efforts are being made to narrow the gap between the number of undergraduates from all major racial and ethnic groups (particularly, but not exclusively, biology majors) and those who apply to medical school. The School of Medicine is engaging in a variety of initiatives to support and publicize this nationwide campaign to change the face of medicine so as to better serve the health care needs of an increasingly diverse American population.

Amphibian Tales

Salamanders and newts can regenerate lost limbs, so why not us? At the McGowan Institute for Regenerative Medicine, Stephen F. Badylak, M.D., D.V.M., Ph.D., coordinates a team that hopes to learn how to regrow a mammalian digit. They believe that amphibians can show them how. Badylak, professor of surgery, has already successfully used biologic scaffolding derived from a pig bladder to regenerate two severed fingertips—bone, blood vessels, nerves, skin, and fingernail. After growing back, the fingertips looked perfect and were perfectly functional. Badylak’s assessment: “It’s really rare. I’m not saying it’s impossible, but nobody would have predicted it [working].” Now, with funding from the Defense Advanced Research Projects Agency (DARPA), he and a team of scientists from throughout the U.S. are reaching for an even loftier goal: regenerating an entire functional digit (joint included) in a mouse—just like a salamander. From this project, they hope to learn much about the genetics of regeneration. The payoff for success would be the prospect of someday being able to regenerate a fully functional human limb or even vital organs. “We’re hoping to learn principles that will make many things possible,” says Badylak.
Focus on the Basics

Before second-year medical students begin their clinical rotations and come face to face with that monolithic (and often confusing and demanding) entity called the health care system, they must take a new course, “The Basic Science of Care,” which is designed to help them better understand how the system works (or sometimes fails to work), identify viable solutions to realistic problems or limitations within the system, and develop an appreciation for collaboration among interdisciplinary members of the health care team in delivering safe, effective, evidence-based medicine. One particular focus of the course is the importance of information technology and communications systems in providing cost-effective, error-free medical care. While the course is required for medical students, it is open to students from all of the University’s health sciences schools and involves faculty from each of these disciplines: medicine, nursing, pharmacy, public health, rehabilitation sciences, and dental medicine.

A Show of Support

Pitt’s Medical Scientist Training Program (MSTP) has received approval for a doubling in the number of student slots funded annually by the National Institutes of Health. The increase from nine to 18 positions will be phased in by 2009 as part of a five-year grant renewal. “This is definitely a demonstration of support for the program and a reflection on how well students are doing in it,” says Clayton A. Wiley, M.D., Ph.D., director of the program. The MSTP provides medical students who are interested in biomedical research the opportunity to earn dual degrees as an M.D. and Ph.D. Pitt’s program, which currently has nearly 100 students enrolled, is also funded by the Office of the Dean. Only 41 such programs across the country receive NIH support. Wiley says the additional funding will give Pitt a further edge in the competition to recruit top-level students.

Bubbles to the Rescue

Imagine being able to detect coronary heart disease, noninvasively, decades before symptoms develop. Such was the idea that prompted Flordeliza S. Villanueva, M.D., associate professor of medicine, to pursue her work with microbubbles, inert gaseous bubbles smaller than red blood cells that can course through the blood stream without causing blockage and that, when used with imaging technology, can reveal blood flow and otherwise hidden processes. Villanueva and colleagues were the first to prove the principle that—with the use of ultrasound—heart disease could be diagnosed in a living being at the cellular level. Microbubbles developed by her research team to make such early detection possible adhere to inflamed cells, which overexpress unique molecules on their surfaces. The shells of the targeted bubbles bear antibodies directed against these molecules, causing them to flock to the inflamed cells. The microbubbles can then be detected with ultrasound imaging. This development, which is now being refined in animal models, may someday be used to detect not only heart disease but also other diseases and conditions, including transplant rejection, tumor angiogenesis, and stem cell activity.

Advancing Biosecurity on the Public Agenda

As the 2008 elections approach, the Center for Biosecurity of UPMC wants to ensure that biosecurity issues are “appropriately emphasized and illuminated” by organizing a bipartisan Congressional Caucus on Biosecurity to serve as “a focal point for information and discussion” for members of Congress and their staffs about biosecurity issues and legislation. The Center for Biosecurity works to advance policies and practices by providing independent research and analysis for decision-makers in government, national security, bioscience, medicine, public health, and private industry. “We plan to brief presidential and congressional candidates on these issues and to prepare recommendations for improving biosecurity that we’ll offer to the next administration,” says Tara O’Toole, M.D., M.P.H., the center’s director and chief executive officer as well as a professor of medicine. “We’ll work to more clearly articulate the national benefits and opportunities to be gained from greater investment and ambition in biological research and development; and we’ll continue to work on a wide range of key biosecurity challenges.”

Looking for Blood in All the Right Places

People undergoing intensive radiation therapy for blood cancers may hold the key to their own treatment. Doctors often reconstitute such patients’ bone marrow; however, the bone marrow stem cells run the risk of already being contaminated with cancer cells. Researchers led by Albert D. Donnenberg, Ph.D., professor of medicine and director of the University of Pittsburgh Cancer Institute’s Hematopoietic Stem Cell Laboratory, have found another source of hematopoietic, or blood-forming, stem cells in human adipose tissue—better known as fat tissue (hey, it should be good for something). After isolating the stromal vascular fraction from adipose tissue, the researchers were able to grow pericytes, cells surrounding small blood vessels, in a blood-culturing medium. Using flow cytometry, they found among these cells many different hematopoietic cells at varying stages of differentiation as well as evidence of progenitor cells that can give rise to all different types of blood cells.

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The evolution from student to physician
hy, you might ask, is having more than a passing familiarity with research so important in medical education and in the practice of today’s medicine? And why do we feel so strongly about this issue that we have woven a scholarly project into our curriculum and made it an integral component of every medical student’s experience here? The simple answer is tied to the never-ending quest for excellence in the education of would-be physicians. However, simple answers don’t tell the full story, which, in this case, is perhaps best approached from the bottom line: What kind of doctor do you want? Our thinking is that physicians schooled in the analytic process are better prepared than those without such a background to retrieve and critically evaluate the information in this week’s *JAMA* and *New England Journal of Medicine*—information that can help them determine patient treatments, for instance, or separate advertising hype from established facts in the process of evaluating new drugs. We believe that physicians schooled in the analytic process will listen to a patient’s medical history and complaints differently. Rather than starting with a set of memorized characteristics and trying to fit the patient into one pathogenic category or another, they listen to all the facts the patient provides and put them together anew. Even if the outcome turns out to be familiar, the realm of diagnostic possibilities is much broader and the practice of medicine much richer than when it is based simply on rote recognition of symptom patterns. We also contend that physicians schooled in the analytic process are more likely than others to get to the bottom of a case and to yield creative clinical decisions based on solid evidence when symptoms don’t fall into common patterns and that they’ll be better equipped to deal with the rapidly changing developments that have become a hallmark of contemporary medicine. So, once again, what kind of doctor do you want?

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Beginning with the Class of 2008, which started medical school in 2004, a scholarly project has been incorporated longitudinally throughout our curriculum and has been broadly defined to provide a wide range of opportunities to appeal to individual students’ interests and aspirations.

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**Case Studies: Five Students and Their Scholarly Projects**

As American folklorist and writer Zora Neale Hurston once said, “Research is formalized curiosity; it is poking and prying with a purpose.” For Pitt medical students since 2004, part of that purpose is to meet a new curricular requirement, which affords them considerable latitude for formulating a mentored scholarly project that meets their personal interests. However, all the projects share a common goal, which is to help them become better physicians. Here are examples of the projects being developed by members of the Class of 2008, the first one required to partake in this “formalized curiosity” process.
While a limited number of other medical schools have incorporated similar research projects into their programs, our scholarly project differs in several significant respects. One hallmark is the thoroughness with which we prepare students to undertake a scholarly project, regardless of whether it involves basic or clinical research, population-based research, or a nontraditional endeavor. Our curriculum leads students through a sequence of courses, examples, and creative implementation steps as well as practice in scientific writing to give them the skills needed to successfully conduct scholarly work.

This preparation is particularly important because today’s medical students matriculate from a broader array of backgrounds and experiences than in generations past, and so they might not have been previously exposed to the basic tools of scientific inquiry. By integrating mandatory didactic components of the program throughout the curriculum, we can maximize the benefits of this experience. Further, the mandatory aspect of the scholarly project doesn’t make it unique but certainly among the more exclusive programs now being offered.

Finally, regular, periodic checkpoints of students’ progress throughout the four-year process, an emphasis on developing strong faculty mentors to ensure the program’s ongoing success, and creative use of electronic technology to foster learning and mentorship are among its other distinctive elements.

The scholarly project represents a novel (and perhaps even prototypical) way to increase the number of medical students who pursue research-based careers or clinical careers grounded in evidence-based medicine—and those are the kinds of doctors we want.

Kristin Robbins

To create a better vaccine, “you have to start somewhere,” Kristin Robbins says, and that means dealing with basic science, which she enjoys. “I kind of like getting in on the groundwork,” says Kristin, who has a degree in genetics from the University of California, Davis, and experience working in a biosecurity lab at the Lawrence Livermore National Laboratory. With that background, it’s easy to see why hardtack science would interest her and how that interest would influence her selection of a scholarly project.

Under the mentorship of Gerard J. Nau, M.D., Ph.D., an immunologist with expertise in infectious disease, Kristin is exploring how to develop a more effective vaccine against tularemia, a relatively uncommon but highly infectious and easily spread bacterial disease. Spurring her interest are the dual facts that tularemia’s virulent properties make it a potential biological weapon and that the current vaccine made from a live strain of the disease’s pathogen, Francisella tularensis, is not approved for widespread use in the U.S.

Kristin’s hypothesis is that a safer, more effective vaccine can be developed by exporting immunogenic proteins from the bacterium to create a more potent immune response. The process of testing her hypothesis has begun; “I should have the results from at least one immunogenic protein by the end of this year,” she reported in early 2007.

Kristin admits to having “a fondness for research” but hasn’t determined how much a part of her career it will be. Doing research “helps you figure out the questions to ask and how to approach those questions,” she says, adding that it parallels somewhat the experience of a clinician who faces a challenging case and must go about trying to solve it; the skill set is similar. Not only that, she says, but research is essential to clinical medicine. “It’s important to have research in order to move forward and continue to develop the kind of treatments that the public expects from us.”

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Amanda Christini

Amanda Christini is puzzled why all health care workers aren’t willingly immunized against influenza each year. The reality is that only about 40 percent of them are vaccinated, according to nationwide studies, which have documented the dangers of nosocomial transmission of the flu, especially to high-risk hospital patients.

Based on nearly 10 years of experience working in the biotech arena, most recently in business development of vaccines and immunotherapy, Amanda brought an interest in the topic with her to medical school along with a biology degree from Tufts University. Her mentor, Karin E. Byers, M.D., an infectious diseases specialist, helped her formulate the focus of her scholarly project, which is designed to gauge vaccination rates and motivating factors among various groups of health care workers.

The study involves 1,042 workers at UPMC Presbyterian, UPMC Shadyside, and Children’s Hospital of Pittsburgh of UPMC. The results, as published in *Infection Control and Hospital Epidemiology*, show that the groups of health care workers with the most patient contact are the least likely to be vaccinated and that approximately half of the health care workers have come to work with flu-like symptoms.

To boost compliance rates among various groups of health care workers, the report suggests educational initiatives targeting the benefits of immunization as well as ways to counter prevailing misconceptions. “What you really have to do is win people over,” Amanda says.

She notes that today’s medical students recognize the importance of research experience to be competitive in their residency applications. “It’s actually nice that there’s a formal structure now that can support people to do the work they need to do anyway and would have done on their own,” she says, adding that coming from an institution with such a high reputation in research gives Pitt medical students clout as they approach the next phase of their education.

Brian Dontchos

Before Brian Dontchos came to medical school, he spent two years in a job harvesting cartilage allografts from cadavers for organ donation. In doing so, he learned how sensitive chondrocytes, or cartilage cells, can be.

The allografts must be captured within 48 hours of death and kept cold for up to two or three weeks to prevent bacteria growth while donor screening and microbiological cultures are performed to ensure the safety of the recipient. However, studies have shown that cold can diminish the chondrocytes’ viability.

Another variable, which has not been explored as much, is the pH of the solution in which the allografts are stored pending transplantation. So, when Brian, who has a biology degree from the University of Denver but little background in biomedical research, needed a topic for his scholarly project, he drew on his work experience, and, with the help of Constance R. Chu, M.D., orthopaedic surgeon and mentor, he designed a study titled “Enhancing Human Chondrocyte Viability.”

What he found and subsequently reported in an article submitted to the *Journal of Orthopaedic Research* is that adding CO₂ to the solution can provide the pH levels that the cartilage cells require; alternatively, he determined that using storage media that maintain the requisite pH can also work.

Admittedly reluctant at first about the scholarly project requirement, Brian says it turned out to be a positive experience: “I was actually excited about it when I first came up with the idea and my mentor was willing to help.” In caring for patients with wide-ranging problems during his clinical rotations, Brian says he has learned that physicians must be able to think critically, develop a plan of action, and solve the unknown—all of which are skills that doing research can engender.
Yvette Tanhehco

Yvette Tanhehco came to medical school with a Ph.D. in biochemistry and cellular and molecular biology from Johns Hopkins University and considerable research experience in viral oncology. She wonders if the time she must devote to a required scholarly project might not, in her case, be used differently; but with lemons-into-lemonade optimism, she admits to seeing the benefits of the experience.

Yvette’s project is based on the premise that individuals with Down syndrome experience obstructive coronary artery disease less often and have a lower mortality rate from atherosclerotic cardiovascular disease than the general population. What she’s doing in her project, with guidance from cardiologist Steven E. Reis, M.D., her mentor, is comparing serologic markers of angiogenesis, inflammation, and endothelial activation as well as atherosclerotic risk factors like lipids and glucose in two groups of adults, one with and the other without Down syndrome, to determine whether the levels of the markers differ. Yvette says the ultimate benefit, which lies beyond the limited scope of her project, would be the insight to develop new therapies to better protect the general population against coronary artery disease and atherosclerosis.

Unlike the basic science with which Yvette is most familiar, this project allows her to explore something new: clinical research, which means learning how to conduct a clinical trial, write an Institutional Review Board application, recruit subjects, collaborate with physicians, and follow the research protocol—all of which she sees as pluses. Yvette adds, “I think there’s a benefit to making students do research, to having a scholarly project, because it allows you to think creatively, and that’s the main reason I love research.”

“...it makes us better physicians.”

Sheena Jain

Sheena Jain is clear how she feels about the scholarly project program. “Personally, my views on it are that this is only going to help us,” she says before ticking off what she sees as its benefits. Developing and testing a hypothesis, learning how to read and critically assess the literature—what’s relevant, what’s not, and what information might be useful in dealing with patients—it’s all valuable. And in competing for residency slots, “it makes us better candidates,” says Sheena, who studied chemistry and biochemistry at the University of Virginia before returning home to Pittsburgh for medical school. “I think it’s making us better physicians.”

Sheena is unsure if she’ll become a physician-scientist someday (if not, it’s because she likes the clinical side of medicine so much), but she knew that she wanted to do some research in medical school. For her scholarly project, Sheena chose the field of radiation oncology, which interests her as a career. Her mentor, Sushil Beriwal, M.D., a clinical assistant professor of radiation oncology, suggested several topics, which she read about and then chose one to tackle beginning the summer after her first year: an assessment of intensity-modulated radiation therapy (IMRT) as adjuvant treatment of endometrial carcinoma. The preliminary analysis, as Sheena, her mentor, and others have reported in Gynecologic Oncology, was “excellent local control and low toxicity” based on a study of 47 patients treated with IMRT (although they noted that longer follow-up and more patients are needed to ascertain the treatment’s long-term benefits).

Sheena says she approached this research experience with a desire to learn more about applying the scientific method to the field in which she hopes to pursue her clinical training. “I was successful in achieving that goal (and others) through the scholarly project program, so I’m grateful to have had that opportunity here at Pitt.”
Jaime Johnston, M.D., punctuates his slides on renal transport with photos of himself in high school (the hair is awesome). Richard Steinman, M.D., Ph.D., uses a trading card game in which paired students attack or defend one another armed with an assortment of pathogens, cancers, defense agents, and health status modifiers. Jules Rosen, M.D., has developed a series of interactive videos to demonstrate the subtleties of geriatric psychiatry; and, in teaching embryology and development, Cynthia Lance-Jones, Ph.D., still loves the immediacy and illustrative opportunities of the classic chalk talk. All four are members of the School of Medicine’s Academy of Master Educators, established in 2005 to recognize and reward excellence in education, advance education through innovation, support and promote scholarship in the field of medical pedagogy—and just give educators a chance to think about why teaching turns them on.

Getting into the academy requires far more than knowing the secret handshake. Each of the group’s 55 members (six of them charter members) had to assemble an educational portfolio that dwarfs War and Peace outlining his or her educational philosophy and teaching goals (this component, paradoxically, limited to 500 words); an overview of educational activities and accomplishments; examples of educational products like curricula, assessment instruments, and Web modules; and a summation of teaching evaluations. All of this info is evaluated by an Academy Membership Committee composed of the applicants’ peers—arguably, their toughest critics—with membership recommendations going to the vice dean and then to the dean for a final decision. The reward for completing this gauntlet? A five-year appointment to the academy and a supplemental incentive payment, with renewal of the appointment based on educational productivity and excellence.
Pitt is neither an early adopter of medical education as a subspecialty in its own right nor a school that’s behind the curve of educational innovation. Today, Pitt’s School of Medicine is clearly a true believer. “Pittsburgh has been progressive in how we think about the value of the clinical and educational experiences,” says the academy’s academic director, Steven L. Kanter, M.D., the School of Medicine’s vice dean. “We want our academy to accomplish something meaningful and every member to be active.” One way in which the Pittsburgh academy differs from other programs is that its focus is not limited to medical student education. Rather, while it recognizes faculty who teach medical students, it also includes those who educate and train Ph.D. students, interns, residents, and both clinical and post-Ph.D. fellows. Pitt’s academy covers all possible teaching venues from the large lecture hall to the small group session, from the laboratory bench to the patient’s bedside. Even the hallways are frequently the loci for one-to-one teachable moments.

The vanguard institution in what has been called the “academy movement” was probably the Medical College of Wisconsin, which formed its Society of Teaching Scholars in 1990, with the goals of mentoring junior faculty, promoting educational scholarship, advocating for educational issues, and recognizing teaching excellence. Since then, a number of medical schools have followed Wisconsin’s lead (but still probably fewer than 20). Among them are the University of Illinois at Chicago (1996), the Mayo Clinic College of Medicine (1998), the University of California, San Francisco (2000), the University of Florida (2000), Baylor (2001), Harvard (2001), Mount Sinai (2001)—and now Pitt. The formal Academy of Master Educators follows the school’s creation of a defined faculty path for the clinician educator in 2001. Nephrologist Jamie Johnston (he of the big high-school hair) was the first member of Pitt’s Academy of Master Educators and currently chairs the academy’s membership committee. “We’re newborns,” he says and credits Kanter as being the modest but still proud father of the rapidly developing enterprise. Johnston sees two themes emerging from the Academy of Master Educators—the mentoring by senior faculty of their junior colleagues who are interested in education, an emphasis that also gives the senior faculty more and different educational opportunities, and connecting a broader swath of faculty members with peers who have been singled out for their teaching excellence. Kanter is now moving the academy to the next level through four task forces designed to jump-start a few key activities; these ad hoc groups will focus on faculty development in medical education, the creation of a virtual center for evidence-based medicine education, mentoring for junior faculty members who are interested in developing careers as clinician educators, and teaching residents to teach.

Meanwhile, the academy has offered validation, affirmation, and a strong peer network to its members. Steinman, Rosen, and Lance-Jones, while using different words, would likely echo Johnston when he says that he finds teaching addictive—“It’s like a comedian feeding off of laughter,” he says. “To maintain knowledge, you need to use knowledge. Abraham Flexner said that in 1910—teach in the clinic and work in the laboratory.” He sums up why he’s hooked on teaching: “To see the light of understanding is as important as seeing a patient get better.”

Learning is mostly visual and auditory only during the first two years of medical school, whereas suddenly, in third year, you’re smelling the patient, you’re hearing the patient and touching the patient on so many levels where so many parts of your brain are receiving information, and the permanence of learning is so much better. You’re no longer learning just to pass a test, and it’s pretty gratifying to see that stuff is sticking with the students.

Our job as formal educators of medical students is to help them understand, retain, and use vital scientific and medical information. A good oral presentation should help medical students do this; but, if we give them a lot of parallel documentation, are we sending the message that listening and focusing on a lecture is not important? Our job as formal educators of medical students is to help them understand, retain, and use vital scientific and medical information. A good oral presentation should help medical students do this; but, if we give them a lot of parallel documentation, are we sending the message that listening and focusing on a lecture is not important?

**Showing your passion is vital.**

**FRANK J. KROBOTH, M.D.**
George H. Taber Professor of General Internal Medicine

**ACADEMY**

**Once you have their attention, you want to inspire them to learn.**

**PETER F. DRAIN, PH.D.**
Assistant professor of cell biology and physiology

**The key thing is using the right tool at the right time and the right place.**

**SAMUEL A. TISHerman, M.D.**
Associate professor of surgery and of critical care medicine

**Our job as formal educators of medical students is to help them understand, retain, and use vital scientific and medical information. A good oral presentation should help medical students do this; but, if we give them a lot of parallel documentation, are we sending the message that listening and focusing on a lecture is not important?**

**CYNTHIA LANCE-JONES, PH.D.**
Associate professor of neurobiology

**Learners are different. Some students need a structure, and they can hang facts on it, and other students need to discover in a messy way and synthesize later.**

**KATHLEEN McINTYRE-SEltMAN, M.D.**
Professor of obstetrics, gynecology, and reproductive sciences

**Showing your passion is vital.**

**FRANK J. KROBOTH, M.D.**
George H. Taber Professor of General Internal Medicine
hat do you usually think about when you’re driving? The weather, the traffic, the annoying morning radio deejays? What you probably don’t think about is driving itself, the complex mechanics of steering and braking, the rhythm of watching traffic from all angles. The actions that constitute “driving” are so deeply engrained that they rarely penetrate your conscious thoughts, even though the stakes can be high if you don’t perform them correctly.

Now think back to the very first time you got behind the wheel of a car. You probably studied hard to prepare yourself for that moment, watching videos in driver’s education class and memorizing the manual of traffic rules. But even if you aced your written driver’s test, nothing truly prepared you for the mental and physical experience of navigating a 3,500-pound vehicle through high-speed traffic. Those first few times on the road, you were acutely aware of every acceleration and turn—yet you were far more likely to make a serious mistake than you are now as an experienced driver.

In medicine as in driving, there’s no substitute for practical experience. That’s why the greeting on the Web site for the Peter M. Winter Institute for Simulation Education and Research (WISER) is a quote from the Chinese philosopher Confucius: “I hear and I forget. I see and I remember. I do and I understand.” WISER is one of the world’s leading academic medical simulation training centers, specializing in the creation of extremely realistic scenarios in which medical students and other health care professionals at all career and training levels can safely learn, practice, and perfect crucial procedures before performing them on actual patients.

Equipped with the latest in computer technology and mannequin simulators, the 12,000-square-foot WISER facility allows students to achieve mastery through repetition of medical procedures. “WISER can get people ready so they can avoid making mistakes,” says Paul L. Rogers, M.D., professor of critical care medicine, professor of medicine, and director of a number of student simulation courses. “We’re trying to teach them to be unconsciously competent, to take them to a level where they automatically know what to do and how to react in a critical situation. And we don’t stop practicing until every single student gets to that level.”

All Pitt medical students spend a minimum of 25 hours in simulation training activities, and two-thirds of them opt for additional elective time to develop mastery of resuscitation, defibrillation, auscultation, and other clinical skills. The following scenarios illustrate what medical students can experience in just 15 minutes at WISER.
“WE’RE GOING TO GIVE YOU SOME OXYGEN TO HELP YOU BREATHE, OK, SIR?”

THE PATIENT IS EXTREMELY SHORT OF BREATH, HAS AN ELEVATED HEART RATE, AND IS HYPOTENSIVE.

10:00 AM
Ryan checks on the placement of the monitor attachments.

10:07 AM
Ryan Brannon concentrates on the correct placement of an endotracheal tube after the patient stops breathing entirely.

10:12 AM
If intubation doesn’t work, the next step is an emergency airway puncture.

10:15 AM
Ryan focuses on his patient.
“AS TEAM LEADER, YOU HAVE TO PRACTICE MAKING SURE YOU ASSIGN SPECIFIC RESPONSIBILITIES TO SPECIFIC PEOPLE AND GIVE THEM SPECIFIC INSTRUCTIONS. IT’S UP TO YOU TO CLOSE THE LOOP.”

A HOSPITALIZED PATIENT GOES INTO SUDDEN CARDIAC ARREST DURING A ROUTINE LAB PROCEDURE.

10:37 AM
Team leader Candace Jones, hoping for an improvement in the patient’s vital signs, checks the monitor.

10:42 AM
Two of Candace’s team members continue cardiopulmonary resuscitation...

10:45 AM
... by providing ventilations and chest compressions.

10:50 AM
The readings on the wall-projected monitor indicate the patient’s return to cardiac stability as Shilpa Patel, part of the hastily assembled code team, listens to feedback from the scenario facilitator.
“WE HAVE TO INTUBATE. I NEED A NO. 4 MAC BLADE, A NO. 8 ET TUBE WITH A STYLETTE, AND A 10CC SYRINGE.”

THE PATIENT, A CAR ACCIDENT VICTIM, IS UNRESPONSIVE AND HAS NO PULSE.

11:02 AM
Observing classmates get caught up in the drama as ECG monitors are attached to the patient.

11:06 AM
Marcus, the exercise leader, monitors his teammates during the intubation.

11:13 AM
A live video feed provides SimMan’s operator with an unimpeded view of the action, which is recorded for later student review.

11:09 AM
Animesh Sabnis watches as a colleague feels for expiratory air, while Marcus Hoffman listens to the stomach to rule out accidental insertion of the breathing tube into the esophagus. Candace Jones is ready with the ventilator tube connector.
I ALREADY KNOW HOW TO MEMORIZE MATERIAL FROM A BOOK. THIS COURSE HAS TAUGHT ME HOW TO THINK ON MY FEET.”
New Technologies in Medical Education

Ah, a new day! Much to do. 8:00 a.m. Set alarm for 7:30.

8:00 a.m. Location: Faculty office. Technology featured: Health Sciences Library system, PowerPoint via desktop computer. Coffee.

Well, my powerful lecture looks good. I just need to check some references.

8:45 a.m. Location: Lecture Room #4. Technology featured: Smart Symposium installed by Office of Medical Education. Student alertness level: 90%. Faculty member emphasizes: Print on slide by circling it with a special pen on transparent screen.

Remember point 1! Circle is projected on projection screen and also recorded as part of podcast.

9:10 a.m. Location: Problem-based learning room. Activity: Case discussion.

T. H. Greenberg: What's your learning objective?

Well.

9:30 a.m. Location: Faculty office. Technology featured: Navigator site, course director's blog, and course homepage. More coffee.

I suppose I better remind them they have an exam tomorrow.

10:30 a.m. Location: Library. Activity: Case discussion.

No problem.

11:30 a.m. Location: Faculty office. Technology featured: Health Sciences Library system, canvas, and course homepage. More coffee.

Reminder: Exam tomorrow. I will be available to answer questions until 10:30 a.m.

Nice to catch up.

12:00 p.m. Location: Bench outside Scaife Hall. Activity: Dreaming about digestion and nutrition.

Okay. I'll just check my email one last time...

Ah ha, there's Mr. Last Minute's question!

1:00 p.m. Location: University of Pittsburgh. Activity: Eating in the Zone. More coffee.

I can almost feel it.

1:30 p.m. Location: Faculty member's home. Activity: Dreaming about digestive enzymes and nutrition.

1:45 p.m. Location: The middle of the night. Activity: Dreaming about digestive enzymes and nutrition.

The end (for today).
When Alfonso Barquera moved to Pittsburgh from Mexico to study English and get an edge in a rapidly globalizing economy, he became interested in the experiences of his fellow immigrants in the city’s growing Latino population. Many of the immigrants he met felt disconnected from the city because of language and cultural barriers; couldn’t find welcoming, affordable health care; and were homesick for far-away friends and family. Barquera connected with their stories on a personal level and even used their experiences as research for his master’s degree in anthropology. He wanted to help improve the lives of Mexican immigrants, so when the School of Medicine’s Office of Medical Education went in search of people with bilingual skills to work in its standardized patient (SP) education program, Barquera saw it as an opportunity to serve the immigrant community in an unusual way.

“I know what it’s like to feel like an outsider in the U.S. health care system, and medical students need to be prepared to interact with someone who may not know what to expect when they go to a doctor here. I like being an SP because I can help students know more about Latinos and our cultural differences,” says Barquera.

SPs are trained by the School of Medicine’s Advanced Clinical Education Center to portray patients in health care situations (often one-on-one patient physical exams) with medical students. Their portrayals of patient cases are invaluable steps in teaching students how to perform in clinical settings.

Barquera isn’t the only SP motivated to improve the quality of communication between doctors and patients—one of the key benefits of the SP experience for students. Bruce Hill worked as an SP for many years and recently returned to the work after he was diagnosed with diabetes in 2001. Being a patient himself helped
him realize how vital trust is in the relationship between patient and doctor and how essential it is in the recuperative process. “Patients have to feel that doctors respect them and their medical issues and that the patients themselves are a part of the healing process. Their emotional states have a great impact on how well, or quickly, their health improves,” says Hill. He likes that his work as an SP could help real patients someday through his interactions now with future doctors.

In the late 1990s, the use of SPs at medical schools blossomed nationally after several studies proved they could be used with rigor and great reproducibility. Pitt’s School of Medicine created its own SP program and figured out how to use SPs to teach its students. Today, Pitt’s program has 92 SPs between the ages of 18 and 77. Many remain for a long time; one person currently in the program has worked as an SP for 13 years.

Before dealing with students, as they do regularly throughout the four years of medical school, SPs are required to have at least 14 to 16 hours of basic training; and each medical school course in which they are involved requires additional training. “One course involves actually being taught how to perform a physical exam,” says Valerie Fulmer, trainer/educator for the standardized patient program. “SPs spend 20 hours with a nurse practitioner and learn how to do things like take blood pressure readings and test reflexes; they also learn medical terminology and how to give students feedback. Then they spend additional time studying the material at home,” she says.

Learning to perform physical exams enables SPs to know whether or not students are performing them correctly, whereas learning to evaluate students fosters the ability to provide consistent and fair assessments. “Being an SP is harder than I thought it would be. You aren’t just portraying a character; you also have to have one ear and one eye always on what the students are doing so you can give them appropriate feedback,” says SP Debbie Berkovitz. Students are evaluated on a point-by-point checklist and given feedback on what they did incorrectly, what they missed, and how they interacted with the patient.

Although some SPs are actors, they aren’t expected to create a character; in fact, they’re told not to consider their interaction with students as a theatrical performance. “We see them as highly skilled workers, not actors. We train them on exactly what to say and how to respond according to what ailment the patient they’re portraying has. And they do it very well,” says John F. Mahoney, M.D., associate dean for medical education and associate professor of emergency medicine. SPs portray real cases adapted for training purposes so students can apply all of their learning to the clinical setting and learn to think on their feet before they treat actual patients.

SPs are used in conjunction with specialized simulation technologies, like the high-fidelity, electronic pelvic examination models used to teach students how to perform a pelvic exam. Some highly dedicated, specially trained SPs participate in gynecological, genital, and prostate exams. “These are people who are committed to contributing to the betterment of health care. For students to be able to gain experience in more sensitive exams on real people, but not yet real patients, is amazing. The students see that as a gift,” says Fulmer.

At a practice testing session, she briefed first-year medical students as to how the afternoon of physical exams would work. When she explained that SPs would be watching students’ ability to accurately measure liver spans, some students looked at each other with surprise. “Oh, yes,” Fulmer said. “We’ve trained them. They will know exactly where their livers are.”

In addition to knowing where his liver is, Barquera knows he is helping other people in the immigrant community as well as the medical students. “I like to see the students get more comfortable with me as we move through the exam. I also like feeling that other immigrants might have an easier time at the doctor’s office because of the training I’m doing,” he says.
You did it—with hard work and support from family and friends. The University of Pittsburgh, which has one of the finest medical schools in the nation, opened the door for you to attain your dream. And so, there you are, Day No. 1. You’re amazed by the diversity of your classmates, not necessarily in terms of race or gender, but rather the dynamic personalities of those around you, of how they carry themselves so differently but with such a presence. At the White Coat Ceremony, the traditional start of medical school, you sit in your sparkling new white coat and hear the dean describe the honor and privilege of a career in medicine—a sentiment that echoes throughout the program. The portraits of distinguished physicians surrounding you on the walls of the auditorium, the reading of the Hippocratic Oath, the flashing cameras of proud parents—it all seems unreal. Your dream of making it to medical school is realized, but it’s just the beginning. What an honor and privilege it would be to make it to the end.

As first year rolls on, you find that, while you were a star in college, you’re struggling to remain average here. You find that you’re jealous of those who go out all the time and still do well, or you’re jealous of those who don’t have kids because a family takes up so much precious time. Or maybe you’re at the top of the heap, and no one can imagine the strain of living up to continued expectations. You find that you don’t talk to friends from home as much as before, because, quite frankly, they just can’t understand. Or you’re in a long-distance relationship that is strained because you know that every hour you aren’t studying could mean another point off your test, and you can’t afford that—but, of course, your boyfriend or girlfriend doesn’t understand. Or you go home to your spouse and—although you thought it would be a welcome thing to have someone outside the medical world around—you find yourself becoming more detached and the relationship fraying, with no time to reconcile differences. Your parents call, but
they don’t understand the world of medicine—or, conversely, one of them is a practicing physician and keeps telling you they understand, but they’re not here, and they don’t know. Your frustration translates into complaining—about the facilities, about the quality of lectures and the minutia you have to memorize. You’re completely enveloped by the world of medicine.

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The end of second year comes, and you have to sit for boards. To prepare for them, you get a suggested study plan—an eight-week schedule of insanity, which you scoff at and discard for your own schedule, which turns out to be 10 weeks of even greater insanity. This one test determines whether you can be an orthopod or a neurosurgeon, whether you’ll be able to match someplace you want for residency, whether you can return home to your family and appease your spouse. As for everyone, the test finally comes and goes. Afterwards, you drive to a friend’s cabin in the middle of nowhere, where you can sit with a fishing rod between your legs and a glass of “milk” at your side, finally able to feel like you’ve escaped. That’s when it hits you—you don’t really know if you like the person you’re becoming.

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Clinical rotations begin, and you don’t know the computers, and you’re not answering the attending’s questions right, and you’re worried about the test being a shelf exam, and you’ve got to go into the patient’s room right now to get your history and physical so you can finish one to turn in. You sit down at the bedside, shuffle some papers, look at your watch, lift up your head…and your eyes meet. They are the eyes of a male, a female, a Hispanic, a Caucasian, a white collar, a blue collar, a no collar, a broken hip, a stage-four cancer, a 10-year-old, a 100-year-old. Suddenly, those feelings that you had so long ago, that you’d almost forgotten, come alive—but they’re so much more real than you remember. You only knew this feeling vaguely when you applied to medical school and tried your best to put it into words when asked, “So, why do you want to be a doctor?” Now, here it is, and words don’t suffice. In that moment, you feel a new burden. You look into those eyes, and they read of fear, of realized mortality, of age, of experience, and those eyes look to you for help. In that moment, burden changes to responsibility, and you’re surprised to realize that you want nothing more than to embrace it—the whole thing. In that same moment, you gain some understanding of those first two years of medical school, that they provided you the intellectual and emotional framework with which to approach this newfound responsibility.

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It’s 4:30 in the morning, and you wake up tired but ready to roll. You hop on the bus, and, though you’ve thought about how tough you’ve had it the past few years, you look at the worn faces of the janitors, the security guards, the line cooks, the public works folks, and you realize the difference between people who “go to work” and what you get to do. As you get off the bus, the driver, as always, says, “Have a nice day,” because that’s what they do in Pittsburgh, and even though it’s Wednesday and summer and 4:45 in the morning, you blurt out, “Go Stillers,” because, well, that’s what they do in Pittsburgh.

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You’re in Children’s Hospital, and you watch as 2-year-old Sally, who came in with a septic joint, waddles with her back to you, her little hand engulfed by her father’s massive paw, she with only a diaper, and you can’t help but smile. You’re at the VA, and there’s old Mr. Perkins with his IV pole and his back to you in the hall, gown on, but he with neither a diaper nor undergarments, and again you
Dr. Conlon, at top left in this family photo, is currently in a combined internal medicine/pediatrics residency program at the University of Pittsburgh Medical Center and Children's Hospital of Pittsburgh of UPMC. He comes from Chicago and, despite his time here, he's still "a die-hard White Sox fan."

You can’t help but smile. You’re at Western Psych, and you give the rundown on a patient to an attending only to have him look at you with hesitation. You’re not supposed to make breakthroughs, but you know, deep down, that you actually connected with the patient. You’re on ortho rounds, and you just benched 250. You’re in surgery, and you cut that fascia really well (or whatever gets surgeons excited). You find that attending who loves to teach and does it in such a way that you actually learn, and you really want to go home and read to continue the process at another level. Not only do some doctors find time to teach, they also allow you to peek into their lives. They’re mothers, fathers, brothers, sisters, and friends who like to go to the opera, fly fish, and watch football or American Idol. They’re real, and they let you feel real, too—that it’s OK to be fallible, OK to enjoy life outside of medicine.

The University of Pittsburgh

School of Medicine

Upon recommendation of the faculty, and by authority of the Board of Trustees, confers upon

Thomas William Conlon
The Degree of

Doctor of Medicine

With all the rights, privileges and responsibilities pertaining to such degree.

In witness whereof, the seal of the University and the signature of the authorized officers are affixed this 27th day of May 2006.
Pushing forward with each new discovery
ith its open, spacious labs filled with high-tech equipment, “plug and play” workstations that can be configured to each researcher’s specifications, and the latest in computing technology, the University’s new Biomedical Science Tower 3 (BST3) is a high-stakes investment in the vision that interdisciplinary research is the only way to solve some of medicine’s most challenging mysteries.

In fact, it is a gleaming, 10-story steel and glass percolator designed specifically to foster collaborations between clinical researchers like J. Timothy Greenamyre, M.D., Ph.D., director of the Pittsburgh Institute for Neurodegenerative Diseases (PIND), and basic scientists throughout the building in hopes — as any one of them would tell you — of making meaningful advancements to biomedical research and its applicability to improving the human condition. Not only are such collaborations becoming common, they’re also occurring among BST3 colleagues who might not otherwise have ever considered working together. Furthermore, the continuous interplay between the work of basic scientists on the lower levels and those on the upper floors who can incorporate these fundamentals into their applied research makes the comparison to a traditional coffee percolator, in which the brewing starts at the bottom and slowly rises to the top to produce the richly desired results, an apt analogy.

“So far, it’s working beautifully,” says Greenamyre, who also is the UPMC Professor of Movement Disorders in Neurology. PIND investigates the mechanisms of diseases of the brain in which neurons die or become prematurely impaired, a process known as neurodegeneration. Current therapies can provide temporary relief from the symptoms of these diseases, but nothing has been found to slow or halt them. As the quest for effective remedies continues, one of the connections Greenamyre has established is with John S. Lazo, Ph.D., Allegheny Foundation Professor of Pharmacology and director of the University’s new Drug Discovery Institute (DDI), which is located above PIND on the top floor of BST3.
“Six degrees of separation” refers to the idea that any two people can be connected by, at most, six other people—demonstrating how small the world really is. The scientific world of BST3 is even smaller, maybe one degree at most. Explore the evolving interdisciplinary research connections percolating through the building by following the arrows.

Zebrafish have become a model of choice for many researchers because a number of their genes have human homologues. The small fish also produce large broods, develop rapidly, and have transparent embryos, making them ideal for studying early development.

Joanne Yeh, Ph.D., associate professor of structural biology and nanotechnology researcher

Yeh is working with DDI to fabricate a nanoneedle probe that can be inserted through a cell wall to monitor the cellular target to which a drug binds.

A nanoneedle probe, like that on which Yeh is working, would be particularly attractive to researchers like Greenamyre for monitoring whether potential compounds for neurodegenerative diseases can actually bind to their target neural cell proteins.

Angelia Gronenborn, Ph.D., UPMC Rosalind Franklin Professor and chair, Department of Structural Biology

PITTsburgh Institute for NeuroDegenerative DIseses (PIND)

PIND is dedicated to both clinical treatment and translational research that explores neurodegeneration from a number of perspectives. The goal is to combine the expertise of many investigators and clinicians into potential new therapeutic options.

J. Timothy Greenamyre, M.D., Ph.D., UPMC Professor of Movement Disorders, in Neurology and PIND director, and Edward A. Burton, M.B.C.H.B., M.D., D.Phil., assistant professor of neurology and of molecular genetics and biochemistry

Yeh is working with Lazo to identify compounds that may be able to protect neurons’ mitochondria from damage, a process that is implicated in most neurodegenerative diseases.

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Drug Discovery Institute (DDI)

DDI has the ability to screen for biologically important compounds and to synthesize completely new ones. It is unusual to have organic chemists and biologists working in such close proximity.

Neil A. Hukriede, Ph.D., assistant professor of molecular genetics and biochemistry

Zebrafish offer a powerful screening tool for testing biologically important compounds, which may then be optimized by DDI.

John E. Lazo, Ph.D., Allegheny Foundation Professor of Pharmacology and DDI director

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The DDI can take advantage of the Department of Computational Biology’s computer simulation capability to screen a large library of molecules against a target molecule, thereby reducing the potential candidates by several orders of magnitude.

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Nuclear Magnetic Resonance (NMR) Spectroscopy Screening

NMR spectroscopy screening is one of the most efficient ways to determine where and how well a molecule binds to a protein, knowledge critical to drug development.

Ivet Bahar, Ph.D., John K. Vries Professor and chair, Department of Computational Biology

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The Drug Discovery Institute is home to the Pittsburgh Molecular Libraries Screening Center, which, as part of a network of facilities recently established by the National Institutes of Health, uses high-tech screening methods to identify small molecules that can be used as research tools in the efforts to learn more about key biological processes involved in human health and disease. PIND is working with the Molecular Libraries Screening Center to look for compounds that may be able to protect mitochondria (sometimes called cellular power sources) from damage. “Mitochondrial protein damage caused by oxidative stress—the same chemical reaction that causes iron to rust—is implicated in most neurodegenerative diseases,” says Greenamyre. “Therefore, we’re looking for compounds that can block this process in mitochondria, particularly in neurons, in the hope they can delay and even prevent the onset of these diseases in susceptible people.”

For PIND, the screening center can test hundreds of thousands of compounds for their therapeutic potential in a very short time—a capability that, until now, has been limited almost exclusively to pharmaceutical companies. Compounds identified by this type of large-scale screening can be further screened computationally and structurally to see how specific their activity is—all without leaving BST3.

A new and extremely powerful tool for testing whether compounds have a desired effect is called in silico screening, which employs computers to model how complex molecules behave in the real world. (This analysis is in contrast to in vitro testing of cells or other biological systems in test tubes and in vivo testing in animal models.) In silico screening of chemicals is particularly useful for compounds designed to interact with molecules of known three-dimensional structure, says Ivet Bahar, Ph.D., John K. Vries Professor and chair of the Department of Computational Biology, which is housed on the third floor of BST3. “If you have a very large library of molecules that you want to screen against a target molecule, such as an enzyme, you can do it much faster via computer simulations than you could by doing it in the test tube or in cells,” explains Bahar. “If we can reduce the set of potential candidates by one or two orders of magnitude, it’s a major leap forward in the discovery process.” In addition to being able to predict whether a compound will bind at a particular active site of protein, for example, in silico screening allows computational biologists to suggest which compounds are the most potent inhibitors of a particular enzyme. Bahar’s group has even developed a Web-based tool for biologists to do this online.

Another powerful screening tool available in BST3 that can be used in addition to or in place of in silico screening is nuclear magnetic resonance (NMR) spectroscopy. NMR is one of the most efficient ways of quickly getting structural results and reality checks, says Angela Gronenborn, Ph.D., UPMC Rosalind Franklin...
Professor and chair of the Department of Structural Biology, which was BST3’s first occupant when it opened in September 2005. “When we do NMR, we see a resonance for each amino acid of a protein. So, we can see very quickly how well a particular molecule binds to a protein and where it binds,” she explains. Before NMR was widely available, drug development was much more of an art than a science and led to many dead ends.

A well-known example of this process was the development of early drugs to treat sickle cell disease, which is caused by the aggregation, or clumping, of hemoglobin molecules in red blood cells. The first anti-sickling drugs were designed to bind to a specific site on each hemoglobin molecule to prevent them from clumping. However, once the drug developers were able to examine these drugs structurally, they found that the agents did not bind to their intended target but, rather, at another location on the hemoglobin molecule. “These days, it’s usually a good idea to check structurally whether a molecule can actually bind where you want it to before putting it through any kind of trial,” says Gronenborn.

One advantage of using such sophisticated screening technologies is a higher likelihood of success in cell culture and animal studies, which means less waste of these valuable resources. At PIND, for example, promising molecules that can protect mitochondrial proteins from oxidative damage based on a number of criteria will be tested in zebrafish that have been genetically engineered to display symptoms similar to Parkinson’s disease (PD), a progressively debilitating neurological disease that causes loss of nerve cell function in the part of the brain controlling muscle movement. As many as 1.5 million Americans have this disease. “My colleague Ed Burton has developed zebrafish in which genes that code for the mutated PD proteins in humans have been inserted into the fish,” says Greenamyre. “Not only do the fish display many of the movement problems seen in people with PD, but they also show pathological and biochemical abnormalities reflecting those seen in the human disease. We should, therefore, be able to rapidly determine which compounds have protective effects.”

Zebrafish, in fact, represent another powerful BST3 screening tool for testing biologically important compounds. Because zebrafish have many genes that are similar in sequence and are expressed at comparable stages of development as human genes, they have become models of choice for many researchers. Furthermore, zebrafish produce large broods, breed all year, are easily maintained, develop rapidly, and have transparent embryos. Therefore, they are particularly useful for directly observing the morphological effects of genetic mutations on development. BST3 houses one of the largest zebrafish colonies in the world, with more than 10,000 separate tanks.

Compounds that pass the zebrafish test may eventually percolate back up to Lazo and the Drug Discovery Institute, which has the ability not only to screen for...
biologically important compounds but also to synthesize completely new ones as well. So, if the screens come up with compounds that have most but not all of the desired characteristics,DDI researchers, who come from the Departments of Pharmacology, Chemistry (School of Arts and Sciences), and Pharmaceutical Sciences (School of Pharmacy), have the capability of altering them to fit their exact needs. Furthermore, the institute has the largest collection of fume hoods—a critical tool for organic chemists who want to synthesize new or alter existing compounds—on campus. “Our situation isn’t unprecedented, but it certainly isn’t the norm,” says Lazo, who chaired the Department of Pharmacology for 17 years before heading DDI. “For example, it’s very unusual to have organic chemists and biologists working on the same floor, much less in the same building. At Yale, my former institution, the chemistry department was more than a mile away, so collaborations were always difficult.”

Although it will take many more months, and perhaps years, to determine how successful such collaborations will be in finding new therapies to treat diseases, there is little doubt that they open up new and exciting avenues of research. For example, Joanne Yeh, Ph.D., associate professor of structural biology and a nanotechnology researcher, is discussing with Lazo’s group the development of a probe that can monitor where a drug goes after it enters a cell. Her group is attempting to fabricate a nanoneedle that can be inserted through a cell wall to monitor the specific target in the cell to which a drug binds. Such a probe would be particularly attractive to researchers like Greenamyre for monitoring whether potential compounds for neurodegenerative diseases can actually bind to mitochondrial proteins in a neural cell. Greenamyre, for one, can’t wait for this and other collaborative ventures in BST3 to come to fruition. “I feel very fortunate to be able to come to work every day in this building,” he says. “It really is a unique place to do research, and I’m confident that it will soon start paying dividends for the patients we’re trying to help.”

Developing Vaccines for Difficult Diseases

Researchers at the University’s new Center for Vaccine Research (CVR) in BST3 are ready to scrabble. They’re prepared to battle a range of diseases from emerging ones, like avian influenza, to older scourges like HIV and tuberculosis, to human-modified diseases that could be used for bioterrorism. With so many dangerous infectious agents, which vaccines does the center tackle first? “Our ongoing focus will be threefold—flaviviruses (like dengue fever), influenzas, and tuberculosis. We’ll also be working on various platforms that can be used for other viral systems and on the assessment of vaccine immunity,” says Ronald C. Montelaro, Ph.D., associate director of the center and professor of molecular genetics and biochemistry.

With initial funding from the National Institutes of Health and the Department of Defense, the CVR is closely aligned with the Regional Biocontainment Laboratory, one of 13 dedicated facilities across the country with specialized capabilities that allow investigators to conduct essential biodefense research into potentially deadly infectious agents under safe, contained, and highly controlled conditions. Faculty members from several School of Medicine departments, including Molecular Genetics and Biochemistry, Immunology, and Pediatrics, the Department of Medicine’s Division of Infectious Diseases, and the Department of Infectious Diseases and Microbiology in the Graduate School of Public Health will conduct research at the center. Headed by a leading expert in the field of infectious diseases, Donald S. Burke, M.D., who is also dean of the Graduate School of Public Health, associate vice chancellor for global health, and UPMC Jonas Salk Professor of Global Health, the center’s initiatives will include basic research, preclinical and clinical trials, and corporate partnerships to make vaccines (although, at some point in the future, the center may build a commercial vaccine operation).

While the task of developing vaccines for notoriously difficult diseases is daunting enough, researchers will also be dealing with the variability of viruses, their potential to change over time, and with learning how to recognize different viral strains. “We use the example of cold and polio viruses,” says Montelaro. “They look the same under the microscope. There are three strains of polio, and we have a vaccine that guards against all three strains; but there are 130 to 140 strains of the common cold virus, and it’s difficult to develop a vaccine for all of them.” CVR researchers will have to first recognize different strains of viruses by making extensive surveys of them worldwide and determining how they evolve; then they’ll examine the strains, arrive at consensus strains, and evaluate those for a vaccine.

Burke is known for his hands-on, global approach to vaccine research and wants the CVR to have relationships with other countries where some of these diseases are found naturally. “We must study these diseases in nature and in animals so that we can understand how the viruses emerged in the first place,” he says. “AIDS, SARS, and influenza viruses jumped from animals to humans; and we don’t have a good handle on how that adaptation occurs.” Montelaro and Burke are still recruiting faculty members to the center and realize that it may be a while before the center is scientifically productive. “I know how hard it is to make a real vaccine,” says Burke. “I was involved with the successful development and testing of the hepatitis A and Japanese encephalitis vaccines, and it’s wonderful to see it through—from the beginning to the end. Being able to cause diseases to disappear is a real motivator.”
Drosophila melanogaster (pictured above), more commonly known as the fruit fly, is one of the most widely used animal models in scientific research. More than half of the fly’s protein sequences have known mammalian analogues, a percentage that is rapidly increasing as more and more genomes are mapped. “Another reason flies are exceptional models is because of the way their short lifespans scale against the longer span of a mammal,” says Michael J. Palladino, Ph.D., assistant professor of pharmacology. “A fly can be normal for the first five or six days of its life and then rapidly progress to a disease state that might take 18 months or more to simulate in a mouse model.” This time scaling also applies proportionately to human conditions, making all Drosophila particularly useful in the study of the onset and development of neurodegenerative and other progressive diseases that often take 40 to 60 years to appear.

The Xenopus laevis is a small African clawed frog that produces a very large egg. Before X. laevis eggs begin division, they exist as single cells called oocytes (pictured right), which at 1.3 mm are actually visible to the naked eye. (In comparison, a human oocyte is considered large for a single cell at 0.1 mm.) When fertilized, the X. laevis egg develops so rapidly that a general body plan for the resulting embryo is evident within 24 hours. The embryo can also be cultured in vitro and microsurgically manipulated, making it an excellent model for identifying and characterizing early developmental processes. X. laevis is being used at Pitt to study plasma membrane transport issues that may be applicable to different types of cells. Neil A. Hukriede, Ph.D., assistant professor of molecular genetics and biochemistry, also uses the frog embryos as models “to identify the earliest cells that give rise to the kidney and to understand the molecular events that lead to kidney development.”

It might be a surprise that the genome of an ordinary-looking worm is 40 percent homologous to the human genome, but that commonality, along with the worm’s low cost, easy maintenance, and ability to revive after being frozen, makes Caenorhabditis elegans (pictured below) a versatile tool with which to address a variety of developmental and pathological questions. “The vast complexity of the vertebrate nervous system makes it difficult to study some neurological disease processes,” says Miguel Estevez, M.D., Ph.D., assistant professor of neurology, who uses C. elegans to study the regulation of serotonin levels. “We can circumvent those complexities by using an organism that is much simpler but has many of the same signaling mechanisms.”

Danio rerio (pictured above), the zebrafish, is not only a common aquarium fish but also an ideal small vertebrate genetic screening model for a number of human characteristics and developmental processes. At the School of Medicine, zebrafish are used as models to answer research questions about the digestive system, kidneys, and nervous system. “Multicellular organisms arrange cells in special patterns to form distinct structures,” says Xiangyun Wei, Ph.D., assistant professor of ophthalmology, “but we don’t fully understand the instructions that direct the formation of these patterns.” Wei studies the zebrafish retina in order to better elucidate the molecular mechanisms that underlie neural and retinal development.

Model Subjects

All living things are organized by the genetic information encoded in their DNA. As new species adapt and evolve, genes and gene sequences that prove effective for fundamental physiological development and functions are held over, or “conserved,” from other species. Because of these genetic homologues and analogues, scientists can gain valuable insight into the human condition by studying the creatures shown here, which represent just some of the research models being explored at the School of Medicine.
Until the mid-1990s, graduate education at most medical schools, including Pitt, was departmentally organized. Although this approach is logical from an administrative perspective, it fails to exploit the rapid pace of change that characterizes biomedical science.

As a way of both responding to and propelling this change, the School of Medicine designed and implemented the Interdisciplinary Biomedical Graduate Program (IBGP), which features a core curriculum the first year followed by the opportunity to pursue research and dissertation work in one of seven interdisciplinary areas: biochemistry and molecular genetics, cell biology and molecular physiology, cellular and molecular pathology, immunology, molecular pharmacology, molecular virology and microbiology, and neuroscience.

This level of flexibility accommodates students whose research interests are still evolving by introducing them to a variety of fields through interdisciplinary courses and laboratory experiences. It also encourages the rapid development of new programs for more focused students as new areas of science come to the forefront. The School of Medicine’s three newest graduate programs are Molecular Biophysics and Structural Biology, the Joint Program in Computational Biology, and the Program in Integrative Molecular Biology.

John P. Horn, Ph.D., associate dean for graduate studies and IBGP director, is a strong advocate of a programmatic approach to graduate education. Horn, also a professor of neurobiology, is himself an accomplished scientist who studies synaptic regulation of information processing in the neural circuits. His understanding of the flow of neurological information is echoed in his understanding of the flow of scientific knowledge in the School of Medicine. In the course of their training, graduate students are encouraged to move freely among departments for the most comprehensive education on their topic. Even if they are ultimately destined for a career at the lab bench, IBGP students are encouraged to think in terms of clinical problem solving. “With a programmatic, rather than departmental, approach,” he says, “graduate students have facilitated development of research projects within clinical departments.”

Horn believes that by encouraging graduate students to move freely from department to department and from bench research to clinical study, both the school and the students reap the benefits. “A programmatic approach allows the graduate students to further strengthen the connection between science and medicine,” he says. “Our goal is to train these people, not just in terms of their own research but to look at the larger picture. We want to educate them about the past, but we also want to prepare them for the future.”

In fall 2006, five students became the first to enter the Program in Integrative Molecular Biology (PIMB), a joint graduate program created by the School of Medicine and the Department of Biological Sciences in the School of Arts and Sciences to appeal to students with a strong interest in the structure and function of molecules that comprise living systems. “We wanted to develop a novel, cross-campus training program to recruit outstanding graduate students to study molecular biology at the University,” says Gerard L. Apodaca, Ph.D., program director and professor of medicine and of cell biology and physiology.

The PIMB curriculum is designed to rapidly immerse students into a research environment and provide mentorship as they develop into independent scientific practitioners. “Having research experience as both an undergraduate and graduate student, I wanted to hit the ground running in pursuit of a doctorate,” says PIMB student Eric de Groh. “The accelerated nature of PIMB has allowed me to do that.”

The goal of the four-year program is to produce scientists who are skilled not only in the art of technical execution but also in the creative thinking required to address important questions in molecular biology. Students may choose between two main areas of focus: The genomics, proteomics, and gene function area takes advantage of the many recent advances in genomic sequencing, gene production, and protein folding. The second area of focus, cellular and developmental dynamics, utilizes technological developments to better understand the dynamics of cell function and interaction and how those interactions lead to organism development.

“Students coming into the program already know what it takes to be a scientist and have the opportunity to produce meaningful research from day one,” says PIMB faculty member Judith Klein-Seetharaman, Ph.D. As assistant professor of structural biology, of pharmacology, and of computational biology at the School of Medicine and as a research scientist for the Language Technologies Institute at Carnegie Mellon University, Klein-Seetharaman knows what it takes to generate high-quality work in a multidisciplinary environment. “The PIMB program is designed to produce scientists who can examine a question by addressing the science at every scale, from molecular to macroscopic,” she says. “The PIMB graduate will be a builder of bridges.”
Molecular Biophysics and Structural Biology (MBSB) is an interdisciplinary doctoral program that explores the intersections of physics, chemistry, biology, and medicine. This program brings together faculty from the School of Medicine, the School of Arts and Sciences, and Carnegie Mellon University to concentrate on fundamental scientific principles that form the basis of the molecular reactions and interactions in biological systems.

Advances in biophysical techniques and developments that allow more sophisticated imaging—increasingly powerful electron microscopes, magnets, and computers, for example—have opened the door to a vast array of new possibilities. Scientists are now able to analyze the structure and movement of molecules with unprecedented accuracy and precision. “For a long time, people have thought of the activities within a cell primarily as a series of chemical interactions. Now, more and more people are thinking in structural terms as well,” says MBSB student Matt Fagerburg. “We’re starting to look at molecules as three-dimensional machines, as dynamic agents with structures that both affect and respond to what’s happening around them.”

Fagerburg, who is studying the development and use of single-molecule techniques to investigate DNA-protein structures, says the greatest strength of the MBSB program is its faculty, “an amazing array of people” whose diverse interests offer students a great deal of flexibility as they develop their research emphases. While common core courses provide a solid grounding in molecular biophysics and biomedical sciences, research rotations in the first year offer students the opportunity to focus their scientific interests. They are then free to select one of seven focal areas of research: macromolecular recognition; virus, lipid, and protein structure and interactions; principles of protein structure and dynamics; membrane proteins; gene regulation and signaling; cellular biophysics; or chemical structure and dynamics.

MBSB Director Angela M. Gronenborn, Ph.D., UPMC Rosalind Franklin Professor and chair of the Department of Structural Biology, says the program opens up a place in the Department of Structural Biology, says the program opens up a place in the MBSB program. “Students who come from more quantitative sciences—physics, chemistry, math—and want to apply those skills in biomedical areas can now do so. I strongly believe that the next generation of scientists will need to be much more versatile in their backgrounds,” says Gronenborn, “and that the development of this multidisciplinary program reflects the integrative movements of science in general.”

The Joint Program in Computational Biology (JPCB) offered by the University of Pittsburgh and Carnegie Mellon University began enrolling students in fall 2005. The development of this program was sponsored by a $1 million grant, one of only 10 such grants awarded nationally, from the Howard Hughes Medical Institute.

Building on Pittsburgh’s strong history of achievement and progress in both the computational and biological sciences, the JPCB is designed to prepare scientists to harness the constantly expanding power of high-level computing and apply it to the fundamental principles of the life and physical sciences. Students learn and design computer-based modeling and simulation techniques that allow an unprecedented level of exploration of the structure and function of cells and molecules. Computational algorithms can save countless lab hours by running virtual scenarios that whittle down massive lists of variables for complex dynamics like DNA site binding and protein folding.

“Not only will our doctoral students have the opportunity to take advanced courses at both universities,” says Program Director Ivet Bahar, Ph.D., John K. Vries Professor and chair of the Department of Computational Biology, “but they also will work side by side with leading computational biologists and their clinical and basic research collaborators on solving complex problems in biological sciences or identifying more rational approaches to the development of new drug targets.”

The JPCB curriculum includes a set of core courses that provide students with a common background in the concepts and methods of computational biology. The program also offers five areas of specialization: computational genomics, computational structural biology, cellular and systems modeling, bioimage informatics, and computational neurobiology. These choices encompass a wide range of research topics, from molecular modeling and protein dynamics to large-scale analysis of genome and proteome data.

One of the ultimate goals of the program is to train researchers to use computation not only as a tool but also as the platform for a fresh way of approaching science. “It’s not just about adding a quantitative element to traditional biology,” says Ivan Maly, Ph.D., assistant professor of computational biology. “It’s about asking new questions.”
Honing Skilled Sequential Movements

Remember how your mother would always remind you not to skip piano practice? “Practice makes perfect,” she’d say. She was right, of course, and Peter L. Strick, Ph.D., knows why. In a recent article in the Journal of Neurophysiology, he and colleagues provide evidence that long-term practice of a sequence of movements (like a piano arpeggio) sculpts the response properties of neurons in the primary motor cortex (M1) and enhances the consolidation and retention of the acquired skill. “In the past, M1 has been thought to be involved in the simple generation of motor output. Our results suggest that M1 is a possible site for the storage of the internal representation of skilled sequential movements,” says Strick, professor of neurobiology and psychiatry as well as co-director of the Center for the Neural Basis of Cognition (CNBC). This finding is just one of many in Strick’s studies of the brain. He recently showed that premotor areas of the frontal cortex—once thought to influence motor function only through connection to the primary motor cortex—link with spinal motor neurons and may be responsible for some direct generation and control of voluntary movement. And he found that the cerebellum—formerly thought to be the seat of movement, coordination, and balance—is also a player in the thinking process. To top it off, he demonstrated that the cerebellum may control functional aspects of the basal ganglia, a region of the nervous system that has long been associated with Parkinson’s disease, Huntington’s disease, and addiction.

Taming Schizophrenia

Using drugs to control the symptoms of people with schizophrenia is nothing new. However, David A. Lewis, M.D., UPMC Professor of Translational Neuroscience, is developing a drug that may restore properly functioning thought processes. Instead of controlling the delusions and hallucinations associated with schizophrenia, the drug may help to lessen cognitive defects like dysfunction of working memory that are associated with the disease. People with schizophrenia have neurons that don’t produce enough gamma-aminobutyric acid (GABA). The drug acts on a class of neurons in GABA that regulate working memory. Lewis thinks the drug will “boost GABA signaling just at the location where the signaling is deficient and not boost it at locations where things seem to be normal.” He hopes that the drug, along with antipsychotic medications and cognitive and social rehabilitation, will help enhance cognitive capacity and, thereby, help people reintegrate into society. His greater hope is that the drug could be used to treat young people with early stages of the disease and reduce the severity of its symptoms.
RESPONDING TO EMOTIONAL STIMULI

By studying the amygdala, an almond-sized region of the brain linked to fear and emotion, Ahmad Hariri, Ph.D., assistant professor of psychiatry and a CNBC member, has shown that some people’s brains have a genetic tendency to react strongly to emotional stimuli.

He and colleagues looked at a variant of the human serotonin transporter gene, long suspected of having a link to anxiety. Using functional magnetic resonance imaging (fMRI) of the brain, they found that people with one or two copies of the short version of the variant, as compared with those having two copies of the long version of the variant, tended to show much greater amygdala activity when they viewed pictures of scared faces. “It’s like taking a hammer and smacking the amygdala, getting it to reverberate, and then measuring those reverberations and understanding what factors determine the magnitude of those reverberations,” says Hariri, whose research focuses on the interconnections of genes, brain function, and behavior. He and colleagues subsequently found that the gene variant also biased communication between the amygdala and the prefrontal cortex—a process that shapes behavior and predicts the degree to which healthy humans are harm-avoidant.

A SIMULTANEOUS SURPRISE

Sure the brain is mysterious, but neuroscientists thought they had at least this much figured out: Some neurons release excitatory neurotransmitters, which help neurons propagate impulses, and some release inhibitory neurotransmitters, which dampen impulses. It’s one or the other, right? Well, apparently not always.

Researchers in the lab of Karl Kandler, Ph.D., associate professor of otolaryngology, were surprised to discover neurons during brain development that simultaneously release not only the inhibitory transmitters GABA and glycine but also—and here’s the surprise—glutamate, the classic excitatory transmitter that is involved in learning and memory, addiction, chronic pain, epilepsy, and other conditions. This finding, which Kandler admits seems to contradict fundamental principles of neuroscience, “sheds new light on how inhibitory synapses evolve and are assembled into functional circuits in the developing brain.” Such research might someday explain the biological cause of brain disorders like epilepsy, schizophrenia, and tinnitus, which involve deficits that prevent normal inhibition of cells. In the meantime, the finding was the lead article in the March 2005 issue of Nature Neuroscience.

MECHANISMS OF MEMORY AND LEARNING

Timing is everything when it comes to learning and memory—or, more particularly, when it comes to the chemical synaptic interactions between neurons that lead to learning and memory. As a postdoc at the University of California, San Diego in 1998, two years before coming to Pitt, Guo-Qiang Bi, Ph.D., clarified and expounded upon the previous work of others and found that for a synaptic connection between two neurons to be strengthened—that is, for learning to take place—the first neuron must fire within about 10 milliseconds of the second, or nothing happens to the synapse. If the second neuron fires before the first, the synapse weakens. His resulting paper, later described as a classic, led to a precise understanding of the time factor involved in making memories. Now, as a member of Pitt’s Department of Neurobiology and of the CNBC, Bi studies ever-changing networks of multiple neurons grown in culture dishes that exhibit persistent reverberatory activity that may represent a mechanism for short-term memory in the brain. “It’s really hard to study the nature of persistent activity in vivo,” Bi says. “There are too many cells in a very complex environment; but in vitro, we can monitor and manipulate the activity of many neurons in a small network and probe the essential mechanisms.” Still, his groundwork, which he hopes will someday lead to a complete set of rules regarding the behavior of neural networks, holds important implications for understanding broad aspects of brain development and activity in addition to the mechanisms of memory and learning.

Guo-Qiang Bi, Ph.D.

“IT’S REALLY HARD TO STUDY THE NATURE OF PERSISTENT ACTIVITY IN VIVO... BUT IN VITRO, WE CAN MONITOR AND MANIPULATE THE ACTIVITY OF MANY NEURONS IN A SMALL NETWORK AND PROBE THE ESSENTIAL MECHANISMS.”
“Embarrassing” is how Thomas Detre, M.D., describes the landscape for cancer care in Pittsburgh in the mid-1980s—and he would know. In 1984, Detre became Pitt’s senior vice chancellor for the health sciences, with responsibility for the University’s six health sciences schools, including the School of Medicine. As such, he also became an unofficial “go-to” person for medical advice or referrals. “I’ve never adopted the parochial attitude that we’re the best in everything,” says Detre, now a distinguished service professor of psychiatry. “When people would ask me where I thought they would receive the best care, I sent them wherever I thought was the best place possible.”

Although Pitt was making great strides at the time in many areas of medicine, for cancer care, the best place to go was usually somewhere else. (The notable exception was pioneering work in breast cancer being done by Bernard Fisher, M.D., who ultimately changed the treatment protocol for the disease and even established a regimen for prevention.) Overall, however, the University was “very thin” in terms of cancer expertise, Detre recalls. Consequently, cancer patients and their families often found it better to travel to Cleveland, Philadelphia, New York, or Washington, D.C., for treatment.

The fact that the University of Pittsburgh Cancer Institute (UPCI) today ranks among the foremost cancer centers in the United States is a testament to how much things have changed in the past 20-some years—as well as to the determination of one man: Ronald B. Herberman, M.D., founding director of UPCI, associate vice chancellor for cancer research at Pitt, Hillman Professor of Oncology, and director of the UPMC Cancer Centers.
Detre dreamed of one day making Pittsburgh a center of excellence for cancer research and treatment, and he largely credits Herberman with making that dream a reality. “I’ve heard people say that Ron Herberman is made of steel, but I tell everyone he’s really made of titanium. … He’s one of the most persistent people I’ve ever met,” Detre says.

That’s high praise, especially from Detre, who bears his own reputation for persistence. In fact, if not for Detre’s dogged efforts to find just the right person to lead Pitt’s cancer center, Herberman might not have come in the first place, and UPCI might be nowhere near the world-class cancer institute it is today.

In January 1984, a University task force concluded that a consortium consisting of Pitt, its affiliated hospitals, and Carnegie Mellon University should work together to establish a regional cancer institute; all of the parties agreed to provide start-up revenue. As luck would have it, not long after assuming his new role as senior vice chancellor for the health sciences, Detre attended a Richard King Mellon Foundation dinner and gave a talk about the future of cancer care. That talk led to a $3 million grant from the foundation to help establish the cancer institute.

With initial funding in hand, Detre appointed a search committee to find a director, but viable candidates were reluctant about Pittsburgh, which still bore the scars of a smoky steel town whose heyday had passed. Eventually, the committee found a well-respected expert in chemotherapy who agreed to an interview. However, as Detre recalls, the candidate “would not do.” He wanted someone more in tune with newer, more innovative cancer therapies, someone who could effectively lead the institute into the future. Eminent oncologists and researchers—one of whom later won a Nobel Prize—were assembled to identify the credentials such a candidate should have. Like Detre, his advisors believed that molecularly targeted cancer treatments would likely come to the forefront and that much could be learned about cancer by better understanding the body’s immune system, why it sometimes fails, and how it can be strengthened when it does.

Gerald S. Levey, M.D., head of the search committee and chair of the Department of Medicine at the time, knew someone who fit that description perfectly. It was Herberman, who had begun a long and notable career at the National Cancer Institute in 1966, two years after earning his M.D. from New York University. Levey and Herberman had been friends since their days as residents at Massachusetts General Hospital. From the outset of Herberman’s career, immunology was the focus of his work.

In the early 1970s, Herberman’s laboratory discovered that a new type of immune cell, called a natural killer cell, could attack cancerous tumors, and he demonstrated its importance in resisting the spread of cancer. Based on evidence that some people develop a natural immunity to cancer, his lab also organized a national program for improving cancer diagnosis based on immune markers, a field now known as immunodiagnosis. Likewise, it developed a novel diagnostic tool by detecting biochemical markers in the blood, urine, and tissues of people with cancer. Herberman played a major role in establishing NCI’s Biological Response Modifiers Program, which funded research on biological and immunological cancer treatments.
like immune messenger molecules, vaccines, gene therapy, and bone marrow transplants. However, when contacted about the Pittsburgh job, Herberman, like the others, was reluctant about it.

“The reaction I got from my colleagues at NCI was that I shouldn’t even bother going to Pittsburgh because there wasn’t much going on in cancer at the time. In addition, the hospitals were too independent and weren’t under control of the University. The general consensus was that it would probably be too much trouble, and it probably would fail,” Herberman recalls. Only after considerable arm-twisting did he agree to an interview.

Herberman had been to Pittsburgh only once before, and it was a quick trip—no sightseeing. This time, he was surprised to find the city so attractive. However, he remained skeptical about the opportunity. Detre listened patiently to his concerns, assured him they were solvable, and suggested he ask around for input from others.

Herberman did and found that Detre was known as a man of his word—and more. Previously, under Detre’s leadership, Western Psychiatric Institute and Clinic had secured tens of millions of dollars in clinical research grants, established three National Institute of Mental Health centers of excellence, recruited top-level researchers and clinicians, and emerged as a research powerhouse with a wealth of groundbreaking studies on topics ranging from psychopharmacology to neurobiology and the genetics of mental disorders. Herberman was also impressed by the collection of University-affiliated hospitals, which subsequently formed the core of the University of Pittsburgh Medical Center (UPMC). At NCI, his access to cancer patients was limited; he saw the setup in Pittsburgh as much more feasible for the kinds of studies he wanted to conduct. Herberman finally agreed to take the job.

In September 1985, the fledgling cancer institute consisted of Herberman, a secretary, and a three-room suite in the former Eye and Ear Hospital that had been converted into offices. Barbara Duffy Stewart soon joined UPCI as one of its first employees. She recalls that on her first day on the job, while helping unpack a pile of boxes shipped from NCI, Herberman never removed the jacket of his corduroy suit despite the sweltering heat. It was a telling sign, because throughout the early frantic days of the institute, Herberman never lost his cool, says Duffy Stewart, who is now executive director of the American Association of Cancer Institutes. “Thank goodness for his personality. When something unexpected would happen, and the rest of us would go crazy, he was able to keep everyone on an even keel."

Not long after Herberman arrived, John Kirkwood, M.D., a highly regarded melanoma researcher from Yale, was recruited as UPCI’s clinical director. Another early recruit was Theresa Whiteside, Ph.D., who was already at Pitt in the Department of Pathology. “Ron wanted me to start an immunological monitoring laboratory for the cancer institute very similar to the one I ran for the Department of Pathology; however, this would be for monitoring patients’ immune responses to cancer therapy,” she recalls.

With Kirkwood and Whiteside on board, Herberman began aggressively recruiting more basic scientists and physicians. Places Rated Almanac had recently named Pittsburgh as America’s Most Livable City for the first time (an accolade
Early-stage breast cancer in postmenopausal women is often treated with a hormone-based chemotherapy, like letrozole, but this therapeutic approach is known to decrease bone mineral density, thus increasing fracture risk. Adam M. Brufsky, M.D., Ph.D., has found that if patients receive zoledronic acid prior to chemotherapy, bone loss in the lumbar spine is prevented.

Lisa H. Butterfield, Ph.D., and John M. Kirkwood, M.D., are testing a new combination immunotherapy vaccine in melanoma patients. This immunotherapy, which builds on previous work, is expected to enhance outcomes because it first triggers immune activation with a tumor-specific vaccine and subsequently “boosts” the effect with interferon alpha treatments, resulting in a more potent therapy.
and clinical space opened in 2002. An adjacent facility, the UPMC Cancer Pavilion, houses administrative offices and a 400-seat auditorium.

In 2005, the Hillmans gave $20 million more—the largest single gift ever to Pitt and UPMC—to create the Hillman Fellows Program for Innovative Cancer Research, which provides seed money to stimulate collaborative and novel cancer research, and to launch a major, five-year initiative to raise $200 million for UPCI's future growth and development. With the Hillman Cancer Center at capacity, attention has turned to the prospect of expanding UPCI’s facilities so that recruitment of top researchers and the march to excellence can continue.

In its relatively short history, UPCI has achieved recognition as a leading contributor to basic, translational, and clinical cancer research. As the institute’s funding and prestige in national rankings have grown over the years, it has, likewise, become more closely associated with the nation’s older, more established cancer centers. In addition, UPCI and the UPMC Cancer Centers now constitute one of the largest clinical cancer operations in the country and provide cancer care to nearly half of the regional market, including more than 25,000 new patients per year. The influence extends far beyond the region, however; among UPMC’s most recent ventures are two new cancer centers in Ireland.

As UPCI’s stature has grown, so has Herberman’s. Among his honors in recent years are the Governor of Pennsylvania’s Award for Excellence in Science and Medicine, a Lifetime Science Award from the Institute for Advanced Studies in Immunology and Aging, and the Solomon A. Berson Medical Alumni Achievement Award in Clinical Science from his alma mater, New York University.

Herberman is himself a cancer survivor who has permanent loss of peripheral vision as the result of surgery to remove a tumor on his pituitary gland. A reserved, intensely personal man not given to idle rhetoric, he prefers to focus on making a difference in the lives of cancer patients rather than talk about himself. It appears that focus is paying off.

For instance, Kirkwood’s pioneering research at UPCI has significantly advanced the treatment of melanoma, the deadliest form of skin cancer. Using a naturally occurring immune-stimulating protein, or cytokine, called interferon, Kirkwood’s group has demonstrated the regression of disease in some patients along with dramatic improvements in long-term survival. “Using interferon, we’ve seen a 25 to 35 percent reduction in relapse rates for patients with advanced melanoma, which is astounding considering this is a disease that has confounded medical science for more than 50 years,” says Kirkwood, director of the UPCI Melanoma Program.

Based on a study he led, the Food and Drug Administration approved interferon as the first-ever adjuvant treatment for high-risk melanoma. Kirkwood is now studying whether interferon can improve melanoma survival rates by giving it to patients in earlier stages of the disease. He’s also working on a number of candidate melanoma vaccines that could give people at high risk for skin cancer a natural immunity against the disease.

UPCI is making significant advances in the diagnosis, prevention, and treatment of many other cancers, including breast cancer, head and neck cancers, lung cancer,
and cancers of the blood and lymphatic systems. For example, the Immunologic Monitoring and Cellular Products Laboratory, where Whiteside is the scientific director, assesses patients’ immune response to therapy; it can measure multiple parameters, including immune cell types and function as well as the cells’ ability to manufacture cytokines. “We now can detect cancer and cancer progression much earlier because we can look for 10 to 15 markers rather than the one or two we were able to study 20 years ago,” says Whiteside. “Using advanced technologies, we also can look for the presence of 30 different cytokines, which give us a good indication of how well a particular cancer is responding to therapy as well as which cancers are likely to respond to a particular therapy.”

Whiteside also oversees a facility for generating cells and cellular products for cancer therapies like vaccines. The facility can genetically modify immune cells so they are better equipped to attack cancers. “At the moment, we’re developing products for as many as nine clinical trials, not only for cancer but also for other conditions such as HIV and diabetes,” Whiteside says. Her laboratory has a number of ongoing collaborations with industry, performing immunological studies on samples from patients involved in company-sponsored clinical trials. In addition, her lab is developing assays for companies that want to be able to measure a particular immunologic or molecular function resulting from a therapy, and it increasingly serves as a consultant to companies interested in developing immune cells for therapy.

Herberman sees collaborations with industry as a significant and growing part of UPCI’s future. “To truly make an impact on cancer, we need to get these better diagnostic approaches and treatment strategies to the patients as quickly as possible. To do that, it will take intensive collaborations with industry,” he says. “Our job is to do the early research, and their job is to take the research to the bedside. However, the more we do this collaboratively, the faster that will happen.”

Such developments make Herberman particularly optimistic about UPCI’s future. Perhaps most encouraging to him is the fact that he now has little trouble attracting people to join UPCI. “Recruiting is much easier these days. We’re now very widely known, and it’s much easier to get people to come and take a look and to take the job,” says Herberman. Indeed, what began with one or two employees in 1985 is now an institute of approximately 500 people, many of them highly respected scientists and physicians in more than 30 disciplines who have come from some of the world’s leading academic research centers. And why not? “We have great facilities, great people, a great environment, and people interact extremely well with one another,” Herberman says. “It’s a very nice place to work and be successful.”

And as for Detre, “embarrassing” is no longer a word he uses to describe the availability of high quality cancer care in Pittsburgh. Now, when someone asks, he advises them to stay right here.
Pitt and UPMC

Student Volunteers

Concussion Program

Biopreparedness

Technology Development

Clinical Care and Community

Treating patients with care and compassion
The paradigm for success that the School of Medicine and the University of Pittsburgh Medical Center have steadfastly followed in their symbiotic ascent to research and clinical excellence in recent years is rooted in a fundamental principle: What’s good for one is good for both. However, the interplay between them is far more complex than the clasp of hands in partnership or the mutual litany of praise about the benefits that each party brings to the table.

This collaborative venture is characterized, first and foremost, by UPMC’s longstanding and robust financial support of the School of Medicine, which, in turn, has made investment in its research enterprise an institutional priority and has leveraged this local capital to garner increasingly favorable levels of external support, most notably from the National Institutes of Health. (See page 3.)

The payoff from this dynamic has resulted not only in an ever-growing portfolio of tangible research results but also in a range of collateral benefits, including the spin-off of new and marketable technologies, improved visibility and stature for UPMC and the School of Medicine (as well as for the University as a whole), and the overall success of the clinical enterprise as evidenced by increases in patient referrals and the quality of clinical services.

A diagram of this interplay would show one step leading to another, and another, and another in a continuous cycle but with an ever-widening sphere of influence, initially emanating from Pittsburgh throughout much of southwestern Pennsylvania and now, more recently, to far-off places, including Italy, Ireland, and Qatar.

“Our mutually beneficial, decades-long relationship with the University of Pittsburgh in the health sciences is viewed as a model for other academic medical centers across the country,” says Jeffrey A. Romoff, UPMC’s president and chief executive officer.
Arthur S. Levine, M.D., senior vice chancellor for the health sciences and dean of the School of Medicine, agrees. Catalyzing the translation of research into groundbreaking clinical models and, thereby, advancing the missions of both the medical school and the health system regionally and internationally has produced “a novel, if not unique, relationship,” he says.

In blunt, no-nonsense language, what that actually means is that “we’re joined at the hip: UPMC can’t function without us, and we can’t function without UPMC,” Levine says. “The success of one is the success of the other.”

The School of Medicine is one of six health sciences schools at the University of Pittsburgh, which today stands among the nation’s leading academic centers for biomedical research. Pitt is home to a growing number of world-class scientists engaged in a wide range of studies on topics as diverse as drug discovery and design, organ transplantation and immunology, tissue engineering and regenerative medicine, artificial organ and medical device development, cancer diagnostics and therapy, cardiology, gene therapy, bioinformatics and computational biology, psychiatry, neuroscience, structural biology, developmental biology, and vaccine development.

One of the few objective benchmarks by which an academic medical center can evaluate its success is NIH support for research. Unlike reputational rankings, the NIH process is the only nationally competitive, peer-reviewed metric available. By this criterion, Pitt has thrived, breaking into the top 10 list of funded institutions in 1997—a shift in rank that occurs only rarely—and subsequently maintaining that enviable position. Since 1998, the University as a whole and the School of Medicine have both more than doubled their level of NIH support.

UPMC, one of the nation’s largest and most financially successful academic health care systems, provides world-class medical services through its vast network of hospitals, cancer centers, specialized outpatient facilities, rehabilitation centers, and other programs. Although legally separate and distinct entities, UPMC and the University share formal contractual bonds that define their relationship.

More importantly, both sides would say, is an appreciation for the mutual interdependence that enables Pitt to provide opportunities for clinical training, educational experiences, and research in virtually any medical specialty and that, likewise, enables the medical center to stand at the forefront of translating new scientific findings into innovative clinical care and to support the development of new medical technology. Together, Pitt and UPMC have raised the standard of medical excellence in southwestern Pennsylvania and positioned health care as a driving force behind the region’s economy.

The School of Medicine’s success in sustaining research productivity stems from its adoption of a growth paradigm centered on this fundamental idea: In an academic medical center, research and clinical success are synergistic and interdependent; therefore, a strategic collaboration between the clinical and the academic enterprises will enhance the success of both beyond that which would occur with an investment in either one alone. The starting point for actuating this philosophy was to invest clinical income in research infrastructure, including facilities, equipment, and investigator start-up packages.
Clinical growth at Pitt was led by organ transplantation, but this growth began with a substantial investment in research. The University recruited Thomas E. Starzl, M.D., Ph.D., in 1981, when liver transplantation was still a controversial concept. Starzl assembled an interdisciplinary team of surgeons, immunologists, pharmacologists, and others and expanded his previous clinical and laboratory research. The Food and Drug Administration's approval of the immunosuppressant cyclosporin in 1983, based largely on Starzl's clinical experience with the experimental drug, greatly improved graft survival and long-term outcome. In 1986, UPMC invested $230 million to expand the transplantation program as well as to provide space for the health system's fledgling cancer institute and other research initiatives. By 1988, more than half the world's liver transplants were performed in Pittsburgh, generating exceptional clinical revenue.

To maximize UPMC's investment of clinical revenue, the School of Medicine created mechanisms to impel new research initiatives, including technologically rich core facilities in genomics, proteomics, bioinformatics, clinical research computing, imaging, and others for use by multiple investigators. Other research-support resources for faculty included technical assistance in grant preparation and active guidance in technology commercialization. The ensuing faculty success in reporting their research findings, especially those related to significant clinical advances, promoted the visibility and prestige of the two partner institutions in the world of academic medicine and biomedical research, leading to the increased clinical volume and robust financial performance that is the cycle's entry point.

This increasingly dynamic research climate also led to more faculty entrepreneurship—along with subsequent benefits. For example, Stentor, a start-up company based on medical imaging technology, was formed in 1998 as a result of collaborative development efforts by University and UPMC researchers. When Philips Medical Systems, a division of Royal Philips Electronics, acquired Stentor in 2005 for approximately $280 million, UPMC realized a $36 million gain from its research investment and the medical school received nearly $11 million as a result of the transaction. UPMC's Strategic Business Initiatives division was subsequently launched, in part, with the profit from this deal to create and manage small companies, many based on faculty-developed technologies.

Meanwhile, the School of Medicine adopted a variety of strategies to sustain this model of success. Interdisciplinary doctorates in fields like integrative molecular biology and molecular biophysics and structural biology were developed, as were research requirements for medical students. In addition, preference was given to hiring basic scientists whose research themes foster translational research and to focusing on platform disciplines like structural and computational biology, pharmacology, developmental biology, and biomedical informatics. Interdisciplinary research and “team science” were not just encouraged but made the cultural norm, with the development of multiple centers and institutes providing a physical or “virtual” environment for topic-specific intellectual interchange that has helped nurture the recruitment and sustain the retention of faculty.

What began as a regional, middle-of-the-pack medical school and a voluntary consortium of six independent hospitals with which it was affiliated for teaching purposes has evolved over the past 25 years into a vast health care system and one of the nation’s leading biomedical education and research institutions. The success shared by the School of Medicine and UPMC has been notable and, in recent years, more far-reaching than ever. Perhaps the most pronounced example of their growing international influence is the Pittsburgh-Palermo connection.

In 1996, UPMC partnered with the Region of Sicily and two hospitals there to establish the Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (ISMETT—the Mediterranean Institute for Transplantation and Advanced Specialized Therapies) in Palermo, Italy. ISMETT opened a new, state-of-the-art, 70-bed specialty hospital, managed and operated by UPMC, in 2004 with a clinical focus on transplantation and other therapies for patients with life-threatening organ failure. UPMC physicians practicing at ISMETT hold faculty appointments in the School of Medicine, and the Palermo facility is linked via a telecommunications system to its affiliated network of UPMC hospitals in Pittsburgh.

As an outgrowth of this venture, planning is now underway for a $398 million Biomedical Research and Biotechnology Center to be built near Palermo. The facility, which would be funded by the Italian government, is to be managed by UPMC. Research, to be directed by the School of Medicine, would focus on such areas as drug discovery, vaccine development, tissue engineering and regenerative medicine, molecular imaging, and computational and structural biology—all of which are the medical school's current and developing areas of research strength.

Other recent international ventures have seen the Whitfield Cancer Centre in Waterford, Ireland, and Beacon Hospital Cancer Centre in Dublin added to the growing network of UPMC Cancer Centers. UPMC also recently entered into an agreement to help improve the emergency medical care system in Qatar by providing training for physicians and other first responders.

For Pitt and UPMC, success has been an outcome with many contributing factors: institutional commitment to excellence in their entire enterprise—research and clinical—backed by strategic investments and initiatives, strong and progressive leadership, strategic facility expansion, and recruitment and retention of personnel with the expertise to ensure sustained results. The most critical factor, however, has been UPMC’s financial and philosophical support, which sparked the School of Medicine’s ascendency to research prominence. The health system’s widening sphere of influence, both at home and abroad, will enable it to continue to invest in the medical school—the starting point of their mutual paradigm for success.
TAKING IT TO THE STREETS

STUDYING, WORKING ON NO SLEEP AND CAFFEINE, AND MORE STUDYING — THIS IS THE IMAGE PEOPLE OFTEN HAVE OF A MEDICAL STUDENT’S LIFE. WHILE THIS IS GENERALLY TRUE, MANY PITT MEDICAL STUDENTS FIND THE TIME AND ENERGY TO VOLUNTEER EXTENSIVELY IN THE PITTSBURGH COMMUNITY — IN ADDITION TO MANAGING THE BUSINESS OF THEIR FOUR YEARS OF LEARNING. HERE ARE SOME OF THE WAYS IN WHICH THEY USE THEIR MEDICAL EDUCATION TO SERVE OTHERS.

SCHWEITZER FELLOWS

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ince 1997, the Pittsburgh Schweitzer Fellows Program, part of the U.S. Schweitzer Fellows Program, has been involving students from various local schools in serving needy individuals and communities and developing in them leadership skills and a commitment to community service. Over the course of one year, Schweitzer fellows receive a $2,000 stipend to create and implement their own program to benefit underserved populations in the Pittsburgh area. Currently, the School of Medicine has several students with Schweitzer Fellowships, and many of them have a long record of volunteering in their communities.

Glaivy Batsuli started volunteering at an early age with her mom, and, as her family tells it, she’s been talking about being a doctor since she was 6 years old. Her parents are immigrants, and witnessing their experiences with health care in the United States further inspired her to spend her free time working in the community while growing up. Medical school keeps her busy, but “it’s good to be around ‘normal’ people—you know, people who don’t study all the time,” Glaivy says with a laugh. She heard about the Schweitzer Program in her first year when she was looking for community involvement activities and became interested in it because, as she puts it, “it allowed me to develop my passion.” For her fellowship, Glaivy and another Schweitzer fellow, Jean Lin, created a program for adolescents at the Sarah Heinz House, a local facility of the Boys & Girls Clubs of America, to promote participation in and better attitudes toward exercise. Glaivy and Jean knew that physical activity decreases in children as they grow older and that some of them dislike sports by the time they enter middle school because of the increasing focus on competition. Both students hope that their program, which begins each session with a short educational component, will inspire a lifelong interest in physical activity. “As a second-year medical student, I don’t often get to directly affect people’s health,” says Jean, “but with this program, I’ll definitely see results.”
The best part of medicine, Schweitzer Fellow Narges Farahi says, is the direct contact with people and the possibility of affecting their lives by bettering their health. Narges says she was raised in a socially conscious family and was taught to use her education and skills to give back to the community. Her interest in health care was sparked by working with an immunization program in Paraguay; her subsequent participation in Teach For America, an education program serving some of the nation’s lowest-income communities, made her realize that medicine was the way that she could most influence people’s lives for the better. Both experiences led her to apply to medical school.

For her Schweitzer project, Narges pulled from her experiences after college of working in children’s health care in Tanzania, where she first heard about rapid HIV testing (the results are preliminary and known in 20 to 90 minutes). She was shocked to realize, while conducting a local workshop on hepatitis C and HIV, that most of the patients there didn’t know their HIV status and were at high risk for contracting AIDS. Many of them had been tested at some point in the past but, for various reasons, had never received their results. She subsequently started a project to use rapid HIV testing for dual-diagnosis patients (those with substance issues and psychiatric conditions) and said she hoped to initiate rapid HIV testing and HIV counseling at other community programs throughout Pittsburgh. “My first year in medical school was really hard because it was all basic science, with few opportunities to have contact with patients,” Narges says. “Working in the community has helped me remember why I wanted to get into medicine in the first place.”

Erin Imler not only knew she wanted to study medicine, but she also earned guaranteed admission to the School of Medicine while still in high school (provided, of course, that she fulfilled certain requirements as an undergrad). Like Glaivy, Jean, and Narges, Erin has volunteered extensively throughout her life and plans to continue doing so when she finally becomes a doctor. At Pitt, she has volunteered at places like the Birmingham Free Clinic (a walk-in center for people without insurance or little access to health care) and the Women’s Center & Shelter of Greater Pittsburgh; her clinical rotation with the Indian Health Service in Arizona helped solidify her interest in working with underserved populations.

Erin set up her Schweitzer project at the Matilda Theiss Health Center as a diabetes self-management group where people can share frustrations, ideas, and information about nutrition and physical activity. She has also arranged for eye exams and glaucoma screenings for people in the group through the School of Medicine’s Ophthalmology Interest Group and hopes to set up similar opportunities for dental and podiatry care. Erin says, “This experience has been really exciting. I hope to continue working with underserved populations, especially in a rural setting.”
Community service is at the heart of Pitt’s chapter of the Student National Medical Association (SNMA), as it is for member Barrett Woods and his medical school experience. He grew up in Pittsburgh and is familiar with some of the communities in which SNMA members regularly work. Westinghouse High School is one of the places he volunteers with SNMA to tutor and mentor students and—most importantly, he believes—to show them that studying and doing well in school will serve them well in the future. “They can see me and where I am and know that school isn’t a waste of time,” Barrett says. When he first began mentoring a group of Westinghouse students, they were failing their courses; but with his consistent presence and the introduction of a little healthy competition among the students, their grades improved. “It was rewarding to see their spark,” Barrett says. “It’s important for them to see that being successful in school is accomplishable and that they’re not any less gifted than students in other schools.”

Barrett has benefited from mentoring himself. He cites Robert D. Bennett, M.D., clinical assistant professor of surgery, and former faculty member Henri R. Ford, M.D., as mentors who supported his decision to go into medicine. Likewise, he credits other medical students, including Nicole Christian and Bradley Stephens, as being instrumental in the progress made by SNMA. One of Barrett’s biggest goals is to secure funding to establish a mentoring program for young adults in the city. Meanwhile, he is also active in some of SNMA’s other programs, including HIV awareness sessions at the Shuman Juvenile Detention Center and health screenings and meal preparations at the East End Cooperative Ministry’s men’s shelter and soup kitchen.

Barrett intends to be involved in any community where he lives, be it Pittsburgh or elsewhere. He says, “I feel blessed in my life, and I have a responsibility to reach back into the community.”

**ESL Health Literacy Program**

Medical student Reggie Anunobi may not know what it’s like to flee on foot to another country to survive a civil war or live a tenuous existence in a refugee camp for years, but, like many of the people he helps, he can relate to how difficult it can be to assimilate to life in the United States. He knows what it’s like to negotiate new situations in an unfamiliar culture and to hide that he feels wildly out of place. His experiences in moving to the U.S. from Nigeria are part of his drive to help Somali Bantu refugees who have been relocated to Pittsburgh. Reggie co-coordinates the English as a Second Language (ESL) Health Literacy Program initiated by Pitt medical student Susan Wong and funded by the Caring for Community Grant Program through the Association of American Medical Colleges and the Pfizer Medical Humanities Initiative. Somali Bantus, a persecuted minority in Somalia, have not been permitted to attend school in their homeland and, therefore, are mostly unable to read or write. After walking for miles out of Somalia and living in refugee camps in Kenya for a number of years, some of them began arriving in Pittsburgh in 2004.

Four times a month, Reggie and other volunteers teach the refugees about hygiene and personal health care-related issues. Many American behaviors are new to them, and the volunteers help the refugees adapt and learn things like the difference between dish soap and detergent, and that all foods available in the store aren’t necessarily nutritious. (Children of the refugees encounter junk food for the first time here, and they must learn that candy bars aren’t meant to be eaten as meals.) “The concept of preventive medicine is very new to them,” says Reggie. “Why would they go to the dentist twice a year if nothing is wrong? Flossing their teeth means very little to them, but we explain how important it is in the long run to maintain healthy teeth and gums.” The Somali Bantu families in Pittsburgh speak a dialect called Maay Maay, which almost no one in the region speaks, so volunteers often use PowerPoint presentations with pictures to help illustrate their lessons.

Reggie is responsible for encouraging other students to participate in the program, writing the curriculum, and getting supplies for teaching sessions. Like other Pitt medical students who volunteer in the community and still manage to keep up with their studies, Reggie says that maintaining the balance is simple; he just makes time to help others. The reason he’s studying medicine is because of its inherent intellectual and human components; medicine is a field that satisfies his interests and allows him to make a difference in other people’s lives. He hopes to do his residency in Nigeria, which is where he worked one recent summer with a doctor from Vanderbilt University to teach physicians how to do procedures with whatever resources were available—like how to diagnose an injury without an X-ray machine. Wherever Reggie ends up, he hopes he can return to Nigeria to work in hospitals for one or two months a year. “I can’t just come to the U.S. and make money,” he says. “That’s too selfish. I have to go back and help with my expertise.”

**A $90,000 Legacy**

Members of the Class of 2009 aim to do more than leave the University of Pittsburgh with a medical degree. With the “90K from 2009” project, they have pledged to raise at least $90,000 before their graduation to benefit Pitt’s Program for Health Care to Underserved Populations (PHCUP). Leading the campaign are Class of 2009 students Brett Michelotti and Lauren Toney, who see this initiative as part of the ongoing legacy of community service by Pitt medical students. Brett calls it “a testament to the calling of our future profession and a model of our commitment to society.”

PHCUP, which operates through the Department of Medicine’s Division of General Internal Medicine, serves the region’s uninsured population through four free health care clinics and operates with only a volunteer staff of clinicians. Many medical students begin working with the Pittsburgh community by volunteering their time and expertise to the Birmingham Free Clinic, one of the four PHCUP facilities. Brett and Lauren have plans for various fundraisers, including a wine-tasting/silent auction event.

The Class of 2009 hopes to end its time in Pittsburgh by strengthening PHCUP and its ability to improve health care throughout the greater Pittsburgh area. “This ambitious endeavor reflects the generous and altruistic spirit that exemplifies the best of our medical school community,” says Arthur S. Levine, M.D., senior vice chancellor for the健康 sciences and dean of the School of Medicine.
HELPING WITH HEALING IN HONDURAS

When the opportunity arose to spend two weeks of her family medicine rotation in a remote village in the mountains of Honduras, Cecily Agcaoili was excited and unfazed by tales of omnipresent mud, no electricity, frigid showers, and people with illnesses of which she had never heard. Instead, she wondered whether, as a third-year medical student, she had enough skills to help people who stood in line for hours at the clinic for a chance to be seen by a student like her. Fellow medical student Benjamin Tu also jumped at the chance to spend his rotation in San José del Negrito. He wondered how he’d be able to work around the language barrier and whether his medical knowledge so far was adequate.

Both students were in Honduras with the Pittsburgh chapter of the nonprofit health care partnership Shoulder to Shoulder. A member of the Global Health Medical Education Consortium, William Markle, M.D., clinical associate professor of family medicine and director of the UPMC McKeesport Family Medicine Residency Program, chose San José del Negrito as a place with which he could form a collaboration with Shoulder to Shoulder to provide health care. The village had established a health committee and had the infrastructure needed to work with a Shoulder to Shoulder team. (All health care in the village is provided in Spanish, Markle says, and caregivers not only become adept at working with interpreters but also find that their own fluency, if limited, improves quite a bit.) With Markle, Randall Kolb, M.D., director of the UPMC Shadyside Family Medicine Residency Program, and Mark Meyer, M.D., a family physician practicing in East Liberty and president of the local Shoulder to Shoulder chapter, have recruited health care professionals and medical students to volunteer in San José for two-week brigades twice a year since 2000. Cecily was in the cohort in spring 2006 and Ben in fall 2005.

Once they arrived, they had no time to worry about their qualifications. Each day after breakfast, group rotations began with either seeing patients at the clinic, running the pharmacy, or working on community projects that students designed themselves, such as monitoring local children’s nutrition and villagers’ compliance in taking medications. Their days ended with a senior physician’s special presentation or talk about cases they encountered that day. Then they’d get to strap on headlamps, play some cards, and maybe play with the local children.

Sometimes they were exhausted from hiking hours a day to set up a temporary clinic for people who lived too far away from the village to travel there easily. Other times, they worked on a way for people who couldn’t read their prescriptions to know when to take their medication. (One way was to attach preprinted stickers with the symbol of a rooster for morning, a sun for midday, and a moon for evening to the plastic bags or bottles containing villagers’ medicines.) In all cases, they had to think quickly and trust what they had learned about medicine so far, even if senior physicians and residents were nearby for a quick consult or question. Often, Cecily and Benjamin had to acknowledge that some ailments required treatments and supplies they didn’t have there. Benjamin remembers meeting an older man who had been relieving a toothache by dabbing it with battery acid. “It was tough,” he says. “I’m not a dentist, but I was able to tell him to stop using the battery acid, dispense some Tylenol for relief, and give him a toothbrush and toothpaste so he’d have a chance for better oral hygiene.”

Both students returned to Pittsburgh with a renewed sense of confidence in their skills, especially when faced with less-than-ideal circumstances. “It was great to see all that I’ve studied, even the small things everyone said you’d never need to know, come to life,” says Benjamin. Cecily was left with an enthusiasm for the rest of her studies. “I feel very prepared for anything,” she says. “It was definitely the best experience I’ve had in medical school.”

Vincent Lee, a Pitt medical student who also completed a clinical rotation in Honduras, provided these photos of some of the sites from his experience.
Doctors at the UPMC Sports Medicine Concussion Program sometimes see famous athletes in their waiting room, but not for the best of reasons. After suffering serious head trauma in a highly publicized, off-season motorcycle accident, followed by a concussion in a game midway through the 2006 season, Pittsburgh Steelers quarterback Ben Roethlisberger came in for evaluation. He had to pass several tests to assess his cognitive abilities and whether or not his symptoms had subsided before being cleared to resume playing football. Other athletes aren’t so fortunate. In early 2007, San Francisco Giants catcher Mike Matheny announced his retirement from baseball after doctors in the program tested him and found that, almost a year after a concussion caused by a series of foul tips to the face mask, he was still experiencing symptoms of head trauma.

The Sports Medicine Concussion Program has established an international reputation in the diagnosis, evaluation, and management of sports-related concussions in athletes at all levels, from professional to college and even high school. Established in 2000, the program’s patient base has grown every year to nearly 2,400 patients in 2006.

The program’s founding director, Mark R. Lovell, Ph.D., associate professor of orthopaedic surgery and director of neuropsychological testing programs for the National Football League and the National Hockey League, can relate to what the athletes experience postconcussion. When he was 18, he was in a car accident and sustained a concussion. “I still can’t remember a lot of what happened in my senior year of high school,” Lovell says.

What primarily draws athletes to the program is a test called imPACT™ (Immediate Postconcussion Assessment and Cognitive Testing) developed by Lovell along with Joseph Maroon, M.D., who is currently a clinical professor of neurological surgery. The computerized test, which is designed to objectively evaluate the severity of concussions and more accurately determine if and when an athlete can return to play, is composed of six sections and evaluates visual processing speed, memory,
attention, and other elements of cognition. Lovell came up with the idea for imPACT when he started working with the Steelers more than a decade ago. He and other doctors were testing each player’s cognitive skills preseason and using stopwatches to time their responses to different tests. “I wanted to do the same tests but more accurately and with fewer personnel, and computers were really starting to get big, so it seemed perfect to create a computerized test,” says Lovell. Now, imPACT is being used worldwide by many high school, collegiate, and professional sports teams. A recent study by Lovell and colleagues confirmed the value of such neuropsychological testing through the use of functional magnetic resonance imaging (fMRI), one of the few scanning tools that can show brain activity, not just anatomy.

Even the Centers for Disease Control and Prevention (CDC) has tapped the Sports Medicine Concussion Program’s expertise. Michael W. Collins, Ph.D., assistant director of the program and assistant professor of orthopaedic surgery, was a key contributor to the CDC’s recently revised multimedia information kit designed to educate physicians about earlier diagnosis, management, and appropriate referral for concussion patients. “No two concussions are alike, and the injury’s effects and recovery period are different in each individual,” Collins says. “That’s why education for both patients and doctors about proper management is essential.”

In addition to clinical care, the Concussion Program is engaged in pertinent research like that of Collins, who conducted a study that supported the commonly held notion that, after one concussion, high school athletes will experience more and increasingly severe symptoms with subsequent concussions. Lovell’s research has shown that NFL athletes recover from a concussion faster than high school athletes, which also underscores the careful handling and proper recovery time that younger people need postconcussion. The number of concussions in younger players is increasing because “there’s increased recognition and we’re better at diagnosing the injury,” says Lovell. “Plus, sports have changed. Kids are stronger, bigger, faster, and hit harder. Women’s sports have definitely gotten more aggressive, and we’re now studying concussions in females specifically,” he adds.

The clinical approach followed by the program is to effectively manage a concussion. “There are two essentials in dealing with concussions. One is properly identifying the injury and getting the player off the field immediately, and the second is giving the player enough time to rest. Too much mental or physical activity can delay the recovery process,” says Lovell. Experiencing a second concussive injury while recuperating from an initial one is especially dangerous in that it can cause even greater brain trauma. Lovell says athletes are not cleared to play again until they undergo a magnetic resonance imaging exam and an imPACT evaluation, do cardiovascular exercise, display no symptoms, and successfully complete this sequence several times.

To more accurately judge the normal cognitive condition of each player, “Big Ben” Roethlisberger and his teammates are tested with imPACT at the outset of their careers with the Steelers. If they do sustain a concussion, then baseline data exist so doctors can assess the extent of their damage in a more individualized manner.

“All of this keeps me busy, but I enjoy the work,” says Lovell. “I get to work with athletes and travel the world, bringing imPACT and concussion education to people. I feel like it’s making a difference.”
andemic influenza. Smallpox. Anthrax. Ebola. Radiation poisoning from a “dirty bomb.” These and other 21st century threats to public health and safety are potentially devastating and require innovative and extensive preemptive planning to counter such risks.

Both the School of Medicine and the University of Pittsburgh Medical Center (UPMC) are actively engaged in extensive and often collaborative efforts to anticipate and prepare for how they as institutions — and how the people who comprise those institutions — would respond.

Even more fundamentally, the approach adopted here to teaching medical students about the public health threats — whether from biological attacks, disease epidemics, or natural disasters — that they might face someday as physicians is inclusive: “Almost anything is a potential threat, the thinking goes, so prepare for all possibilities,” says John F. Mahoney, M.D., associate dean for medical education and associate professor of emergency medicine.

While this approach might seem inordinate, the logic is clear. Modern threats to society are so pervasive that preparing intensively to deal with any single one of them is unlikely to pay off. “Twenty hours of anthrax training won’t counter an ebola outbreak,” Mahoney notes. “Instead, the all-hazards approach to preparedness provides a basic understanding and awareness of specific threats but emphasizes fundamental principles that can be followed regardless of what the specific threat turns out to be.”

UPMC echoes this emphasis on all-hazards disaster planning. “UPMC’s innovative approach to preparedness must extend beyond expected types of emergencies. It must address potential threats about which there are limited scientific facts and multiple variables,” says Loren H. Roth, M.D., M.P.H., the health system’s chief medical officer.

At the School of Medicine, various aspects of preparedness are woven throughout the curriculum rather than addressed in a single course. Topics like bioterrorism agents and pandemic influenza, for instance, are covered in the first-year medical microbiology course, while pharmacologic aspects of chemical weapons agents are integrated into second- and fourth-year pharmacology courses. Every eight weeks during the third-year medicine clerkship, a lecture on emerging infectious diseases is presented. Such initiatives are ongoing and subject to constant review to keep them current. Likewise, specific, hands-on training is being developed and implemented. All students are taught how to select and fit-test an appropriate breathing apparatus; still to come are lessons on personal protective equipment and decontamination. An annual exercise for third-year students simulates the drama of a pandemic influenza outbreak that inundates a hospital with infected patients. This role-playing drill is designed to teach students not only how to care for patients in a crisis as supplies run short, hospital workers themselves fall ill, and the mortality rate climbs, but also the importance of leadership, cooperation, and teamwork.

In the early planning stages is an initiative to prepare students to assist UPMC in the event of a major disaster, if needed, in providing patient care on a massive scale to the extent that their level of training would allow. First-year medical students, for example, could take vital signs and help move patients, whereas third-year students could variously assist a patient care team. Students would be trained each year to anticipate — regardless of what the crisis might be — what types of tasks they could be expected to perform, whereas UPMC personnel would be briefed regularly to know what each level of student is capable of doing and, therefore, what kind of help to expect from them.

The logistics of this initiative, which could encompass other health sciences students beyond the School of Medicine, are being developed in synchrony with UPMC’s comprehensive planning efforts, which entail the anticipation of quarantine, protection, and vaccination issues in the event of an outbreak of a contagious disease like smallpox or avian flu as well as the vast range of other considerations in preparing for natural or man-made disasters or other emergencies. “UPMC makes emergency preparedness a top priority,” Roth says.

Underlying all of these efforts on the parts of both UPMC and the School of Medicine is not only anticipation of the leadership that would be expected of them in the event of a cataclysmic event but also the realization that the best time to grapple with one is before it occurs.
olor, calor, rubor, and tumor—pain, heat, redness, and swelling. These are the four classic signs of the inflammatory response. For years, Raphael Hirsch, M.D., chief of pediatric rheumatology at Children’s Hospital of Pittsburgh of UPMC, had been trying to figure out how to measure these signs in his young patients with juvenile rheumatoid arthritis (RA) in a more quantifiable way than the routine physical exam of the joints. He knew from his own experience, as well as from published research, that even experts will evaluate the severity of the same inflamed joint differently and that the same expert’s judgment may vary from exam to exam. He also knew that available technologies, like X-ray, MRI, and ultrasound, were not effective in evaluating disease activity in RA and were not economically viable or user-friendly for routine office-based use. Hirsch was determined to find something better. However, it wasn’t logic but location that put him on the path to success.

Hirsch’s next-door neighbor happens to be Richard D. McCullough, Ph.D., vice provost for research at Carnegie Mellon University. The two were talking about Hirsch’s challenge, and McCullough put him in touch with faculty at Carnegie Mellon’s famed Medical Robotics Technology Center. Then, with C. Kent Kwoh, M.D., a Pitt rheumatologist who cares for adults with RA, the group came up with an off-the-shelf combination of three-dimensional and thermal imaging and their own proprietary rating algorithms to quantify two of the four signs of inflammation—swelling and localized warmth. And these two seem to be enough. “Combining that information, we can derive an index of what the disease is like in a given joint,” says Hirsch. The quantitative measures provided by the imaging technology offer a more consistent and reliable way to track disease over time. Because the process is fast (less than a minute) and noninvasive, patients can have images made while waiting to see the doctor. “Instead of spending half an hour trying to physically examine every joint,” says Hirsch, “you can focus on the joints of interest.”

Hirsch and colleagues tried for two years to get research funding from the National Institutes of Health to optimize their technology, but to no avail. They also submitted an invention disclosure to Pitt’s Office of Technology Management, and Children’s Hospital decided to file a provisional patent on the technology. When he reviewed the invention disclosure, Marc Malandro, Ph.D., Pitt’s associate vice chancellor for technology management and commercialization, thought Hirsch and colleagues were onto something. However, he knew the group needed business expertise to move to the next levels in refining their technology, defining their target market, and outlining their value proposition. He suggested that they get in touch with two local economic development organizations with which Pitt collaborates regularly. The Pittsburgh Life Sciences Greenhouse (PLSG) provided not only $150,000 of early-stage funding but also the expertise of Fred Marroni, a PLSG executive in residence with significant international experience in imaging-related industries. A second regional commercialization enterprise, the Idea Foundry, came up with an additional $175,000.

With Marroni on board, the group decided to participate in the Pittsburgh Technology Council’s business plan development contest, Enterprise 2006. The venture took top honors in phases one through three of its business development process. “But it wouldn’t have worked without PLSG and Fred,” confides Hirsch.

In July 2006, the entrepreneurs took the plunge of forming a biotech start-up among three partners—the University of Pittsburgh, Children’s Hospital, and Carnegie Mellon University. But they didn’t make a public announcement about the new
Everyone likes to invest in a winner. The University of Pittsburgh is indeed fortunate that as our reputation and national rankings have continued to rise in recent years, so has the number of individuals, corporations, and foundations that recognize us as a wise investment. Thanks to this generosity, the Schools of the Health Sciences, led by the School of Medicine, helped the University reach the $1 billion goal of its capital campaign, begun in 1997, nearly a year ahead of schedule.

Our success has given us the confidence to move forward, expanding the campaign goal to $2 billion, with the expectation that, when complete, the campaign will have raised at least $1 billion for our six health sciences schools, of which $600 million will have been earmarked specifically for the School of Medicine.

Since the formation of the University of Pittsburgh and UPMC Medical and Health Sciences Foundation in 2003, we’ve started to think differently about the way we engage our supporters. We know that philanthropy creates a partnership, which means responsibility on both sides to keep the lines of communication open so that we understand the things that each of us can do to have a positive effect on the way medicine is taught, the way research is funded, and the way health care is provided.

INVESTMENT BY THE NUMBERS

“Innovation commercialization takes considerable time, investment, finesse, and generous doses of University support and perseverance,” says Marc Malandro, Ph.D., Pitt’s associate vice chancellor for technology management and commercialization. The University’s Office of Technology Management evaluates its success by the number of faculty who submit invention disclosures, the number of those ideas that can be turned into products, and the number of those products around which new companies can be developed, among others. In 2006, the most recent year for which data are available, more than 350 faculty members participated in the innovation and commercialization process, many of them from the School of Medicine. This increasing faculty involvement highlights the school’s desire to make innovation a central component of its academic endeavors.

These 2006 numbers characterize the growing role of the School of Medicine in the University’s technology commercialization efforts.

- Invention disclosures: **112**
- U.S. patents issued: **13**
- Licenses/options executed: **18**
- Total revenue: **$10.1 million**

INNOVATION BY THE NUMBERS

company until January 2007, at which time the formation of Arthritis Imaging Inc. was formally announced by PLSG. However, Marroni, applying his business development savvy, could clearly forecast applications for the technology beyond arthritis to other diseases that manifest as surface inflammation like skin diseases and pressure ulcers. The corporation was renamed Cartesia Dx, while its initial product remained Arthritis Imager. And, true to the intent of the PLSG executive in residence program, Marroni thought Cartesia Dx was the next good fit for his own expertise, so he became the company’s founding president and CEO. Hirsch and Kwoh serve on the company’s scientific advisory board, along with Carnegie Mellon’s James Osborn.

The product, which, in its ultimate form, will probably look something like a small desktop igloo, will be targeted initially to pharmaceutical and contract research organizations conducting arthritis-related clinical trials. Since the Arthritis Imager can provide objective measures and patient documentation taken at different time points (for example, before and after treatment), it promises to substantially reduce both the number of subjects required for a clinical trial and the time to market for the intervention being evaluated. Once the technology is optimized and priced competitively (ideally under $100,000), Hirsch hopes to see it in every rheumatologist’s office.

At Pitt, which is intensifying its technology commercialization efforts and its outreach to faculty about the potential innovation opportunities waiting to be realized from their research, Malandro points to Cartesia Dx as a multidimensional success story-in-process: “We have technology licensed from two universities, active partnership with UPMC, and both financial and business development support from two regional economic development organizations. This is exactly how we like to see the process work. It’s good for Pitt and it’s good for the region.”

INNOVATION BY THE NUMBERS

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The generosity of our alumni and friends is the key to our having the resources needed to remain an institution of choice for the best and brightest. For example, our School of Medicine is consistently ranked among the nation’s finest and competes directly with Harvard, Yale, and other leading institutions for prospective students, but we don’t have the multi-billion-dollar endowments that many of those schools have. What will make the difference in our ability to attract and keep top students—and to ensure that they graduate without crippling debt—is our ability to offer the same type of financial assistance and scholarships that those schools are offering.

At the same time, we need to keep recruiting and retaining top researchers and faculty members and to make the ongoing capital investments needed to ensure that we have the most up-to-date facilities in which they can do their work. Because of the growing need for investment in research, the School of Medicine is committed to further expansion of facilities, and that expansion is possible only through partnership with philanthropy. Likewise, as essential research funding from the National Institutes of Health continues to stagnate, institutions like ours are finding that the gap can be made up only through private giving.

It’s encouraging to see that more and more people are coming to understand that if they care about changing the face of academic medicine, then the University of Pittsburgh School of Medicine offers a wise investment. I can’t think of a better way to back a winner.

Clyde B. Jones III
President
University of Pittsburgh and UPMC Medical and Health Sciences Foundation

With grateful appreciation for their generosity, we acknowledge the following individual, corporate, and foundation donors whose contributions of $500 or more to the University of Pittsburgh School of Medicine, University of Pittsburgh Cancer Institute, and Western Psychiatric Institute and Clinic between July 2003 and December 2006 have supported us in our academic, research, and clinical missions.

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Before an individual’s name indicates the person is deceased.
Frank Sarris smiles when you call him the “Candyman.” After growing Sarris Candies from a family-sized operation in the basement of his Canonsburg home into a beloved and enduring brand, he’s earned the right to the title.

Even after receiving a life-saving kidney transplant in 2002, Mr. Sarris made sure that the people around him had plenty of candy. For the 45 days post-transplant that he spent in UPMC Montefiore, doctors and nurses from all over the hospital were drawn to his room by the smell of chocolate. His family kept him stocked with a steady supply from the company headquarters at the Sarris Chocolate Factory and Ice Cream Parlor, a Canonsburg landmark. “It makes people happy,” he says. “And I knew that more people would come in and check on me if they could pick up a handful of candy on their way out.”

Mr. Sarris has nothing but praise for the quality of care he received during this crucial time. “I wouldn’t be here without the transplant program,” he says. “No doubt about it.” He and his wife, Athena, were so grateful for his second chance that they wanted to give something back.

“We asked my doctors, ‘What do you want?’” he recounts. “They said they could always use some money. So we gave them $5 million.”

This generous gift went to support the Thomas E. Starzl Legacy Endowment, named for legendary transplant pioneer Thomas E. Starzl, M.D., Ph.D. The fund is used for ongoing basic science research to improve the success of transplantation procedures and subsequent patient care. In appreciation, the transplantation clinic on the seventh floor of UPMC Montefiore was renamed the Frank Sarris Outpatient Clinic. The newly remodeled facility was reopened with a chocolate ribbon-cutting ceremony in March 2006.

The Sarris family has forged permanent friendships with a number of the medical personnel there. “I’ve just enjoyed getting to know everyone. I’ve met so many nice people,” Mr. Sarris says. At first he was concerned that he wouldn’t be able to communicate with his transplant specialists in medical jargon. “I can’t talk like they talk, you know. But it turns out that they don’t want to talk about medicine. They want to know about the chocolate business.”

Of the many features in the refurbished outpatient clinic, one in particular stands out. The Athena Sarris Café is a free-of-charge coffee station for transplant patients and their families. But this isn’t just any coffee station. Athena planned every detail: two state-of-the-art coffee systems sit on a marble-topped credenza that’s backed by a hand-painted mural of the Greek isles. There’s a choice of no fewer than 12 varieties of coffee, tea, and hot cocoa.

“People getting post-transplant care are in and out of that clinic a lot. Some of them don’t have the money to pay $3 or $4 every time they want a cup of coffee,” says Mr. Sarris. “And even sick people—especially sick people—need to take time out for a treat.”
Arnold Palmer

A white-haired man is standing on his back deck, golf club in hand. Just a few feet away, his dog is literally dancing with anticipation. Suddenly the club goes back and then down again in a fluid, seamless motion that is completely inseparable from the man himself. The swing connects—and then down again in a fluid, seamless anticipation. Suddenly the club goes back feet away, his dog is literally dancing with back deck, golf club in hand. Just a few

Arnold Palmer with Mulligan

“I’ve had to deal with cancer a lot in my life,” says Mr. Palmer. He had already witnessed the emotional and physical tolls of the disease firsthand when his daughter, Amy Saunders, discovered she had breast cancer in 1990. A 32-year-old mother of four at the time of her diagnosis, Amy fought and survived. (On the morning this photo was taken, Amy’s daughter, Katie, had just given birth to a baby girl, making four at the time of her diagnosis, Amy fought and survived. (On the morning this photo was taken, Amy’s daughter, Katie, had just given birth to a baby girl, making

Mr. Palmer had served as benefactor to a number of cancer-related causes and funds. Thanks to his recent generosity to the University of Pittsburgh, the University of Pittsburgh Cancer Institute (UPCI) is now home to the Arnold Palmer Endowed Chair in Cancer Prevention. This $2 million gift has enabled UPCI to recruit Emanuela Taioli, M.D., Ph.D., an internationally recognized hematologist/oncologist and epidemiologist, to head a new UPCI division devoted to cancer risk and prevention.

“I’m encouraged by many things that are happening that are leading toward the eventual cure or elimination of cancer from our lives,” says Mr. Palmer. “There are a lot of developments out there. So one thing I’m particularly interested in is the flow of information from the medical community. What I try to support and encourage is better communication among hospitals and doctors and researchers.

“But on an individual level,” he continues, “the best advice you can give anyone is to pay attention. Early detection is key. Take your general physical every year. Go to your doctor in the meantime if you think anything is the least bit wrong.”

“You have to go,” adds Mr. Palmer’s administrative assistant of 40 years, Doc Huckestein. “And I’m glad I did.”

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Before an individual's name indicates the person is deceased.
The Family of Jane Citron

Professional cook, writer, teacher, traveler: the rich, creative career of culinary arts expert Jane Citron was far too multifaceted to be described by any single label. When she died on December 15, 2006, after a six-year battle with colon cancer, her passing was mourned by countless friends and readers who would miss the rare balance of passion and common sense with which Mrs. Citron approached both food and life. As a tribute to Jane Citron, her family, including her husband, Carl; son Alan and his wife, Susan; son Stanley and his wife, Andrea Cohen, established the Citron Family Endowed Fund in Honor of Dr. Kenneth Lee. The goal of the fund is to raise $2 million to support research on colorectal cancer and its prevention, as well as clinical programs that support excellence in patient care. The Citrons are quick to point out that the fund was developed before Jane’s death and that it was her idea to dedicate it to Kenneth K.W. Lee, M.D., associate professor of surgery and her primary physician throughout her illness. “She blessed the fund,” says Alan, “and she loved Ken. The fact that he was so exceptional has helped us all fight through the inertia of this disease.”

It’s clear that the Citron family’s admiration runs both ways. Dr. Lee remembers Mrs. Citron as a “glowing” woman who, even while struggling with cancer, found the energy to form personal connections with the caregivers she encountered during her treatments. “I first met the Citron family when Mrs. Citron came to see me. And I can see her in all of them,” says Dr. Lee. “They are doing, their shear commitment, is extraordinary.”

“Dr. Lee was always caring and compassionate with all of us,” says Carl Citron, “and he was always available for my father, waiting and eager and nervous a.m., but Dr. Lee came back and stayed there all night working to save her. That’s the kind of doctor he is.”

In May 2007, the Citrons organized and hosted a highly successful dinner event, “Cooking Up A Cure,” at Oakmont Country Club; it was attended by 270 people. The family is developing a number of ideas for future fund-raising activities, including the release of a cookbook of recipes written and compiled by Jane before her death. “We hope to continue raising enthusiasm for the fund so we can raise awareness about colon cancer,” says Susan. “We realize that there are so many people suffering from this disease. It’s the second leading cause of cancer death in the United States. We know what it’s like to be that family, waiting and eager and nervous and scared,” she says. “We just want to help other people who are going through the same thing.”

Alan adds, “We just couldn’t believe that nothing is being done about this on a local basis, particularly since we’re so fortunate to have such a world-class cancer institute in the area. So we decided to do something.”

Susan, Alan, and Carl Citron, with Dr. Kenneth Lee
The Doctors S. Sutton Hamilton

If something like an M.D./Ph.D. program had been available when Sylvester Sutton Hamilton III started his medical education in 1957, he would have been first in line. A Pitt School of Medicine alumnus from the class of 1961, Dr. Hamilton is the former chair of psychiatry at the University Medical Center at Princeton and former director of the psychiatry residency program at the Hospital of the University of Pennsylvania. Although technically retired, he still maintains a private practice in Princeton.

Dr. Hamilton, along with his wife, Carol; daughter, Julie; and son, S. Sutton IV, recently established the Drs. S. Sutton Hamilton Medical Scientist Training Program (MSTP) Scholar Award for Pitt M.D./Ph.D. students. The scholarship is designed to support students who are interested in both the research and clinical aspects of medicine. Students are eligible for the award if they have completed their Ph.D. work and are two years away from their M.D. degree. The award covers the last two years of tuition and includes a $2,000 stipend for the duration of the scholarship.

The Hamiltons created the award in honor of their family’s four uninterrupted generations of physicians. Dr. Hamilton’s grandfather, the original S. Sutton Hamilton, maintained a practice in Punxsutawney; his father, S. Sutton Hamilton Jr., was an intern at Presbyterian and Magee Hospitals in the 1930s before returning to Punxsutawney to practice; and S. Sutton Hamilton IV received his medical degree from Pitt in 1997 and is now assistant director of the Family Medicine Residency Program at Underwood-Memorial Hospital in Woodbury, New Jersey.

While the other S. Sutton Hamiltons focused on general medicine, Dr. S. Sutton Hamilton III chose to specialize in psychiatry. “I’ve always enjoyed the whole breadth of medicine,” he explains, “but I guess I’ve always figured the most interesting and exciting approach is to go straight to the top. It’s the brain that makes us human. It’s the control center.” He cites his service as a military internist on an Air Force base in Texas as one experience that brought home the fact that “lots of physical problems have psychological aspects, and vice versa.”

Dr. Hamilton says that what intrigued him most when he was in training were the exciting things happening in the field of neuroscience. “It was clear that people who were using technology like magnetic resonance imaging and even early versions of computers were on the brink of being able to produce models that would teach us a great deal about the brain, but they just weren’t quite there yet.”

The family hopes its gift will serve as an incentive for medical students who are interested in furthering their research education but are concerned about a lack of resources or the accrual of student loan debt. By focusing their support on the education of a clinician/scientist, the Hamiltons believe the scholarship will benefit not only the student but also other physicians, researchers, and patients with whom he or she comes in contact.

“I believe in the power of leverage,” says Dr. Hamilton, “and in the ability of a well-placed person.”

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Mildred Danch

Mildred Danch may not be the only lady whose vehicle of choice is a bright red Corvette, but she’s likely the only one in Columbiana County, Ohio, where her family farm is located. “I love my car,” she says. “It’s fun, and it gives me a lot of independence.”

Independence has always been a guiding principle in Ms. Danch’s life, as has helping others. So at a time when many women were discouraged from working outside the home, Millie, as she prefers to be called, forged not one but two full-fledged careers. She graduated from the Youngstown Hospital Association’s nursing school as a registered nurse in 1952, then trained as a flight attendant as well. In 1953, she began her 50-plus-year career in the aviation industry with Capital Airlines and then continued with United Airlines after it purchased Capital in 1961.

“When I was flying out of Chicago, we would bid our schedules by the month, and I would give my schedule to Holy Cross Hospital,” she recalls. “Sometimes I would take my uniform to the hospital; and after I helped deliver babies, I would dress there in my stewardess uniform and rush out to Midway Airport to take my flight out. Then I would come back to Midway on a return flight, dash to the hospital, don my scrubs, and deliver more babies. I just loved it.”

After her father’s death brought her back to the area, Millie continued to fly out of Pittsburgh. When she was called to serve on overseas flights, she moved to San Francisco, where she still maintains a home and lives part-time.

When recent orthopaedic problems threatened to diminish Millie’s trademark energy, she turned to Lawrence S. Crosetti, M.D., and William F. Donaldson III, M.D., both faculty members in the Department of Orthopaedic Surgery at the School of Medicine. “I couldn’t have asked for better treatment, from beginning to end,” Millie says—high praise, indeed, from an accomplished nurse with a lifelong commitment to top-quality health care.

To help ensure that fewer orthopaedic patients will suffer the loss of their independence in the future, Millie has made plans to bequeath a substantial portion of her personal assets to the School of Medicine, including part of the family farm where she grew up and still lives. Her gift will honor and support the research of Drs. Donaldson and Crosetti and their successors. She also plans to provide personal support to other fundraising activities for research and clinical medicine and hopes to inspire others to give as well. “Any time that I can do, I will do,” she says.

The orthopaedic surgeries have made her “100 percent pain-free,” Millie says. The main drawback? “They wouldn’t let me drive for a while afterwards. But I’m go-go-going again now.”
University of Pittsburgh School of Medicine

DEPARTMENTS

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Every effort has been made to ensure the accuracy of these records. Any errors or omissions may be brought to the attention of the University of Pittsburgh and UPMC Medical and Health Sciences Foundation: 412-647-8462 or spaul@medschool.pitt.edu.
Residency and Fellowship Training

Anesthesiology residencies prepare young physicians to specialize in perioperative medicine and pain management. Each major area of surgery is fully represented, and all subspecialty rotations are intramural. The faculty provides expertise on the anesthetic problems and procedures specific to each patient population so that graduating residents are comfortable managing complex intensive medical care for some of the most challenging and acutely ill patients. The department offers accredited fellowships in pediatric anesthesiology, pain medicine anesthesiology, and anesthesiology in critical care medicine. Additional fellowships are offered in cardiac, neuro, hepatic, regional, and obstetric anesthesiology.

Selected Research Highlights

Using a reproducible model of cardiac arrest and resuscitation in rats, Yan Xu, Ph.D., and colleagues have examined potential therapeutic effects of Oct-4(+) rat umbilical cord matrix (RUCM) cells in treating cerebral global ischemia. The researchers pretreated animals with Oct-4(+) RUCM cells by injection into the brain’s left thalamic nucleus, hippocampus, corpus callosum, and cortex. Histological analysis of the hippocampal CA1 region one week after cardiac arrest revealed that pretreatment with Oct-4(+) RUCM cells significantly reduced neuronal loss. Xu and colleagues also observed that the transplanted cells survived but had migrated significantly, with very few found directly in CA1. Therefore, the researchers concluded that the Oct-4(+) RUCM cells may repair tissue damage through an extracellular signaling mechanism, a finding that shows promise for the treatment of cerebral global ischemia.

Li Meng, M.D., M.P.H., and Joseph J. Quinlan, M.D., have observed that after retromastoid craniectomy with microvascular decompression (MVD) of cranial nerves, patients frequently experience postoperative nausea and vomiting (PONV). In addition to patient discomfort, PONV can produce dehydration, electrolyte imbalance, and pulmonary aspiration; furthermore, the physical act of vomiting may increase intracranial pressure. Therefore, the researchers wanted to examine risk factors associated with PONV to enable physicians to target high-risk patients. Meng and Quinlan found that despite the use of intraoperative prophylactic endotracheal intubation in 99 percent of patients, the overall incidence of PONV was 60 percent during the first 24 postoperative hours. PONV incidence was highest for patients with MVD of cranial nerve V, and both female sex and use of the anesthetic desflurane were independent predictors of PONV. The researchers noted that administration of a prophylactic peritumoral scopolamine patch before surgery resulted in significantly less PONV. Based on these results, Meng and Quinlan recommend that a combination of anesthetics be administered in advance to decrease the incidence of PONV after retromastoid craniectomy.

Patients with visceral pain often experience pain referral to distant sites due to the viscerosomatic convergence of neurons at the spinal cord. Gerald F. Gebhart, Ph.D., and colleagues have examined whether hyperexcitability in referral sites is triggered by inflammation or by transient overexpression of nerve growth factor (NGF). The researchers found that inducing bladder inflammation increased NGF levels in bladder walls and significantly increased the response sensitivity to mechanical or thermal stimulation in the hindpaw of a rat. Gebhart and colleagues then injected a viral vector expressing NGF into the bladder to determine whether increased NGF levels, without direct inflammation, would produce a similar effect. The researchers again found that hindpaw mechanical and thermal stimulation was sensitized following NGF overexpression in the bladder. Based on these results, Gebhart and colleagues concluded that sensory pathway sensitization by inflammation or NGF contributes to the development of hypersensitivity in cutaneous referral sites, providing a potential explanation of the mechanism underlying the coexistence of pain syndromes in patients with functional diseases.

Yan Xu, Ph.D.

Gerald F. Gebhart, Ph.D.

Peter J. Davis, M.D.

Joseph J. Quinlan, M.D.

Yan Xu, Ph.D.

Molecular Epidemiology and Pain Program

Mitchell B. Max, M.D.

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Pittsburgh Center for Pain Research

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Graduate Training

The Pittsburgh Biomedical Informatics Training Program prepares individuals for research and development careers emphasizing the application of modern technology to health care, basic biological and clinical research, and the education of health professionals. The program offers both master’s and doctoral degrees in biomedical informatics and includes a range of training experiences to accommodate the diverse backgrounds and aspirations of its students. Active participation in research and development projects is a key element of the training experience, and opportunities are available for both applied and theoretical research. If requested, specific concentrations of study can be obtained in the areas of bioinformatics, dental informatics, health services, and biosurveillance.

Selected Research Highlights

Advances in molecular biology and biomarker validation studies have generated a need for tissue banks to provide quality-controlled tissue samples with standardized clinical annotation. The National Cancer Institute’s Cooperative Prostate Cancer Tissue Resource (CPCTR) is a distributed tissue bank that comprises four academic centers and provides thousands of clinically annotated prostate cancer specimens to researchers. Michael J. Becich, M.D., Ph.D., and colleagues have helped to establish and evaluate CPCTR information management system architecture, common data element development, query interfaces, data curation, and quality control. Since its inception, CPCTR has made available several thousand cases of highly characterized prostate cancer biopsies, including several tissue microarrays. Researchers working with CPCTR developed a Web site and public, research, and member groups have used the Web tools for public querying of summary data on available cases, preparing requests and receiving tissues.

The efforts of Becich and colleagues ensured that CPCTR can provide large volumes of carefully annotated prostate tissue for research initiatives and biomarker validation studies and can help to develop collaborative, large-scale, virtual tissue banks in other organ systems.

Rebecca S. Crowley, M.D., and colleagues have examined the effects of computer-based tutoring on diagnostic performance gains, metacognition, acceptance, and the diagnostic skills required for task performance in a medical training setting. The researchers designed two external problem representations: a case-focused representation, providing an open learning environment for students to freely explore evidence-hypothesis relationships within a case but not visualize the entire diagnostic space, and a knowledge-focused representation, providing an interactive representation of the entire diagnostic space but with more tightly constrained student actions. Metrics included results of pretest, post-test, and retention test for multiple choice and case diagnosis tests; ratios of performance to student-reported certainty; results of participant surveys; learning curves; and interaction behaviors during tutoring. Crowley and colleagues found that students showed significant learning gains after one tutoring session but observed no differences between the two interfaces in learning gains on post-test or retention test. However, only students in the knowledge-focused interface exhibited significant metacognitive gains from pretest to post-test and pretest to retention test. Student ratings were significantly higher for the knowledge-focused interface as well, indicating a higher metacognitive effect and user acceptance for the knowledge-focused external problem representation.

Electronic surveillance systems can be used to monitor triage chief complaints in efforts of detecting a disease outbreak sooner than with traditional reporting methods. Wendy W. Chapman, Ph.D., and Michael M. Wagner, M.D., Ph.D., have measured the accuracy of a Bayesian chief complaint classifier called CoGo, part of the Real-time Outbreak and Disease Surveillance (RODS) system developed previously by the researchers, as a first step in evaluating its utility in detecting outbreaks. The classifier assigns patients to one of seven syndromic categories (respiratory, botalenic, gastrointestinal, neurologic, rash, constitutional, or hemorrhagic) based on free-text triage chief complaints. The investigators compared CoGo’s classifications with criterion syndromic classification from the International Classification of Diseases, Ninth Revision discharge diagnoses. CoGo’s accuracy was tested on a set of 527,228 chief complaints from patients at a University of Pittsburgh Medical Center emergency department over a 13-year period. Approximately 16 percent of the patients were classified according to the criterion standard into one of the seven syndromes. CoGo’s classification performance (percent sensitivity, percent specificity) was as follows: respiratory (63.1, 94.3); botalenic (30.3, 99.3); gastrointestinal (69.0, 99.6); neurologic (67.6, 92.7); rash (46.8, 99.3); constitutional (45.8, 96.6); and hemorrhagic (75.2, 98.5). These results indicate that while CoGo’s specificity is high, sensitivity levels vary by syndrome classification, suggesting that further symptomatic system training in those conditions showing lower sensitivity (e.g., botalenic) will improve CoGo’s overall accuracy in identifying relevant syndromic presentations.

Center for Clinical and Translational Informatics

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Fu-Chiang Tsul, Ph.D.
DEPARTMENT PROFILE

The Department of Cell Biology and Physiology supports a diverse research portfolio, ranging from the study of fundamental cellular processes to structural mechanisms of protein interaction and the regulatory mechanisms that govern complex physiological processes in mammalian organisms. Research in the department is focused on four major areas: function and dysfunction of ion channels, cell polarity and the membrane traffic of proteins and lipids, reproductive biology, and signal transduction in diabetes and metabolism. The department houses the Center for Biologic Imaging, the Cystic Fibrosis Research Center, and the Center for Research in Reproductive Physiology. Faculty members contribute to research outside the department involving cancer; diabetes; and cardiovascular, renal, and other diseases. The department’s grant revenue has tripled since 1995; it has established core facilities for imaging, quantitative assay of molecular expression, and protein biochemistry; and the diversity of its research has been nourished by the steady recruitment and mentoring of new junior faculty.

Selected Research Highlights
Jennifer C. Condon, Ph.D., and colleagues are elucidating the molecular events involved in maintaining uterine quiescence during pregnancy and isolating the triggers for uterine contractions at term. To better understand fetal regulatory mechanisms that time labor’s onset, they are studying fetal cell trafficking to the maternal uterus with the idea that fetal cell migration is critical in triggering the onset of labor. Condon and collaborators have discovered that fetal lung maturation activates fetal cells to migrate into the pregnant uterus, where they trigger an inflammatory reaction that ultimately leads to labor. The research team is now working to engineer fetal-specific knockout mice to identify the labor-related triggers, and it has initiated additional collaborations to confirm its findings in humans. Condon and colleagues hope that by understanding the events leading to uterine contraction during pregnancy they can reduce the incidence of preterm labor.

Successful cryopreservation of gonadal tissue is critical for fertility preservation via germ cell or testicular tissue transplantation. Stefan Schlatt, Ph.D., and his research team are developing tools to preserve fertility in cancer patients who receive treatment before puberty. The researchers have optimized protocols in primate testis tissue and determined that cryopreservation of immature primates testis is a feasible approach to maintain spermatogenic stem cells. The ability to delay transplantation of cooled samples suggests an option for central localization of testicular tissue cryopreservation and may serve as a means to preserve fertility of prepubertal boys undergoing chemotherapy. Schlatt’s studies provide a better understanding of testicular stem cell’s regulation and function and open the way toward preclinical studies to preserve male fertility during cancer treatment.

Yong Wan, Ph.D., and colleagues are studying the role of ubiquitin-dependent proteolysis in biological regulation. Skp2, a ubiquitin ligase subunit, facilitates cell cycle progression via degradation of various protein targets. The researchers found that cellular stimulation by the cytokine TGF-beta rapidly degrades Skp2, thus blocking cell cycle progression and promoting cell cycle arrest. Wan and colleagues also found that blocking Skp2 degradation greatly reduces TGF-beta-induced cell cycle arrest. These results identify a novel mechanism for tumor suppression using TGF-beta and provide an explanation for why dysfunction of the TGF-beta pathway has been associated with cancer.

Anthony J. Zeleznik, Ph.D., and colleagues are studying the physiology and cell biology of ovarian function. Granulosa cells, which produce steroids and are associated with oocyte development, express the closely related orphan nuclear receptors steroidogenic factor-1 (SRF-1) and liver receptor homolog-1 (LRH-1). To determine whether SRF-1 and LRH-1 have differential effects on steroid production, Zeleznik and colleagues compared the effects of LRH-1 and SRF-1 overexpression on estrogen and progesterone production by differentiated rat granulosa cells. Neither LRH-1 nor SRF-1 alone stimulated estrogen or progesterone production, however, when combined with follicle stimulating hormone (FSH) and testosterone, each significantly increased progesterone production, with SRF-1 having a greater effect. LRH-1 did not augment FSH-stimulated estrogen production, and SRF-1 produced a slight, but not significant, increase of FSH-stimulated estrogen production. These findings demonstrate that LRH-1 and SRF-1 have qualitatively similar actions on FSH-stimulated estrogen and progesterone production, which would suggest that these factors may have overlapping actions in steroidogenesis regulation accompanying granulosa cell differentiation. Hormones have been suggested to play a role in cell-cell communication by influencing the availability of gap junction proteins at the cell surface. Sandra A. Murray, Ph.D., and her laboratory have conducted in vivo and in vitro examinations of the ability of adenocorticotropin (ACTH) to affect gap junctions in adrenal cells. ACTH treatment increased the size and number of gap junction plaques on cell membranes in hypophysectomized animals and in adrenal culture, and intracellular (cytoplasmic) annular gap junctions were observed in both models. To investigate the relationship of annular gap junctions to cell-cell contact, cultured adrenal cells were transfected with cDNA encoding a green fluorescent protein tagged connexin 43 construct (Cx43-GFP) and studied by time-lapse video microscopy, immuno-cytochemistry, and transmission electron microscopy (TEM). Internalization of part or all of a surface gap junction plaque resulted in annular gap junction formation. These studies support the hypothesis that cytoplasmic vesicles, initially described with TEM methods, can result from removal of gap junction plaques from the cell surface and indicate that this hormonally sensitive process might provide a method to alter intercellular communication.
Graduate Training
The department’s educational mission is to introduce computational biology problems and methods to chemistry, physics, engineering, mathematics, and computer science students as well as to provide basic physical, engineering, and computational background to biology and biomedical sciences students to tackle complex biological problems on a computer by managing and integrating databases and by simulating biological phenomena at different levels. Students are trained through the Joint Program in Computational Biology, a collaboration with Carnegie Mellon University; the Molecular Biomedical Graduate Program; and the Interdisciplinary Biomedical Graduate Program.

Selected Research Highlights
Ivet Bahar, Ph.D., and her laboratory study the dynamics and machinery of supramolecular protein complexes. They have explored equilibrium motions of proteins that exhibit relatively large conformational changes upon protein binding using the Gaussian and anisotropic network model of protein dynamics. These studies emphasize the preexisting equilibrium/conformational selection as a mechanism for protein-protein interaction and lend support to the concept that proteins, in their native conformation, are predisposed to structural fluctuations that are relevant to, or even required for, biological functions. Bahar and colleagues have shown that equilibrium motions also determine communication patterns, which can be delineated by spectral graph methods applied to biochemical reactions. Applications to a series of allosteric systems demonstrate that key mechanical sites (e.g., hinge centers) and functional regions (e.g., adenosine triphosphate (ATP) binding sites, catalytic residues) are distinguished by their enhanced signal transduction propensities. Efficient communication through a network of key residues thus emerges as a required property for mediating allosteric responses. These observations suggest that biomolecular structures have evolved to facilitate the collective dynamics and allosteric communication mechanisms required to achieve appropriate biological function.

Panayiotis V. Benos, Ph.D., and colleagues have conducted a detailed analysis of transcription factor (TF) purposes, which recognize limited DNA sequences with high specificity and control the expression of surrounding genes. A number of studies have attempted to use TF binding preference to predict new target sites, but the distance metrics and alignment algorithms used to compare the binding profiles have not been fully explored or optimized. Benos and colleagues evaluated various comparison metrics and alignment algorithms, being careful to include not only structural information but also distinctions between subfamilies in predicting the identity or structural class of a protein. The researchers found that local alignments were better than global alignments at detecting eukaryotic DNA motif similarities and tested multiple alignment strategies for finding profile and tree-building method efficiency. They also developed a new method to automatically determine the optimal number of clusters and apply it to constructing a new set of familial binding profiles to improve TF classification accuracy. Benos and colleagues then combined all of these testing methods into a software tool called STAMP, which is now available publicly. Detecting similarities between DNA motifs is critical for comparative study of transcriptional regulation. The tools developed by these researchers offer a strong foundation for future transcriptional modeling studies.

MicroRNAs (miRNAs) are a type of small RNAs thought to negatively regulate protein production; further- more, aberrant expression of miRNAs is linked to cancer and other diseases. Using a new computational method called K-Factor, Bino John, Ph.D., and colleagues have identified numerous upstream regulatory elements that are likely essential to the transcriptional and posttranscriptional regulation of miRNA: K-Factor is unique in that it can predict regulatory motifs in functionally related sequences without relying on evolutionary conservation. The researchers noted that the regulatory motifs appear frequently, exist in multiple copies, and are highly enriched in G and C nucleotides. John and colleagues also determined that certain disease-associated transcription factors appear to contribute to abnormal miRNA expression in diseases like cancer. After further examination, the researchers found that the transcription factors c-Myc, NFY, Sp-1, MTF-1, and AP-2 are all master regulators of miRNA expression. Based on these results, John and colleagues concluded that focused studies of miRNA-regulating transcription factors will be critical in developing treatment for miRNA-related diseases.

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DEPARTMENT PROFILE
Created in October 2004, the Department of Computational Biology pursues three areas of specialization: computational structural biology, molecular biology, bioinformatics, and systems or mathematical biology. The department’s mission is to develop new computational models and methods for simulating complex biological processes, to advance the scientific understanding of biological systems through computational tools and theoretical approaches, to design new computational/mathematical models and methods for simulating complex biological processes, and to play a leading role in launching educational programs in computational biology and bioinformatics. Research in the department integrates biological, biomedical, computational, physical, mathematical, and engineering sciences to formulate and solve critical biological problems.

Ivet Bahar, Ph.D., and John K. Vries Professor and Chair

DEPARTMENT PROFILE
In January 2002, the School of Medicine established the first Department of Critical Care Medicine at a U.S. medical school. The department is a natural extension of the work begun by the late Peter Safar, M.D., a pioneer in the field of critical care medicine, and further developed by Gregg D. Eger, M.D., Ph.D., in the former Department of Anesthesiology and Critical Care Medicine. The decision to spin off critical care medicine into an independent department, under the founding chairmanship of Mitchell P. Fink, M.D., solidified the school’s leading role in this field. Each year, the department trains more than 30 fellows in adult and pediatric critical care medicine, oversees $42 million in research grants, and routinely cares for patients in 13 different intensive care units at the various Oakland hospitals.

Panayiotis V. Benos, Ph.D.

Residency and Fellowship Training
Since 1963, the Multidisciplinary Critical Care Training Program, which is now part of the Department of Critical Care Medicine, has trained more than 600 intensivists—physicians who specialize in the management of critically ill patients in hospital intensive care units (ICUs). The program combines critical care fellowships in anesthesiology, medicine, and surgery and provides a broad, patient-centered curriculum in medical, cardiac, surgical, cardiothoracic, burn, trauma, transplan- tation, neurovascular, obstetric, and pediatric critical care. Senior fellows may participate in laboratory research, clinical investigation, ICU administration, critical care ethics, and additional clinical training.

Selected Research Highlights
Inhaled nitric oxide (INO) is a selective pulmonary vasodilator that has been shown to improve short-term outcomes for hypoxic respiratory failure in full-term neonates. Derek C. Angus, M.P.H., M.R.C.P., M.K.H., and colleagues are extending these earlier findings to include a randomized controlled trial of 36-week (post-conception) prematurity newborns with respiratory failure to determine the treatment efficacy of INO for them. Respiratory failure in premature infants has a different etiology than respiratory failure in full-term infants and includes a wide array of long-term consequences. Angus and his team hope to determine whether INO is a viable treatment option for prematurity-associated respiratory failure in both the short- and long-term care of critically ill infants. This study is generating contemporary data on the long-term consequences of prematurity-associated respiratory failure and the effects of INO. It follows newborn to school-age children, examining survival, neurobehavioral social development, and the effect on families. The study will aid future clinical trials by providing information about the appropriate follow-up duration and the robustness of surrogate endpoints.

Patrick M. Kochanek, M.D., is conducting preclinical testing of novel nitric oxide-based resuscitation strategies for combined head injury and hemorrhagic shock, a common but challenging form of combat casualty. The rising incidence of improvised explosive devices in combat areas (as well as in terrorist attacks in the civilian sector) increases the need for this type of intervention. Because hemorrhagic shock exacer- bates damage in traumatic brain injury, first responders in battle must administer an effective resuscitation fluid. Currently used fluids can contribute to brain swelling after head trauma and are relatively ineffective. Kochanek and others at the Safar
Center for Resuscitation Research

Believe that a nitroxide-based resuscitation fluid will offer important advantages over conventional fluids in the resuscitation of head trauma/hemorrhagic shock patients. To establish the efficacy of this treatment, they are using a rat model to test a battery of nitroxide-based resuscitation fluids. Additional applications of this research include treatment of traumatic brain injury from motor vehicle accidents and other causes.

Severe sepsis, which can cause acute onset of organ failure as a result of bloodstream infection, is a major health problem that kills nearly 250,000 Americans each year and costs billions of dollars; available therapies for sepsis are suboptimal.

John A. Kellum Jr., M.D., and Gilles Clermont, M.D.C.M., are working with a multidisciplinary team of basic and clinical researchers, bioengineering and biomaterials experts, and complex systems modelers to design and test an extracorporeal device for treating severe sepsis using hemo-therapy, they are using a rat model to develop a cytokine capture model and test an extracorporeal device for complex systems modelers to design and functional outcome assessment for further development of acute therapies and chronic rehabilitation strategies for cardiac arrest and HIE.

Select Research Highlights

The researchers have already developed and used this approach for the analysis of dermatopathologic and pathologic images. Jukic and colleagues believe that type-1 polarized dendritic cells (DC1) might reconstitute patient antitumor CD4+ T-cell responses toward TH1-type immunity. The researchers found that stimulation of CD4+ T-cells with peptide-pulsed DC1 promoted robust TH1-type, epitope-specific T-cell responses. In addition, DC1-based stimulation seemed capable of revitalizing defective TH1-type responses within a subset of antigen-experienced CD4+ T-cells in melanoma patients. Overall, the DC1-based stimulation promoted elevated levels of IFN-γ from responders CD4+ T-cells and led to increased levels of the IL-12Rβ2T cell receptor. These results suggest that pre-existing CD4+ T-cell immunity to cancer may be corrected via the application of DC1-based vaccination protocols.
The Department of Emergency Medicine is dedicated to improving the outcomes of acutely ill and injured patients through high quality, cost-effective care, education, and research. The specialty of emergency medicine has a unique position in the health care system because of its involvement in prehospital programs and because it is often the door to the institution. Forty percent of all patients admitted to UPMC receive their first care in the emergency department. Synergistic efforts among department faculty; local emergency medical services personnel; and the Center for Emergency Medicine, a multihospital consortium in western Pennsylvania aimed at advancing emergency medicine, have enabled the department to provide outstanding academic programs. One of the department’s current research projects is a collaborative study with the Department of Critical Care Medicine of optimal early sepsis care, including the biology and genetics involved in patient outcomes.

Residency and Fellowship Training
The University of Pittsburgh Affiliated Residency in Emergency Medicine is a three-year program to train emergency physicians in clinical care, research, teaching, and administration. UPMC, Mercy Hospital of Pittsburgh, and Western Pennsylvania Hospital jointly sponsor the program. In addition, emergency care is provided at Children’s Hospital of Pittsburgh of UPMC and affiliated community and specialty hospitals. Together, these facilities serve more than 170,000 emergency patients per year. Residents have at their disposal the resources of the Center for Emergency Medicine and its air medical transport system (STAT MedEvac), the Bureau of Emergency Medical Services of the City of Pittsburgh, the Pittsburgh Poison Center, and the School of Medicine. The program provides training in internal medicine, surgery, anesthesiology, pediatrics, orthopedics, critical care, emergency medical care in prehospital and hospital settings, as well as service with STAT MedEvac and experience in clinical and basic research. The department also offers board-approved fellowships in research and emergency medical services. All fellows are required to participate in research and to obtain an advanced degree in an appropriate field.

Selected Research Highlights
Many low-risk patients with pneumonia are hospitalized despite recommendations to treat such patients in an outpatient setting. Donald M. Yealy, M.D., and colleagues have analyzed data collected by retrospective chart review for low-risk patients (pneumonia severity index [PSI] risk classes I to III without evidence of arterial oxygen desaturation) who were enrolled in a cluster-randomized trial conducted in 32 emergency departments. The researchers found that 44.7% percent of all low-risk patients were treated as inpatients. Factors independently associated with increased odds of hospitalization included PSI risk classes II and III, the presence of medical or psychosocial contraindications to outpatient treatment, comorbid conditions, multilobar radiographic infiltrates, and home therapy with oxygen, corticosteroids, or antibiotics before presentation. Although some inpatients did exhibit a true contraindication to outpatient treatment, 20.1% percent had no identifiable risk factors other than PSI risk classes II and III. Based on these results, Yealy and colleagues concluded that hospital admission appears to be justified for one-third of low-risk inpatients based on the presence of one or more contraindications to outpatient treatment. However, at least one-fifth of low-risk inpatients did not have a contraindication to outpatient treatment or an identifiable risk factor for hospitalization, suggesting that treating those patients in an outpatient setting would not adversely affect patient outcomes.

Previous research by Clifton W. Callaway, M.D., Ph.D., and colleagues has shown that inducing hypothermia of 32°C to 34°C after resuscitation from cardiac arrest improves neurologic recovery. The researchers have conducted a follow-up study to establish optimal cooling levels. Using a rat model of asphyxial cardiac arrest, Callaway and colleagues tested post-resuscitation temperatures of 33°C, 35°C, or 37°C using computer-controlled cooling fans and heating lamps. Neurologic scores were measured daily, and histologic analysis was conducted at 14 days post-intervention. The researchers found that neurologic scores were poorest for rats in the 37°C group compared to the other two hypothermia groups on days one through three. In addition, hypothermia increased the number of surviving neurons, with no difference between the groups cooled to 33°C and 35°C. Callaway and colleagues concluded that hypothermia improves neurologic scores and neuronal survival following cardiac arrest in rats with little to no measurable difference in outcomes among the exact temperature used to achieve hypothermia.

James J. Menegazzi, Ph.D., and colleagues have demonstrated that using cardiopulmonary resuscitation (CPR) as a first intervention for prolonged ventricular fibrillation is more effective than proceeding directly to countershock. However, poor quality CPR has been associated with poorer patient outcomes. With these findings in mind, Menegazzi and colleagues examined the quality of CPR delivered on the floor compared with CPR delivered on a moving stretcher. Trams were assigned to perform two- rescuer CPR on a recording resuscitation mannequin on the floor or on a moving stretcher. After a five-minute rest, the teams performed CPR under the opposite condition. Compression and ventilation data were collected and included compression depth, compression rate per minute, percentage of correct chest compressions, tidal volume, and percentage of correct ventilations. The percentage of correct compressions and depth of compressions was much greater when performed on the floor than on a moving stretcher. In addition, the percentage of correct ventilations, although not the number of ventilations, was greater when performed on the floor than on a moving stretcher. Menegazzi and colleagues concluded that CPR quality is significantly compromised while in motion, a finding that could assist hospital personnel and first responders in taking steps to ensure the best possible outcome for patients.
The Department of Family Medicine teaches medical students the basic tenets of family medicine by modeling universally valued competencies in patient care with a focus on high quality, family-centered primary care. Community-based research in primary care, prevention, and clinical epidemiology explores barriers to immunization and management of chronic disease through the department’s Center for Primary Care Community-Based Research (CPCR). The center aims to improve the health of community residents by promoting patient education, adherence to disease prevention and treatment strategies, and research networking and collaboration among primary care disciplines in particular disease areas. Diabetes, stroke, cardiovascular disease, physician-patient communication, and prostate cancer are among CPCR’s current externally funded clinical project areas. The department’s clinical division provides care in various local communities, including the Hill District, Squirrel Hill, Bloomfield, Lawrenceville, Garfield, Hazelwood, McKeesport, and New Kensington. Underserved population care, primary care sports medicine, comprehensive family care, and health care team coordination are additional focal areas.

Residency and Fellowship Training
The department provides leadership for family medicine residency programs at UPMC St. Margaret, UPMC Shadyside, and UPMC McKeesport, which also serve as the primary clinical sites for medical student education in family medicine. The UPMC Consortium of Family Practice Residencies and Affiliates serves as a collegial academic forum for faculty from the three UPMC residency programs, three affiliated residency programs, and the department. In collaboration with the residency programs at UPMC St. Margaret, UPMC Shadyside, and UPMC McKeesport, the department offers accredited primary care sports medicine fellowships as well as geriatrics fellowships. UPMC St. Margaret also offers a faculty development fellowship focusing on the clinician educator.

Selected Research Highlights
Donald B. Middleton, M.D., is evaluating ways to increase the proportion of hospital inpatients vaccinated against pneumococcal infection by establishing a standing orders program (SOP) to vaccinate patients over 65 and those with a chronic condition predisposing them to pneumococcal. With SOP, the nursing staff screens all new admissions and places a pre-printed order form for the pneumococcal polysaccharide vaccine (PPV) in the charts of eligible patients. Following a physician’s order, the nursing staff administers and records the PPV. Middleton notes that using electronic medical records can significantly improve the assessment and documentation of patient vaccination status. He hopes to identify and provide recommendations for overcoming barriers to establishing SOP in acute care inpatient facilities. Middleton has found that vaccination rates in hospitals with SOPs are generally higher than in hospitals requiring individual physician orders.

Although colorectal cancer is a leading cause of cancer-related deaths in the United States, screening rates are low. Richard K. Zimmerman, M.D., M.P.H., is studying the determinants of colorectal cancer screening to assess what interventions might increase these rates. Using patient records, he considers factors like geography, socioeconomic status, and practice setting as well as number of office visits, type of visit, immunizations, and cancer tests given. In this study, the fecal occult blood test (FOBT) was the primary screening method, followed by the endoscopy/barium enema and colonoscopy. Factors that Zimmerman suggests are barriers to intervention are cost, access to screening, and productivity incentives for providers (seeing more patients equals less time per patient). He recommends that clinicians mail reminders to patients, perhaps combining reminders for mammograms, vaccinations, and cancer screenings into one card. In addition, FOBT screenings could coincide with influenza vaccine clinics (or other yearly contacts) in an effort to increase patient screening rates.

Jeanette E. South-Paul, M.D., and colleagues are conducting a community-based pilot study to examine the barriers to care for pregnant teens in Allegheny County. These barriers can include financial considerations, regulations regarding parental notification, access to health care facilities, and knowledge about the importance of early prenatal care. Consequently, pregnant teens often experience premature labor, and their offspring are at greater risk for low birth weight, infant mortality, and delays in behavioral and cognitive development. Given these risk factors, the research team is also expanding the pilot study to determine what changes could be implemented to promote longer pregnancy spacing (time between pregnancies) for teens.

Selected Research Highlights
Yasaqiq M. Abrams, M.D., Danforth N. Lincoln, M.D., Karen Melissa Moyer, M.D., Dawna Hoyte Woodyear, M.D., Yaqin Xia, M.D.

Visiting Assistant Professors
James C. Dewar Jr., M.D., Michael A. Yonas, Dr.P.H., M.P.H.

Research Assistant Professor
Mary P. Nowalk, Ph.D.

Graduate Training
Immunology is one of the concentrations offered through the medical school’s Interdisciplinary Biomedical Graduate Program. The curriculum provides broad exposure to a variety of biomedical fields in the first year, followed by concentrated studies in a particular field—in immunology, in this case—in subsequent years. Immunology affects many aspects of health and disease, and program faculty often hold additional appointments in other medical school departments, the University of Pittsburgh Cancer Institute, or the Thomas E. Starzl Transplantation Institute. The diversity of faculty backgrounds strengthens the program and broadens the research and academic experiences available to students.
result in exuberant T-cell activation and autoimmunity. Lu hopes to elucidate the molecular and cellular mechanisms underlying tissue inflammation during the course of chronic diseases like autoimmune diseases and cancer.

Karen A. Norris, Ph.D., uses mouse and primate models to examine immune responses to parasites and opportunistic infections. She studies Trypanosoma cruzi, a parasite that is transmitted by insect vectors and via blood transfusions and that causes Chagas disease, a potentially fatal illness prevalent in Latin America. Norris has developed a highly sensitive method for diagnosis of Chagas disease using a recombinant complement regulatory protein from the parasite; she is currently developing recombinant vaccines based on the complement regulatory protein and other parasite proteins. Norris has also made significant progress in examining pulmonary complications of AIDS using a primate model that produces pulmonary function changes due to persistent inflammatory responses to subclinical infections, as is commonly seen in HIV-infected patients. These studies should ultimately lead to interventions to prevent HIV-associated lung damage.

Binfeng Lu, Ph.D., is studying the molecular network that controls the initiation, effector function, and long-term fate of cell-mediated immune responses. He has demonstrated that this pathway involves the kinase Akt, and dysregulation has been implicated in tumorigenesis. Kane and his laboratory are also studying the biochemical mechanisms for T-cell costimulation by a novel regulatory receptor known as TIM-1. His research team was among the first to show that TIM-1 activates intracellular signaling pathways that cooperate with signals derived from TCR to increase the efficiency of T-cell activation. A better understanding of T-cell activation may lead to novel therapeutics for inappropriate or undesirable T-cell activation, as occurs in many autoimmune diseases and in organ transplantation.

DEPARTMENT PROFILE

The Department of Medicine is organized into the following divisions: Cardiology; Clinical Pharmacology; Endocrinology and Metabolism; Gastroenterology, Hepatology, and Nutrition; General Internal Medicine; Geriatric Medicine; Hematology/Oncology; Infectious Diseases; Pulmonary, Allergy, and Critical Care Medicine; Renal-Electrolyte; and Rheumatology and Clinical Immunology. The department and its divisions are turning from individual grant support to multidisciplinary program project and center grants to emphasize collaborative research so as to better understand many important diseases and translate this understanding into improved patient care. Educating the next generation of academic physicians is a priority for the department, which provides more than one-third of the teaching to medical students and offers postgraduate training at the residency and fellowship levels.

Residency and Fellowship Training

The Division of General Internal Medicine takes a lead role in developing and coordinating the series of training programs for the department; each subspecialty works closely with the programs to assure high quality education and access to faculty in each area. The General Internal Medicine Fellowship Program, which trains physicians dedicated to primary care, is divided into two tracks: the Clinical Research Training Program for physicians interested in research careers and the Clinician Educator Training Program for those who wish to pursue a career in medical education. In addition, the Geriatric Internal Medicine Residency Track is a flexible program providing specific training in the care and advocacy required for older adults. Analogously, the Medicine-Pediatrics Residency Training Program provides residents with the special skills required in caring for children. The Community-Based Categorical Residency Training Program at UPMC Shadyside prepares residents for work in primary care and numerous subspecialties by providing exposure to a variety of venues, including the VA Pittsburgh Healthcare System and the University of Pittsburgh Cancer Institute. The Primary Care Residency Training Program prepares physicians for the challenge of primary diagnosing and treating patients in an ambulatory setting; it emphasizes longitudinal and ambulatory care while also stressing the inpatient skills of an internist. The Women’s Health Training Program combines obstetrics, gynecology, psychiatry, and adolescent medicine into a multidisciplinary experience that prepares residents to provide a variety of routine health care and screening services to women. The Global Health Training Program allows residents to practice worldwide in both indigent and community settings with which the department and the University/UPMC have developed relationships. Residents may apply for additional training through the Biomedical Informatics Training Program, the Consortium Ethics Program, the Clinical Ethics Training Program, and the Mentorship Program Initiative.

Divisions

Cardiology

Barry London, M.D., Ph.D.

Chief

The Division of Cardiology operates clinically as the UPMC Cardiovascular Institute and specializes in congestive heart failure and cardiac transplantation, invasive cardiology, including cardiac catheterization, percutaneous intervention, peripheral interventions (including carotid stents), and percutaneous closure of atrial septal defects; electrophysiology, including device placement and ablations; noninvasive imaging, including echocardiography, nuclear cardiology, computed tomography angiography, and multiplanar reformation; and preventive cardiology. Major division research efforts include basic mechanisms underlying the pathogenesis of congestive heart failure; the molecular genetics of inherited forms of heart failure and sudden death; genetic factors predicting clinical outcomes and drug response in sudden death, heart failure, and coronary stent restenosis; vascular biology and atherosclerosis; novel cardiovascular imaging techniques, including molecular imaging; stem cells and gene therapy for myocardial infarction and heart failure; and identification of novel, noninvasive predictors of heart disease and methods of pre-symptomatic intervention. Active collaborations are under way with the Department of Cell Biology and Physiology; the Department of Molecular Genetics and Biochemistry; the Heart, Lung, and Esophageal Health Training Program, the Consortium for Biomedical Informatics Training, the Consortium Ethics Program, the Clinical Ethics Training Program, and the Mentorship Program Initiative.

Clinical Pharmacology

Robert A. Branch, M.D.

Chief

The division’s Center for Clinical Pharmacology (CCP) conducts preclinical and clinical research, drug development, pharmacotherapy evaluation, and clinical pharmacology education for medical students. Clinical service includes decision analysis and information technology that is used to evaluate pharmacotherapy within the UPMC system.
CCP's research program, which is supported by a well-equipped infra-
structure, includes a series of success-
ful collaborations within and outside
the University. Three major themes,
each supported by multidisciplinary
core laboratories and multiple part-
nerships, comprise CCP's focus: The
Preclinical Pharmacology Research
Program and Core Labs focus on
molecular and cellular preclinical
pharmacology, organ/tissue pre-
clinical pharmacology, and whole
animal preclinical pharmacology.
The Clinical Pharmacology Research
Program and Core Labs conduct
clinical research using high-through-
put pharmacogenomics, pharma-
cokinetics, drug metabolism, and
mass spectrometry-based meta-
bolomics. The Drug Optimization
Program and Information Technology/
Bionostics Core provides clinical
outcome-based information tech-
nology (IT) for decision analysis of
clinical use and support to lab-based clinical research
collaborative projects and grants.
Endocrinology and Metabolism
Andrew F. Stewart, M.D.
Chief
The Division of Endocrinology and Metabolism focuses its clinical
services on treating diabetes, obesity, hyperlipidemia, thyroid
diseases, pituitary disease, osteoporosis and calcium disorders,
phosphorus disorders, and male and female reproductive
disorders. These services are delivered in part through the
outpatient center for Diabetes and Endocrinology at UPMC Presbyterian,
the Shea Clinic at UPMC Shady-side, the Obesity and Nutrition Research
Center, the Osteoporosis Prevention and Treatment Center, and
through community-based clinics in Mt. Lebanon, Monroeville, and else-
where. Division research is broad and includes dietary and lifestyle manage-
ment in obesity; coronary artery angioplasty and bypass surgery for
diabetic patients; mechanisms that
link body fat with insulin resistance;
novel therapies for osteoporosis;
development of methods to expand
pancreatic beta cell numbers and
function, gene therapy approaches
to improve pancreatic islet transplan-
tation, parathyroid-related protein
for treatment of postmenopausal
osteoporosis and its role in arterial
restenosis following angioplasty; and
animal models of obesity, type 1
and type 2 diabetes, and insulin
leptin action and resistance.
Gastroenterology, Hepatology,
and Nutrition
David C. Whitcomb, M.D., Ph.D.
Chief
The core clinical programs of the
Division of Gastroenterology, Hepatology, and Nutrition are the
Center for Liver Diseases, Inflammatory
Bowel Disease Center, Pancreas and
Biliary Center, Neurogastroenterology
and Motility Center, Gastrointestinal
Cancer Prevention and Treatment Center,
Center for Intestinal Health and Nutrition Support, and the
Center for Women's Digestive Health.
These centers are complemented by
the clinical and procedural support of the
Divegic Disorders Center and
Gastrointestinal Laboratory and by
collaborations with the VA Pittsburgh
Healthcare System, UPMC Shady-side,
and Magee-Womens Hospital of
UPMC. The division's focus on clinical
gastroenterology and hepatology includes translational research in the follow-
ing key areas: inflammatory bowel
disease, pancreas and biliary system,
neurogastroenterology and motility,
pain, liver and transplantation
medicine, colorectal cancer, and
neoplastic sciences.
General Internal Medicine
Wishwa N. Kapoor, M.D., M.P.H.
Chief
Inpatient clinical services in the
Division of General Internal Medicine
include treating all unassigned
patients admitted through the
emergency department, providing
hospitalist care for private practices,
and providing consultative services
to other departments. Outpatient
services are diverse and are incor-
porated into the Comprehensive
Multidisciplinary Women's Health
Program, Primary Care Service Line
and Emergent Care Center at the
VA Pittsburgh Healthcare System,
Shea Medical Center at UPMC
Shady-side, Program for Health Care
to Underserved Populations, Smoking
Cessation Clinic, Pittsburgh AIDS
Center for Treatment, and Compre-
prehensive Palliative Care Program.
Research is focused in two major
centers: the Center for Research on
Health Care and the Center for Health
Equity Research and Promotion.
Additional research occurs in the
Section of Palliative Care and Medical
Ethics, the Section of Women's Health,
under Section and Clinical Services and Clinical Systems
Modeling. The division develops and
provides leadership for the Institute
for Clinical Research Education,
which supports the Clinical Research
Training Program, Clinician Educator
Training Program, and the Clinical
Scientist Training Program. The
Institute is dedicated to the develop-
ment of high quality clinical
researchers throughout the schools of
the health sciences.
Geriatric Medicine
Neil M. Resnick, M.D.
Chief
The Division of Geriatric Medicine
provides consultative and primary
care for patients in all settings,
including the home, office, and hos-
pital as well as rehabilitation, assisted
living, and nursing home facilities.
Three major centers of ambulatory
care, which are a joint venture with
the Department of Psychiatry, are the
Benedum Geriatric Center at
UPMC Presbyterian, the Senior Care
Institute at UPMC Shady-side, and
Classic Care at UPMC St. Margaret.
Division activities fall under the
umbrella of the University of
Pittsburgh Institute on Aging, which
was established in 2002 to coordinate
all age-related activities at
the University and UPMC. The institute
links UPMC's clinical expertise in
geriiatrics with the University's
expertise in gerontological research and
t raining focuses on common but underinvestigated
conditions, including falls, frailty,
sarcopenia, osteoporosis, bladder
dysfunction, chronic pain, sleep
disorders, polypharmacy, and sub-
clinical cardiovascular and peripheral
vascular diseases, as well as the
biology of aging.
Hematology/Oncology
Ronald B. Herberman, M.D.
Chief
Division of Hematology/Oncology
includes all aspects of general
consultative hematologic, renal trans-
plantation, peritoneal dialysis, and
hemodialysis. A focal area of research
is the identification and characteriza-
tion of cellular processes within the
kidney that are associated with
normal physiology and pathophysi-
ology. Division research also includes peritoneal dialysis infections, new
methods of peritoneal dialysis, con-
tinuous renal replacement therapy,
and therapeutic trials for glomerular
diseases. The division oversees the
Acute Renal Failure Trial Network
Study, a clinical trials conglomeration
with 31 study centers nationwide,
including the local VA Pittsburgh
Healthcare System.
Rheumatology and Clinical Immunology
Larry W. Moreland, M.D.
Chief
Research in the Division of Rheumatology and Clinical Immunology is conducted through the Arthritis Institute, an interdepartmental program designed to foster integrated clinical and research activities related to arthritis, autoimmune diseases, and regional rheumatic disorders. Faculty-led research and patient care programs exist for systemic sclerosis (scleroderma), systemic lupus erythematosus, rheumatoid arthritis, polymyositis, systemic vasculitis, and osteoarthritis. The clinical component of the institute sees more than 45,000 outpatients per year and includes care for children and adults with arthritis, connective tissue diseases, and regional rheumatic disorders.

Selected Research Highlights
John M. Kirkwood, M.D., and colleagues have identified protein markers in abnormal moles that can help predict whether they will progress into melanoma, the deadliest form of skin cancer. Their research found that a mole’s abnormality is positively correlated with expression of a signaling protein called STAT3 (signal transducer and activator of transcription 3), which has been linked to melanoma progression. Study participants with the highest history of melanoma and were treated for three months with either low- or high-dose interferon, an immune protein used to attack tumor cells. Kirkwood and his team then compared abnormal moles removed from participants immediately before and after treatment. Results indicated that high doses of interferon reduced levels of STAT3 in abnormal moles by 55 percent. In addition, levels of STAT3, an antimutator marker, increased by nearly eight times over baseline. The study demonstrated that protein marker examinations in abnormal moles provide a useful indication of a mole’s potential malignancy and could be used to monitor interferon treatments.

Mary Chester M. Waso, M.D., M.S., and colleagues conducted a multicenter observational study of 4,905 adults with rheumatoid arthritis and found that hydroxychloroquine, a common antimarial medication also used to treat rheumatoid arthritis and other autoimmune disorders, reduces the relative risk of developing diabetes by 77 percent. In addition, those individuals who developed diabetes were less likely to require medications to manage their disease. Even when the investigators adjusted for other risk factors like body mass index, degree of disability, and medication use, the reductions persisted. Since diabetes incidence was measured through patient self-reports of diagnosis and medication use, the underlying mechanisms by which hydroxychloroquine contributes to diabetes risk reduction are not yet known. However, the results suggest that hydroxychloroquine might be a preventive therapy for individuals with prediabetes and others at risk for the disease.

Anna Lokshin, Ph.D., has identified a series of protein markers in blood that in one study were able to diagnose ovarian cancer in 96 percent of cases. Because no single protein can be used to diagnose early-stage ovarian cancer, which is particularly difficult to detect, Lokshin examined 80 different proteins that have been associated with ovarian cancer and used a computer algorithm to analyze a series of protein markers that, in combination, could reveal the presence of the disease. In a follow-up study, Lokshin is using blood samples collected yearly from 80,000 women in a national trial. Once those results are available, she will be able to determine more clearly whether the protein panel is accurate and how early it can detect the presence of ovarian cancer.

James H. Dauber, M.D., and Naftali Kaminski, M.D., have developed a technique that provides strong evidence against Crohn’s disease, and certain non-coding IL23R variants are associated with the disorder’s presence. Additional studies confirmed that IL23R associates with Crohn’s disease as well as with ulcerative colitis. Based on these results, Duerr and colleagues have proposed the IL-23-panlaminflammatory signaling pathway as a therapeutic target for inflammatory bowel disease.

David C. Whitcomb, M.D., Ph.D., and colleagues study the mutated genes underlying inherited forms of pancreatic cancer, a highly deadly disease. The researchers previously identified a susceptibility locus for familial pancreatic cancer on chromosome location 4q22-34 and conducted additional studies to identify the associated gene and its function. A customized microarray of this chromosomal region revealed the greatest expression change in palladin (PALLD), a gene that encodes a cytoskeleton component controlling cell shape and motility. A mutation in a highly conserved region tracked with all affected family members and was absent in the nonaffected members. In addition, Whitcomb and colleagues observed overexpression of PALLD mRNA in preneoplastic dysplasia and pancreatic adenocarcinoma tissue in both familial and sporadic disease. The researchers were also able to induce cytoskeletal changes, abnormal actin bundle assembly, and an increased ability to migrate in cultured cells transfected with mutant PALLD. Based on these findings, Whitcomb and colleagues concluded that abnormal PALLD causes cytoskeletal changes in pancreatic cancer and may be responsible for, or contribute to, the tumor’s strong invasive and migratory abilities.

Pancreatic disorder and generalized anxiety disorder are prevalent in primary care, but those who go unrecognized, are associated with poor functional outcomes, and generally are ineffectively treated. Bruce L. Rollman, M.D., M.P.H., and colleagues have examined whether telephone-based collaborative care for these disorders improves outcomes for primary care patients compared to standard care where patient and physician are simply informed of the disorder. Intervention involved non-medical health professionals who provided patients with psychoeducation, assessed preferences for guideline-based care, monitored treatment responses, and informed physicians of their patients’ care preferences and progress. The researchers assessed patients for anxiety and depressive symptoms, mental health-related quality of life, and employment status at baseline and two, four, eight, and 12 months after the primary care contact. At 12 months, intervention patients reported reduced anxiety and depressive symptoms, improved mental health-related quality of life, and improvements relative to baseline in hours worked per week and work days absent. Rollman and colleagues concluded that telephone-based collaborative care for panic disorder and generalized anxiety disorder is more effective than standard care in improving anxiety symptoms, health-related quality of life, and work-related outcomes.

Alfred L. Fisher, M.D., Ph.D., and colleagues study the Gastroenbacteria elegans orphan nuclear hormone receptor gene daf-12, which plays a key role in developmental regulation and determination of adult longevity. The researchers have examined the effects of daf-12 on aging by characterizing the lifespan of loss-of-function and gain-of-function daf-12 alleles. Fisher and colleagues determined that these mutations have opposing effects on longevity and resistance to oxidative and thermal stress, thus making daf-12 the first gene with alleles found to extend or shorten lifespan. Fisher and colleagues determined that the loss-of-function mutation’s shortened lifespan is due to accelerated aging in young adulthood rather than an adverse effect on development. Microarray analysis of worms carrying the two alleles revealed that while the generic profiles of the two alleles are largely different, there is significant overlap among the genes down-regulated, but not upregulated, in all profiles. Fisher and colleagues concluded that daf-12 modulates aging and stress responses, in part, through the repression of specific genes.

Anuradha Ray, Ph.D., and colleagues have examined whether different types of dendritic cells (DCs) initiate different immune outcomes, like tolerance or inflammation. The researchers characterized DCs from the lung-draining lymph nodes of mice immunized for allergic airway inflammation or tolerance and examined their interactions with T cells. The DC population derived from tolerized mice resembled plasmacytoid type DCs and were poor inducers of T-cell proliferation. However, DCs from the inflammatory condition resembled myeloid-type DCs. In both conditions, DCs induced interferon-4 (IL-4) production, but the T cells cultured with tolerogenic DCs were unresponsive to IL-4. These data suggest that DC phenotype in lung-draining lymph nodes determines whether an airway will experience tolerance or inflammation. Primary biliary cirrhosis (PBC), which can cause a strong autoimmune component, is an autoimmune disease characterized by biliary ductular inflammation with eventual liver cirrhosis. William M. Ridgway, M.D., and colleagues have determined that nonobese diabetic (NOD) B6C3Fl mice develop an autoimmune biliary disease (ABD) that models human
The serologic hallmark of PBC is antimitochondrial antibodies that react with the pyruvate dehydrogenase complex, targeting the inner lipoyl domain of the E2 subunit (anti-PDC-E2). NOD.c3c4 mice develop antibodies to PDC-E2 that are specific for the inner lipoyl domain. Affected areas of biliary epithelium are infiltrated with CD3+, CD4+, and CD8+ T cells, demonstrating a central role for T cells in pathogenesis.

Using a spontaneous mouse model of PBC, the NOD.c3c4 mouse as the first locus, Abd1. These results establish a central role for the inner lipoyl domain. Affected areas of biliary epithelium are infiltrated with CD3+, CD4+, and CD8+ T cells, demonstrating a central role for T cells in pathogenesis. Using a gene-mapping approach, Ridgway and colleagues defined the first AB2 locus, Ab1. These results establish the NOD.c3c4 mouse as the first spontaneous mouse model of PBC.

Sharon A. Riddler, M.D., M.P.H.

The researchers found that a triple-drug approach using two nucleoside reverse transcriptase inhibitors (NRTIs) plus efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), suppressed the virus to undetectable levels in more individuals than the other triple-drug combination of two NRTIs and a protease inhibitor (lopinavir/ritonavir). Riddler and colleagues have conducted a clinical trial to evaluate the efficacy of two commonly used HIV treatments. Additional analyses revealed that while treatment with lopinavir/ritonavir plus NNRTI produced a greater CD4+ T cell count, both regimens using efavirenz experienced less virologic failure, or rebound, of the HIV virus.

Inflammatory Bowel Disease Research Center
Richard H. Duer, M.D.
Miguel D. Regueiro, M.D.
Co-directors

Institute for Clinical Research Education
Wisnawa N. Kapoor, M.D., M.P.H.
Director

Institute for Doctor-Patient Communication
Robert M. Arnold, M.D.
Director

Institute to Enhance Palliative Care
David Barnard, Ph.D.
Director

LHAS Women’s Heart Center
Steven E. Reis, M.D.
Director

Neuropsychotology and Motility Center
Klaus Bielfeldt, M.D., Ph.D.
Director

Center for Research on Health Care
Wisnawa N. Kapoor, M.D., M.P.H.
Director

Comprehensive Lung Center
Christopher N. Faber, M.D.
Director

Data Center
Doris M. Rubio, Ph.D.
Director

Gastrointestinal Cancer Prevention and Treatment Center
Robert E. Schoen, M.D., M.P.H.
Director

General Infectious Diseases Clinical Program
Karim E. Byers, M.D.
Director

HIV/AIDS Clinical Research Program
Deborah D. McMahon, M.D.
Director

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D. A. Henderson, M.D., M.P.H.
21st Century Professor of Medicine and Public Health

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Hilman Professor of Oncology

Wisnawa N. Kapoor, M.D., M.P.H.
Falk Professor of Ambulatory Care

Frank J. Kroboth, M.D.
George H. Taber Professor of General Internal Medicine

Barry London, M.D., Ph.D.
Harry S. Tack Professor

Thomas A. Medsger Jr., M.D.
Dr. Gerald P. Rodnan Professor of Rheumatology

Steven D. Shapiro, M.D.
Dr. Jack D. Myers Professor and Chair

David C. Whitcomb, M.D., Ph.D.
Mount Eagle Foundation Professor of Cancer Genetics

Lawrence Ellis Chair in Hematology and Oncology (open)
Margaret Jane Miller Chair in Arthritis Research (open)

James A. Shaver Chair in Cardiovascular Education (open)

Osteoporosis Prevention and Treatment Center
Susan L. Greenspan, M.D.
Director

Pancreas and Biliary Center
David C. Whitcomb, M.D., Ph.D.
Director

Simmons Center for Interstitial Lung Disease
Naftali Kaminski, M.D.
Director

University of Pittsburgh Institute on Aging
Neil M. Resnick, M.D.
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Albert D. Donnenberg, Ph.D.
Marnell J. Egorin, M.D.
Lawrence D. Ellis, M.D.
D. Michael Elnicki, M.D.
Michael J. Fine, M.D., M.Sc.
William P. Follansbee, M.D.
Kenneth A. Foos, M.D.
John Gorcsan Jr., M.D.
Rosanne Granieri, M.D.
Susan L. Greenspan, M.D.
Lea H. Harrison, M.D.
Elmer J. Holzinger, M.D.
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Rajiv Jain, M.B.B.S.
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James R. Johnston, M.D.
John M. Kirkwood, M.D.
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C. Kent Kwoh, M.D.
Arthur S. Levine, M.D.
David S. MacPherson, M.D.
Kenneth S. McCarthy, Jr., M.D., Ph.D.
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Melissa A. McNeil, M.D.
John W. Mellors, M.D.
Robert R. Muder, M.D.
Tara J. O’Toole, M.D.
Chester V. Oddis, M.D.
Thomas D. Painter, M.D.
Paul M. Paleysky, M.D.
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Margaret V. Ragni, M.D.
R. Harsha Rao, M.D.
Anuradha Ray, Ph.D.
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Neil M. Resnick, M.D.
Mark S. Roberts, M.D., M.P.P.
Robert M. Rogers, M.D.
Garson David Roodman, M.D., Ph.D.
Fred H. Rubin, M.D.
Mark H. Sanders, M.D.
Robert E. Schoen, M.D., M.P.H.
James A. Shaver, M.D.
Adam Silvka, M.D., Ph.D.
Thomas C. Smitherman, M.D.
Andrew F. Stewart, M.D.
Stephanie Anne Studenski, M.D.
Mark E. Thompson, M.D.
Philip Troen, M.D.
Victor V. Voit, M.D.
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Frederick London Mooteen, M.D.
Larry W. Mone, M.D.
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Roy E. Smith, M.D.
Sally Wenzel, M.D.

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William W. Barrington, M.D.
Anthony J. Bauer, Ph.D.
Klaus Bielfeldt, M.D., Ph.D.
Lori Ann Birder, Ph.D.
Franklin A. Bontempo, M.D.
James Edward Bost, Ph.D.
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Timothy M. Carlos, M.D.
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Gary S. Fischer, M.D.
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Joan Harvey, M.D.
Peggy B. Hasley, M.D.
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Steven L. Kantar, M.D.
William E. Katz, M.D.
Joseph E. Kiss, M.D.
Kevin L. Kraemer, M.D.
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The department contributes to training grants in gene therapy, neuroscience, immunology, virology, and biotechnology. In addition to extensive federally funded research, faculty members are also engaged in entrepreneurial ventures involving research alliances with industry.

Graduate Training

The Interdisciplinary Biomedical Graduate Program combines a rigorous academic environment with modern biomedical research. Ph.D. students take interdisciplinary core courses during the first year and then focus on a particular area of biomedical research for the remainder of their degree program. Faculty members provide expertise in both basic and clinical research, and collaborative efforts between basic and clinical investigators establish a translational research environment, facilitating the transfer of knowledge from bench to bedside.

Selected Research Highlights

Laura J. Niedernhofer, M.D., Ph.D., and colleagues are studying the health effects of DNA damage. The research team engineered mice deficient in a DNA repair gene called Ercc1 and discovered a severe and spontaneous phenotype of accelerated aging and shortened lifespan. Using this model, Niedernhofer and colleagues demonstrated that Ercc1-deficient mice exhibit stress, including DNA damage, induces a metabolic response mediated by the IGF1 receptor pathway that reallocates cellular resources toward maintenance rather than proliferation and helps preserve life. The data also demonstrate that DNA damage promotes rapid aging.

Fibroblast growth factors (FGFs) are secreted molecules that activate signaling pathways required for proper embryogenesis. Using gene expression (in situ hybridization) screening studies in zebrafish, Michael Tsang, Ph.D., and his laboratory have identified a group of genes that exhibit expression patterns similar to those of FGF genes. The researchers have characterized the zebrafish protein MAP kinase phosphatase 3 (MKP3), a member of the FGF signaling pathway, and implications that MKP3 may act in concert with DNA damage and cell cycle checkpoints as an early anti-tumor barrier.

Borrolie burgerdorferi, the spirochete responsible for Lyme disease, is spread by the bite of an infected ixodid tick. James A. Carroll, Ph.D., has used a multiplex two-dimensional gel technique combined with proteomics to show the full humoral immune response of mice and Lyme patients to membrane-associated proteins isolated from B. burgdorferi. A subset of immunogenic membrane-associated proteins was recognized by mice experimentally infected with B. burgdorferi, but most of the proteins were recognized by sera from patients diagnosed with early disseminated Lyme disease. By examining the humoral response in Lyme patients over time, Carroll identified the sequence of immunoreactive proteins as the disease progresses from early to late stages. This serologic proteome analysis enabled the identification of novel membrane-associated proteins that may serve as new diagnostic markers and, importantly, as second-generation vaccine candidates associated with viremia in F. tularensis and other pathogens. In addition, after growth in a chemically defined medium, ACV reverted to the IVS phenotype. These data show that viral vector ts mutants in F. tularensis are an effective tool for islet-based gene transfer and transplantation.

Francisella tularensis, the causative agent of tularemia and a Category A biodefense agent, replicates within host macrophages, though its pathogenesis is poorly understood. Gerald J. Nau, M.D., Ph.D., and colleagues have isolated a variant of F. tularensis live vaccine strain (LVS) based on colony morphology and effect on macrophages. Human monocyte-derived macrophages produced more tumor necrosis factor alpha, interleukin (IL)-1beta, IL-6, and IL-12 p40 following exposure to the variant, designated as the activating variant (ACV). Although LVS and ACV lipopolysaccharide immunoreactivity was comparable to that described in a previous variant, the researchers showed that soluble protein fractions of LVS and ACV differed. Further investigation using two-dimensional gel electrophoresis demonstrated differential protein expression, featuring several proteins associated with virulence in F. tularensis and other pathogens. In addition, after growth in a chemically defined medium, ACV reverted to the IVS phenotype. These data show that virulence factor levels in F. tularensis are modulated by culture conditions and that this modulation affects host responses.

Justus B. Cohen, Ph.D.

Vesna Rapic-Otrin, Ph.D.

William F. Goins, Ph.D.

Jaspal S. Khillan, Ph.D.

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Justus B. Cohen, Ph.D.
The Department of Neurobiology has established strengths in neural development; circuit and systems function; cellular communication through receptors, channels, and synapses; and neurological and psychiatric diseases. Research in these areas is integrated with work being done in other departments of the School of the Medicine (Psychiatry, Pharmacology, and Neurology), the School of Engineering, and the School of Arts and Sciences. In addition, department faculty members are involved in research and training activities of the cross-campus Center for Neuroscience as well as the Center for the Neural Basis of Cognition, a joint program with Carnegie Mellon University.

Selected Research Highlights

Ole V. Mortensen, Ph.D., and Susan G. Amara, Ph.D., have determined that two atypical dopamine transporter (DAT) inhibitors, benzotropine and bupropion, show greatly different psychostimulant effects than another DAT inhibitor, cocaine. Because benzotropine has been suggested as a target for drug development against cocaine abuse, the investigators wanted to characterize this difference. Despite a high degree of sequence similarity, DATs and noradrenergic neurotransmitters (NETs) express distinctive pharmacology, including the DAT's higher sensitivity to benzotropine and bupropion. Mortensen and Amara used site-directed mutagenesis to produce NET mutants as a means to isolate the DAT sequences responsible for the differential sensitivity. The investigators demonstrated that incorporating alanine 279 in transmembrane domain 5 (TM5) and serine 359 in TM7 increased the NET's sensitivity to benzotropine and benzotropine. Mortensen and Amara used site-directed mutagenesis to produce NET mutants as a means to isolate the DAT sequences responsible for the differential sensitivity. The investigators demonstrated that incorporating alanine 279 in transmembrane domain 5 (TM5) and serine 359 in TM7 increased the NET's sensitivity to benzotropine and benzotropine. These results identify residues that are important for the unique molecular interactions of benzotropine and bupropion with DATs and may contribute to the distinct behavioral actions of these drugs.

Gonzalo E. Torres, Ph.D., and colleagues have studied early-onset torsion dystonia (EOTD), an autosomal dominant movement disorder characterized by involuntary and sustained muscle contractions that often result in severe disability. EOTD is usually caused by deletion of one glutamic acid in the carboxyl terminus of the protein torsinA, resulting in protein aggregation in perinuclear inclusions. The investigators have shown that torsinA regulates cellular trafficking of the dopamine transporter, as well as other polytopic membrane-bound proteins, and that this effect can be prevented by mutating the torsinA adenosine triphosphate (ATP) binding site. The dynamin-associated torsinA deletion mutant (DeltaE-torsinA) did not affect the cell surface distribution of polytopic membrane-associated proteins, suggesting that the EOTD-linked mutation produces a loss of function. However, a mutation in the ATP binding site in DeltaE-torsinA reversed the mutant's aggregate phenotype and produced a dominant negative of wild-type torsinA. These results provide evidence for a functional role for torsinA and a loss of function and a dominant-negative phenotype of the DeltaE-torsinA mutation that may contribute to the autosomal dominant nature of the condition.

The peripheral regeneration of sensory neurons following nerve transection often results in the misalignment of previously precise connections between primary sensory neurons and cells in the spinal cord, resulting in a loss of tactile acuity. H. Richard Koerber, Ph.D., studies specific changes in the organization of the spinal cord's dorsal horn that result from reinnervation following transection. These changes may contribute to the rate of recovery for tactile acuity, as measured by two-point discrimination, and the possible onset of chronic pain. Koerber's laboratory has shown that synaptic efficacy between regenerating sensory neurons and the dorsal horn may be altered dramatically, and that the results from both a loss of input and the establishment of new connections. These alterations influence the dorsal horn's somatotopy as it recovers, and behavioral studies have shown that the dorsal horn's reorganization pattern correlates well with the recovery of two-point discrimination thresholds. The Koerber lab is also investigating a novel class of nociceptive connections that are formed during reinnervation of the dorsal horn.

Guo-Qiang Bi, Ph.D., examines population activity in networks of cultured neurons as a model of neuronal circuit development in the brain. This activity, or reverberation, is reminiscent of Hebbian dynamics, by which neuronal activity causes increased synaptic strength between two neurons. Bi has determined that this reverberation can either strengthen or weaken a synapse depending on the precise timing of pre- and postsynaptic activity. In addition, he has found that this activity-induced synaptic modulation can spread to specific neighboring synapses. Bi and his laboratory are working to characterize a complete set of rules for activity-dependent synaptic modification and to elucidate the underlying cellular mechanisms. His findings are then being paired with those of theoreticians to create neural network models for additional insights into the functional implications of cellular modification and plasticity.
The Department of Neurological Surgery is organized into various centers, including image-guided, functional, radiosurgery, endoscopic, skull base, cranial nerve and microvascular, spinal, exovascular and endovascular, pain control, trauma, and pediatric neurosurgery. The department offers clinical care aimed at maximizing patient recovery and outcomes and minimizing alterations in quality of life. For this reason, the department has focused on traditional surgical procedures while also implementing the growing fields of endoscopic transnasal surgery for intracranial tumor resection; stereotactic radiosurgery for intracranial and spinal tumor, pain syndrome, and vascular malformation treatment; endovascular surgery for vascular abnormalities and stroke; and percutaneous and minimally invasive approaches to spinal disorders. In addition to direct patient care, the department has an active basic and clinical research portfolio.

Residency and Fellowship Training
The neurological surgery residency program is an internationally renowned, six-year, accredited program with a reputation for training exceptional neurosurgeons. Residents receive training in a number of neurological areas such as pediatric, adult microvascular, trauma, spinal, vascular, stereotactic and image-guided surgery, neuro-radiology, and neuropathology. Advanced residency training includes experience in complex spinal procedures, craniotomies for intraaxial tumors and meningiomas, and posterior fossa surgery. Residents also spend one to two years conducting clinical or basic science research on focused projects. Neurosurgical fellowships are also available, lasting from six months to two years, and currently include basic science research, image-guided neurosurgery, pediatric neurosurgery, spinal neurosurgery, endovascular neurosurgery, and skull base surgery.

Selected Research Highlights
Hideto Okada, M.D., Ph.D., has developed a vaccine approach to produce an immune response against gliomas, the lethal, difficult-to-treat primary tumors that aggressively invade the folds and creases of the brain. The vaccine is based on four tumor antigens commonly found on the surface of gliomas. Rather than taking antigens from a particular patient to evoke an immune response, Okada’s technique uses a more general collection of antigens. Because gliomas grow quickly, the time needed to isolate patient-specific peptides would allow the disease to progress to the point at which treatment would be futile. Okada’s vaccine uses a multi-antigen approach, in which different antigens are modified to look more “dangerous” to the immune system, potentially eliciting a stronger immune response.

C. Edward Dixon, Ph.D., leads a research team that focuses on developing therapies for traumatic brain injury (TBI), which initiates pathological biochemical cascades that can persist long after event survival. Better understanding of these cascades and their attenuation by translatable therapies is the team’s primary goal. Specific studies involve nitrative stress and PARP (poly(ADP-ribose) polymerase) activation, statin therapies and their interaction with amyloid β in cell death, effects of calcium entry inhibition on neuronal death and plasticity, Fas-mediated cell death, and mechanisms underlying the endogenous beneficial effects of INOS (inducible nitric oxide synthase). These studies allow Dixon and his team to correlate basic scientific investigations with human clinical TBI to define the acute and chronic molecular mechanisms of secondary brain injury and to identify treatments most likely to benefit TBI patients.

Ian F. Pollack, M.D., and colleagues are investigating novel strategies for brain tumor therapy, especially for pediatric brain tumors, which constitute the leading cause of cancer-related deaths in children. Despite advances in neurosurgical, radio-therapeutic, and chemotherapeutic techniques, the overall prognosis of children with brain tumors has not improved significantly in the last decade. In fact, for a particular tumor class, gliomas, only 20 percent of patients survive long term. Pollack and his colleagues are exploring why there are such differences in individual response to therapy, even when considering clinical prognostic factors. The team has proposed that molecular and immunohistochemical markers provide a means to supplement clinical and histological information to refine prognosis assessments. The study determined that differences in p53 mutation and expression, MB-1 proliferation index, and fibrolast growth factor immuno-reactivity are strongly correlated with progression-free and overall survival. Establishing exactly which markers are on the outcome predictors would allow molecular categorization of the tumors and could lead to risk-adapted stratification for future studies.

Michael B. Horowitz, M.D., and colleagues are studying aneurysmal subarachnoid hemorrhage (SAH) and resulting cerebral vasospasm, a complication that occurs in as many as 67 percent of SAH patients and contributes to death and disability. The team has determined that intravenous administration of magnesium sulfate within 48 hours of SAH significantly reduces symptomatic cerebral vasospasm incidence. In addition, Horowitz and colleagues have found that within five days after SAH, a subset of patients display elevated tropomycin I levels, which are indicative of myocellular ischemia and infarct. The team is evaluating the incidence of myocellular ischemia and infarct following SAH to determine whether myocellular ischemia increases symptomatic vasospasm risk. The research project focuses on catecholamine, which surges immediately after SAH and provides a common mechanism for vasospasm of both myocellular and cerebral vessels.
Residency and Fellowship Training
Because of the relationship between the department and UPMC, residents in neurology are trained to a high level of competence in diagnosing and treating neurological disorders, interpreting diagnostic techniques, developing core knowledge in clinical and basic neurosciences, and searching for information from a variety of electronic sources. The University provides training resources through its world-renowned Department of Neuroscience, a full-time neurology staff, top-level treatment facilities in western Pennsylvania, and a 3:1 ratio of full-time faculty to residents. Clinical training covers such areas as movement disorders, stroke, neuromuscular conditions, epilepsy, neuro-otology, neuro-ophthalmology, cognitive and memory disorders, and multiple sclerosis. Advanced training includes pediatric neurology and electives in electroencephalography (EEG), electromyography (EMG), cardiot duplex, neurosurgery, psychiatry, and basic neuroscience research.

Selected Research Highlights
Paula R. Clemens, M.D., studies gene therapy for the treatment of skeletal diseases, with a primary focus on Duchenne muscular dystrophy (DMD) and muscle cachexia. Her laboratory has successfully delivered systemic marker genes and minidystrophin constructs to skeletal muscles of fetal mouse pups in utero using an adeno-associated viral vector. Prenatal diagnosis of DMD is possible, and the disease pathology is well-established before birth. The gene therapy technique developed by Clemens and her team would allow widespread therapeutic gene transfer to skeletal muscle at the earliest possible stage. The researchers are also pursuing a preclinical study using NF-kB (nuclear factor kappa B) activation as a means to ameliorate disease pathology in DMD.

Using the invertebrate model Caenorhabditis elegans, Miguel Estevez, M.D., Ph.D., studies amyotrophic lateral sclerosis (ALS) and epilepsy. His ALS model is produced by exposure to selenium, a known human motor neuron toxicant. The Estevez laboratory has developed many selenium-resistant C. elegans mutations, which show resistance to selenium’s neurotoxic effects. These studies have highlighted the mitogen-activated protein kinase-associated neurodegenerative cascade that works through an insulin-like growth factor as well as mutations in a superoxide dismutase gene, which is involved in human ALS-type neurodegeneration. Estevez plans to develop an RNA interference technique to confer selenium toxicity resistance and determine its effect on human ALS.

Cognition in Alzheimer’s patients can be improved with the use of computer-based tasks aimed at increasing mental activity and enhancing mental function. Oscar L. Lopez, M.D., and collaborators in Barcelona, Spain, have determined that Internet-based computer activity, in combination with common Alzheimer’s medications, is more effective at improving cognition than traditional cognitive therapies aimed at dementia. Their study has determined that study participants who received traditional cognitive therapy in combination with Internet-based therapy showed 24 weeks of significant improvement on standard cognitive function and performance measures compared to both the control (untrained) and traditional cognitive therapy groups. While the traditional therapy did produce cognitive improvements over the control group, the effect lasted only 12 weeks, and by 24 weeks had disappeared.
The Department of Obstetrics, Gynecology, and Reproductive Sciences provides clinical care in a wide array of gynecologic and obstetric specialties, including services for women with complications of pregnancy, gynecologic problems and malignancies, infertility and endocrine disorders, consultation needs in infectious diseases and genetics, and diagnostic ultrasound services. Much of the department’s research is conducted at Magee-Womens Research Institute (MWRI), which emphasizes innovative and interactive translational research. Faculty members at MWRI provide expertise in clinical and fundamental research, epidemiology, and health services research. The department includes the following divisions: Developmental and Reproductive Genetics, Reproductive Infectious Diseases and Immunology, and Urogynecology and Pelvic Reconstructive Surgery.

Residency and Training Programs

The department’s residency program balances academic and scholarly activities with clinical experience in inpatient and ambulatory medicine, adult intensive care, gynecology, and surgical emergency room rotations. Training is designed to prepare a physician as both an obstetrician/gynecologist and as a primary care physician. Residents are required to complete a clinical or basic science research project and present their work at the annual T. Terry Hayashi Resident Research Day. In addition, the department offers a variety of fellowships. The Fellowship in Female Pelvic Medicine and Reconstructive Surgery provides clinical and basic research training as well as exposure to NIH-funded trials through the urinary incontinence treatment network and the clinical trials network for pelvic floor disorders. Expertise in family planning, including international population control, is promoted through the Family Planning and Contraception Fellowship. The Genetics Fellowship offers broad exposure to clinical and laboratory research experiences and specialized training in the role of heredity in gynecologic cancer. The Maternal-Fetal Medicine Fellowship provides training in ultrasound procedures, neonatology, statistical methodology, and basic or clinical research. The Reproductive Infectious Diseases and Immunology Fellowship focuses on infectious diseases, including sexually transmitted diseases and neonatal infections in obstetric and gynecologic patients.

Divisions

Developmental and Reproductive Medicine

Gerald P. Schatten, Ph.D. Director

The Division of Developmental and Reproductive Medicine focuses on clinical, translational, and fundamental research and education encompassing developmental and reproductive biology, prenatal medicine, and stem cells for regenerative medicine. The division’s core resources encompass assisted reproductive technologies, imaging, transgenic and molecular research, and education and outreach.

Diagnostic Ultrasound

Lyndon M. Hill, M.D. Chief

The Diagnostic Ultrasound Division performs 45,000 obstetric and gynecologic examinations each year, including sonograms, Doppler studies, sonographically guided amniocentesis procedures, and specialty procedures like ovarian cyst aspiration and sonographic guidance for operative cases. Research includes assessment of amniotic fluid volume in normal twin gestations, determination of twin chorionicity and amnioncytosis, evaluation of adrenal masses in pregnancy, and the validation of transabdominal ultrasound in detection of a two-vehicle umbilical cord. Research has contributed to the creation of CD-ROM programs on placental pathology and other conditions and Web-based programs on biophysical profile score, oligohydramnios, and ectopic pregnancy.

Gynecologic Oncology

Joseph L. Kelley III, M.D. Chief

The Division of Gynecologic Oncology treats gynecologic malignancies, directs chemotherapy, oversees radiation therapy, and performs gynecological and gyneco-oncologic surgery. Clinical initiatives include the Ovarian Cancer Assessment and Surveillance Program and the Ovarian Cancer Center of Excellence. In addition, the division maintains a specimen bank for oncological study. Division research primarily investigates cancer immunology, quality of life during cancer treatment, and molecular analysis of human tumors. This research is done in conjunction with the University of Pittsburgh Cancer Institute, Magee-Womens Research Institute, and the UPMC Gynecologic Oncology Group.

Gynecologic Specialties

Mitchell D. Creinin, M.D. Chief

The Division of Gynecologic Specialties provides consultation, evaluation, and care for women with gynecological conditions related to infectious diseases, family planning, menopause and geriatric gynecology, vulvar disorders, cervical dysplasia, pelvic pain management, minimally invasive pelvic surgery, and adolescent gynecology. Division research includes screening and management of preneoplastic disease, endoscopic surgery, nonsurgical treatment of urinary incontinence, and the molecular biology of pelvic organ prolapse.

Maternal-Fetal Medicine

Steve N. Curtiss, M.D. Chief

The Division of Maternal-Fetal Medicine provides clinical care for women with complications of pregnancy and provides education about normal and high-risk obstetrical for medical students, residents, nurses, and practicing obstetricians. Division research focuses on preeclampsia development and expression, epidemiologic factors contributing to perinatal mortality; preterm labor treatment, prediction, and relation to infectious diseases; diabetes and pregnancy; renal disease in pregnancy; smoking, and maternal-fetal pharmacology. The division supports the Magee-Womens Hospital midwife practice.

Reproductive Endocrinology and Infertility

Joseph S. Santulliparo, M.D. Chief

The Division of Reproductive Endocrinology and Infertility evaluates and manages infertility and endocrine disorders relating to reproduction. Clinical programs provide patients with state-of-the-art assisted reproductive techniques.

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The division coordinates basic and clinical research involving individuals with reproductive and endocrine disorders through collaborative investigations involving reproductive neuroscience, clinical epidemiology, molecular biology, ovarian physiology, and the physiology of puberty.

Reproductive Genetics

Brian A. Clark, M.D., Ph.D. Chief

The Division of Reproductive Genetics provides genetic counseling and clinical evaluation as well as dysmorphology consults for infants, children, and adults suspected of having genetic disease. Cancer risk analysis is available to women with a family history of breast cancer or gynecologic malignancies. The division’s Pittsburgh Cytogenetics Laboratory conducts peripheral blood, bone marrow, maternal serum screening, and other types of tests. Division research includes the etiology of recurrent pregnancy loss and the genetic basis of tumor formation.

Reproductive Infectious Diseases and Immunology

Harold C. Wiesenfeld, M.D.C.M. Chief

The Division of Reproductive Infectious Diseases and Immunology focuses on infections of the female reproductive tract and their effect on women’s health. The division’s multidisciplinary patient care team includes specialists in clinical infectious diseases, microbiology, immunology, virology, epidemiology, and molecular biology. Division research includes studies on pelvic inflammatory disease, genital tract mucosal immune response, the epidemiology of recurrent pregnancy loss, preterm delivery, and intrauterine growth restriction, maternal antibody and group B streptococcal neonatal infection, female HIV infection, molecular diagnostics of sexually transmitted diseases; intrauterine fetal infection; and intra-amnionic infection.

Urogynecology and Pelvic Reconstructive Surgery

Halina M. Zyczynski, M.D. Chief

The Division of Urogynecology and Pelvic Reconstructive Surgery is part of the Center for Continence and Pelvic Floor Disorders at Magee-Womens Hospital of UPMC. The center offers consultations and diagnostic and treatment services for women with pelvic floor disorders, including pelvic organ prolapse and fecal or urinary incontinence. Clinicians include experts in urogynecology and reconstructive pelvic surgery, urology, neurology, minimally invasive surgery, pelvic pain management, gastroenterology, colorectal surgery, gynecians, and physical therapy. The most current research and clinical standards are used to provide individualized treatment plans, which may involve behavioral, medical, nonsurgical, and surgical approaches.

Selected Research Highlights

Carl A. Hube, Ph.D., and colleagues have studied factors underlying preeclampsia in pregnant women. Women with preeclampsia develop activating autoantibodies to type 1 auto-antibodies (ATI-As) and experience increases in insulin resistance and serum concentrations of soluble fms-like tyrosine kinase 1 (sFlt-1). Hube and colleagues measured ATI-As, sFlt-1, insulin resistance, and related cardiovascular risk factors in groups of women with previous preeclampsia and previous normal pregnancies at nine to 27 months after the first completed pregnancy. ATI-As were detected in significantly more women with previous preeclampsia (17.2 percent) than with previous uncomplicated pregnancies (2.9 percent). Women with activating autoantibodies also had significantly increased sFlt-1 and higher insulin resistance compared with autoantibody-negative women.
The researchers concluded that, unlike sFlt-1, AT1-AA does not regress uterine ischemia more effectively than ICI 182,780. The researchers concluded that, while any solutions will not be a matter of simply treating the woman. At least 15 percent of clinically recognized pregnancy losses end in early pregnancy failure (EFP); and, for many women, the products of conception are not spontaneously aborted, requiring medical inter- vention. Mitchell D. Cunin, M.D., and colleagues previously found that misoprostol, a vaginal medication, worked as well as surgical curettage for intervention following EFP. They subsequently examined bleeding patterns following misoprostol or curettage use and determined that bleeding is heavier and more pro- longed with misoprostol than with curettage (although rarely requiring intervention) and that the heavier misoprostol-induced bleeding correlates with greater decreases and larger changes in hemoglobin levels. Cremin and colleagues suggest that although both treatments are safe, women should be informed of the differences.

Institute
Magee-Womens Research Institute
Yool Sadowsky, M.D.
Scientific Director

Residency and Fellowship Training
The Department of Ophthalmology trains residents in a three-year, accredited program in medical and surgical ophthalmology in facilities at the Eye & Ear Institute and VA Pittsburgh Healthcare System and in an intensive clinical and surgical service at the University of New Mexico in Albuquerque. Residents can also take advantage of the Eye & Ear Institute’s laboratory, which allows the practice of medical techniques and procedures before entering an operating room. All residents are required to collabo- rate with faculty in clinical research. The department offers fellowships in several areas of ophthalmology, including cornea, glaucoma, ocular surgery, pediatric ophthalmology and strabismus, and vitreoretinal surgery.

Selected Research Highlights
Paul R. Kinchington, Ph.D., in collaboration with researchers at Erasmus Medical Center in Rotterdam, The Netherlands, has studied primary infection with herpes simplex virus 1 (HSV-1) and varicella-zoster virus (VZV), both of which result in lifelong latent infections of sensory ganglia neurons like the trigeminal ganglia (TG). It is believed that T cells play a role in viral latency, and the researchers observed high numbers of activated CD8+ T cells expressing a late effector memory phenotype in latently infected TG. However, the activity of the CD8+ T cells was directed against HSV-1 and not VZV, despite neuronal expression of VZV proteins.

The researchers concluded, that, like sFlt-1, AT1-AA does not regress uterine ischemia more effectively than ICI 182,780. The researchers concluded that, while any solutions will not be a matter of simply treating the woman. At least 15 percent of clinically recognized pregnancy losses end in early pregnancy failure (EFP); and, for many women, the products of conception are not spontaneously aborted, requiring medical inter- vention. Mitchell D. Cunin, M.D., and colleagues previously found that misoprostol, a vaginal medication, worked as well as surgical curettage for intervention following EFP. They subsequently examined bleeding patterns following misoprostol or curettage use and determined that bleeding is heavier and more pro- longed with misoprostol than with curettage (although rarely requiring intervention) and that the heavier misoprostol-induced bleeding correlates with greater decreases and larger changes in hemoglobin levels. Cremin and colleagues suggest that although both treatments are safe, women should be informed of the differences.
the cultured isolated cells, ACG2 and PA60 expression was lost. These results demonstrate a cell population in the human corneal stroma expressing stem cell markers that appear to be the first human cells identified with keratocyte progenitor potential. Future analyses of these cells could elucidate molecular mechanisms underling corneal development, differentiation, and wound healing and may provide a resource for corneal stroma bioengineering and cell-based therapies.

One potential side effect of laser in situ keratomileusis (LASIK) surgery is diffuse lamellar keratitis (DLK). Because many clinicians use a prophylactic antibiotic following surgery, Jerold S. Gordon, M.D., and Francis S. Mah, M.D., have investigated whether the topical fluoroquinolone antibiotics could cause DLK. Using a rabbit model, the researchers created LASIK flaps and treated with ciprofloxacin 0.3%, ofloxacin 0.3%, balanced salt solution (BSS), or Pseudomonas aeruginosa endotoxin before flap closure and continued to apply the same drug four times daily following the procedure. Gordon and Mah observed significantly higher median DLK scores than the other two treatments. Gordon and Mah concluded that topical fluoroquinolones caused and exacerbated DLK in rabbit models and that ciprofloxacin was associated with more DLK than ofloxacin, suggesting the need for further assessment in clinical trials.

Residency and Fellowship Training

The Department of Orthopaedic Surgery is committed to the successful training of residents and fellows as well as continued education for attending orthopaedic surgeons. The training program prepares residents for a successful career in academic or clinical orthopaedic surgery, with an emphasis on disorders ranging from complex trauma to musculoskeletal tumors. The diversity of the department’s residency programs attracts top candidates from around the world. All residents are required to present clinical outcome projects at national meetings, and half of all residents are selected to enter a research track residency in which they conduct basic research and are expected to publish and present this work. Fellowship opportunities are available in foot and ankle surgery, hand and upper extremity surgery, spine surgery, sports medicine, trauma surgery, and adult reconstruction.
observed improved cartilage repair in osteochondral defects at 12 weeks after AAV-TGFB1-transduced HMSc implantation. Based on these results, Chu and colleagues conclude that AAV is a suitable vector for gene delivery to improve HMSc cartilage repair potential.

Neurocognitive testing is an important tool to assess sports-related injuries and avoid the potential for additional injury from premature return to contact sports based on athletes’ self-report of symptoms. Michael W. Collins, Ph.D., Mark R. Lovell, Ph.D., and colleagues have used computer-based neurocognitive testing to detect postconcussive abnormalities two days after injury in athletes with a diagnosed concussion. Postinjury symptom scores (self-reported) and neurocognitive performance (test-based) were compared with presymptomatic (baseline) scores and with those of a noninjured athlete control group. The researchers found that in the concussed athlete group, 64 percent reported a significant increase in symptoms and 83 percent showed significantly poorer neurocognitive test results relative to their own baseline performance. In this study, adding neurocognitive testing resulted in a net sensitivity increase of 19 percent. Based on these results, Collins and colleagues concluded that reliance on athletes’ self-reported concussion symptoms is likely to result in underdiagnosis and may result in premature return to play. However, the combination of self-reported symptoms and neurocognitive testing significantly increases diagnostic accuracy for concussive injuries.

Hans-Christoph Pape, M.D., studies “damage control orthopedics,” a concept that mandates stabilization of seriously injured patients prior to surgical repair of orthopedic injuries. Pape and colleagues have examined whether differences in outcome for polytrauma patients can be attributed to the degree of initial surgery. The researchers examined multiple patients in the German Trauma Registry with pelvic ring fractures requiring surgery whose injury severity score was at least 16. The effects of duration (short, intermediate, and long) and timing (early, intermediate, and late) of the initial pelvic surgical stabilization were analyzed. Pape and colleagues found that longer surgical durations were associated with significantly higher rates of liver failure. In addition, earlier surgery times were associated with a significantly higher rate of renal failure, multiorgan failure, and mortality. The researchers noted that in patients with a higher injury severity score, procedures lasting less than three hours resulted in improved mortality and decreased rates of multiorgan failure and sepsis. Overall, Pape and colleagues found that early, short surgery as well as delayed surgery are associated with a lower rate of organ failure and mortality in patients with multiple injuries.

Zong-Ming Li, Ph.D., and Robert A. Kaufmann, M.D., have studied precision grip impairment caused by lower median nerve block at the carpal tunnel, which acutely simulates a median neuropathy. Individuals were asked to grip, lift, and hold an instrumented handle during a 60-second period using precision grip both before and after nerve block. The investigators quantified precision grip by calculating the safety margin, which is the difference between actual grip force and the minimal grip force required to keep an object from falling; the variation of grip force; and the migration area of center of pressure, which is defined by the center of pressure at a digit-transducer surface. Median nerve block caused significant increases in the safety margin (≥50 percent), grip force variation (≥80 percent), and area of center of pressure migration (≥250 percent). Fine motor control during precision grip was impaired, thus confirming the important role of sensory function in hand fine motor control. These findings can potentially be used to quantify hand function impairment caused by neuromuscular disorders, monitor hand disorder progress, and evaluate treatment efficacy.

Regular Faculty

Endowed Chairs
Freddie H. Fu, M.D., D.Sc. (Hon.), D.P. (Hon.)
Dr. David Silver Professor and ChairChristopher D. Hamer, M.D.
Blue Cross of Western Pennsylvania ProfessorJohnny Huard, Ph.D.
Dr. Henry J. Mankin ProfessorJames D. Kang, M.D.
UPMC Professor of Orthopaedic Spinal SurgeryMorry S. Moreland, M.D.
Dr. William F. and Jean W. Donaldson Professor of Pediatric Orthopaedics Dr. Albert B. Ferguson Jr. Chair in Orthopaedic Surgery (open)Arthur J. Rosen I Shr. Chair in Sports Medicine (open)
ProfessorGary S. Orian, M.D.
Associate ProfessorsConstance R. Chu, M.D.
William F. Donaldson III, M.D.
Robert Goetz, M.D.
Zong-Ming Li, Ph.D.
Mark R. Lovell, Ph.D.
Hans-Christoph Pape, M.D.
Huicong Wang, Ph.D.
W. Timothy Ward, M.D.

Visitng Associate Professors
Mark Alvin Goodman, M.D.
James J. Impang, Ph.D.
Scott Tashman, Ph.D.
Adolph J. Yatasi, M.D.
Xudong Zhang, Ph.D.

Assistant Professors
Michael W. Collins, Ph.D.
Lawrence S. Crosslett, M.D.
Vincent F. Deeney, M.D.
Jeanne Marie Doperak, D.O.
Jan S. Gruzziak, M.D., Ph.D.
Tanya J. Hagen, M.D.
Robert A. Kaufmann, M.D.
John Lee, M.D.
Yong Li, M.D., Ph.D.
Richard L. McCough III, M.D.
Stephen A. Meldersen, M.D.
Mark W. Rodosky, M.D.
David A. Stone, M.D.
Ivan Seth Tarkin, M.D.
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Robin Venevce West, M.D.
Vonda Joy Wright, M.D.
Dane Kent Wukich, M.D.

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Scott David Wissink, M.D.

Research Assistant Professors
Brigette M. Deasy, Ph.D.
Burhan M. Gharabeh, Ph.D.
Rebecca K. Studer, Ph.D.
Nam V. Vo, Ph.D.

Instructor
Jamie Eileen Lee Pardini, Ph.D.

Residency and Fellowship Training

The otolaryngology residency program is a five-year commitment, with the first year spent in a general surgery internship and the remaining four years in the department. Also available is a seven-year program that includes two years of research integrated with the five-year program. The decision to pursue the research track is not required until the third year of residency. Research is undertaken in an area of interest during the fifth and sixth postgraduate training years. On a limited basis, fellows may pursue a six-year postdoctoral training program in head and neck oncology. Fellowships are offered in otology/neurotology, head and neck oncology, cranial basal surgery, pediatric otolaryngology, rhinology, and voice disorders.

Selected Research Highlights

Jennifer Grandis, M.D., has shown that expression of STAT1 (signal transducers and activators of transcription 1) at levels higher than typically found in cancer cells may help prevent the spread of squamous cell cancer of the head and neck (SCCHN). Normally, STAT1 is expressed at lower levels in tumor cells than in normal cells, indicating that a loss of STAT1 may promote tumor growth. To test this theory, Grandis exposed SCCHN cells to chemotherapy alone or in combination with azacytidine, an agent that increases STAT1 production. Those cells exposed to the drug combination were more responsive to treatment and more likely to stop growing and eventually die. More than two-thirds of SCCHN patients are at an advanced stage when diagnosed, and the disease carries a poor five-year survival rate. Current treatment options are limited, so the utility of gene therapy to increase STAT1 expression could have a positive effect on survival rates.

Robert L. Ferris, M.D., Ph.D., is identifying ways in which tumor cells evade the immune system. His laboratory has identified defective processing of tumor antigens (proteins) as a way that tumor cells can avoid recognition and elimination by the immune system. In particular, a peptide transporter complex inside tumor cells, called TAP1/2, was crucially important for head and neck cancer cells to be recognized and killed by tumor antigen-specific T lymphocytes, and it was lost in aggressive, metastatic cancers. These findings may explain the lack of clinical responses to cancer vaccines to date and point to improved efficacy of cancer immunotherapy in future vaccine trials.

Joseph M. Furman, M.D., Ph.D., has observed in older persons that vestibular signals generated during rotation interfere with concurrent cognitive activity and, conversely,
that performance of a cognitive task modifies the characteristics of vestibular-induced eye movements. These findings suggest that loss of balance in older persons may be more likely while they are engaging in cognitive tasks or among those with cognitive impairment.

Bill J. Yates, Ph.D., has observed that vestibular signals generated during changes in posture specifically increase sympathetic nervous system outflow to regions of the body where blood pooling might occur, thereby shunting blood away from these areas. This response presumably contributes to maintaining consistent venous return to the heart, thereby preventing orthostatic intolerance.

Shortly after dermal injury, cyclo-oxygenase-2 is upregulated and produces prostaglandin E2 (PGE2), which modulates both inflammatory and fibrotic wound-healing processes. Wound healing in fetal tissue has been shown to have altered PGE2 signaling and holds the unique property of being scarless. Patricia A. Hebda, Ph.D., Joseph E. Dohar, M.D., and Ha-Sheng Li-Korotky, M.D., Ph.D., have examined PGE2 regulation of fibroblast migration in fetal and adult fibroblasts.

The investigators then examined fibroblast migration in a dose-dependent manner, although fetal fibroblasts exhibited higher contraction rates and a blunted response to exogenous PGE2 modulation. These findings indicate that fetal dermal fibroblasts are partially resistant to PGE2’s effects, which may have significant and specific relevance to the scarless fetal wound-healing phenotype.

Regular Faculty
Endowed Chairs
Margaretha L. Casselbrant, M.D., Ph.D.
Elderly Professor of Pediatric Otolaryngology
Jonas T. Johnson, M.D.
Dr. Eugene N. Myers Professor and Chair
Head and Neck Surgical Research Chair in Otolaryngology (open)
Distinguished Professor
Eugene N. Myers, M.D.
Professors
Carey D. Balaban, Ph.D.
Charles D. Bluestone, M.D.
Ricardo L. Carrau, M.D.
William J. Doyle, Ph.D.
David E. Elding, M.D.
Joseph M. Furman, M.D., Ph.D.
Jennifer Grandis, M.D.
Jeffrey P. Simons, M.D.
Ryan J. Soose, M.D.
Research Assistant Professors
Quan Cai, M.D.
Ann M. Egloff, Ph.D.
Sufi M. Thomas, Ph.D.
Assistant Professors
David Hyunjoo Chi, M.D.
Neear Gandhi, Ph.D.
Jacqueline L. Gartner-Schmiidt, Ph.D.
Grant S. Gillman, M.D.
Riovann Diez Gross, Ph.D.
Stephen Y. Lai, M.D.
Daniel M. Mandell, M.D.
Todd D. Otterson, M.D.
Yael Raz, M.D.
Libby Jo Smith, D.O.
John Douglas Swarts, Ph.D.
Elizabeth Hui-Yee Toh, M.B.B.S.

Pathology
Pathology exists at a crossroads between laboratory diagnostics and medical discovery. Pathologic analyses are often essential for clinical diagnoses, and diagnostic advances generally precede advances in therapeutics. In this rapidly evolving field, new techniques permit biochemical analysis of solid tissue samples, and advanced histologic methods are routinely used to detect abnormal cells in body fluids. Coordinated activities involving microbiology, histopathologic and electron microscopy, basic sciences, molecular diagnostics, and pathology informatics allow the Department of Pathology and its various divisions to support clinical and research efforts throughout the School of Medicine and UPMC. The divisions include Anatomic/Surgical Pathology—UPMC Presbyterian, Head and Neck Pathology, Neuropathology, Transplantation Pathology, Molecular Anatomic Pathology, Hematopathology, Immunopathology, Molecular Diagnostics, Clinical Chemistry, Clinical Microbiology, Transfusion Medicine, Magee-Womens Hospital Pathology, Pediatric Pathology—Children’s Hospital of Pittsburgh, Pathology at the VA Pittsburgh Healthcare System, Pathology at UPMC Shadyside, Community Pathology, Pathology Informatics, and Cellular and Molecular Pathology.

Residency and Fellowship Training
The department offers residencies in anatomic pathology, clinical pathology, and combined training in both. Most residents train four to five years; the core program lasts three years, and additional elective time allows individuals to tailor the program to meet specific career objectives. The Clinical Fellow Program provides advanced training in general surgical, head and neck, hematology, gastrointestinal, genitourinary, and pulmonary pathology; other fellowships throughout the department emphasize advanced clinical training and research in a pathology subspecialty.

The graduate program in cellular and molecular pathology, one of the disciplines included in the school’s Interdisciplinary Biomedical Graduate Program, combines Ph.D. level basic science and clinical research to explore fundamental questions related to the biology of normal tissue differentiation and growth as well as the cellular and molecular pathways leading to pathobiology of disease in human and animal models.

Department Profile
Pathology plays an integral role in the organ transplantation program at UPMC in Pittsburgh as well as at the medical center’s satellite transplant center in Palermo, Italy. The division provides services in pre-transplant...
tissue typing as well as post-transplant tissue biopsies to look for lymphocyte reactivity, cytokine production, and detection of cytomegalovirus, Epstein-Barr virus, and hepatitis virus. The division maintains a Transplant Pathology Internet Service, a collaborative tool for trans- plant physicians and an interactive educational resource for healthy care professionals. Division research focuses on chimerism, viral infections, drug tolerance and toxicity, and malignancies in transplant patients.

Molecular Anatomic Pathology

Yuri Nikiforov, M.D., Ph.D.
Director

The new Division of Molecular Anatomic Pathology (MAP) oversees existing and new molecular diag- nostic tests based on tissue sections. In particular, the division uses molecular techniques to analyze gene expression patterns and genomic alterations in tissue sections to predict treatment and guide therapy, especially to oncology groups. The MAP lab is of key importance for developing opportunities for translational research by members of the department. The lab works closely with the Division of Molecular Diagnostics to share techniques, know-how, and planning.

Laboratory Medicine Section

Alan Wells, M.D., D.Med.Sci.
Vice Chair

The Laboratory Medicine Section includes the following divisions:

Hematology

Steven H. Swerdlow, M.D., Ph.D.
Director

The division has active consultation services, accepting fresh or previously fixed specimens for full evaluation or special studies. Division research concerns the role of cell signaling abnormalities in the development and progression of acute leukemia and the use of multiparameter approaches in the study of non- Hodgkin’s lymphomas and related lymphoid proliferations, specifically mucosa-associated lymphatic tissue lymphomas, other extranodal B-cell lymphomas, diffuse large B-cell lymphomas, and post-transplant lymphoproliferative disorders.

Immunopathology

Bruce S. Rabin, M.D., Ph.D.
Director

The Division of Clinical Immunopathology offers a wide range of clinical testing procedures as well as patient evaluation and consultation for autoimmune diseases, acute and chronic infections, autoimmune disorders, and suitability for allo- grafts. Division research is highly collaborative and includes investiga- tions of the neural bases of stress and lymphocyte regulation, susceptibility to infectious diseases, stress-induced immune alterations, autoimmune diseases, hepatitis and HIV infections, and xenograft rejection.

Molecular Diagnostics

Jeffrey A. Kant, M.D., Ph.D.
Director

The Division of Molecular Diagnostics integrates molecular biology into the practice of pathology, translating complex techniques into simplified protocols suitable for use in a hospital diagnostic laboratory. Specifically, the division diagnoses and classifies neoplastic diseases with new, molecular-based markers to provide insight into prognosis and thera- peutic monitoring of cancer patients for residual disease. The division also aids in the diagnosis of acquired infectious diseases, with emphasis on DNA and RNA viruses associated with solid organ transplantation; cooperates with the Department of Human Genetics in the Graduate School of Public Health to diagnose inherited disorders, including cystic fibrosis, Gaucher’s disease, and muscular dystrophy; and investigates the molecular basis of cell survival and apoptosis as well as oxidative mechanisms of disease, viral latency, hereditary cancer, and generic disorders.

Clinical Chemistry

Jorge Sepulveda, M.D., Ph.D.
Acting Director

The Division of Clinical Chemistry coordinates a full range of biochemi- cal analytic services for regional hospitals. Clinical support by the division includes therapeutic drug monitoring, toxicology analysis, hormone and tumor marker assays, biochemical tests for metabolic diseases, and organ transplant and lipids analysis. The division conducts research in pharmacokinetics, assays of novel immunosuppressants, nutritional assessment of transplant patients, biomarkers for cancers, cholesterol biosynthesis during cell growth and regeneration, apoptosis, computer applications in clinical labs, and biochemical and molecular genetics of metabolic disorders.

Clinical Microbiology

A. William Pascule, Sc.D.
Director

The Division of Clinical Microbiology supports special sections in aerobic and anaerobic bacteriology, myco- bacteria, and antibiotic sensitivity testing related to the diagnosis and treatment of legionellosis and atypical mycobacteria. The division promotes clinical research and development activities in bacteriology, virology, and antiviral immunology with emphasis on cytomegalovirus (CMV) and Epstein-Barr virus infections after transplantation. It houses one of the nation’s four NIH-supported Multicenter AIDS Cohort Study groups involved in a major epi- demiologic and laboratory study of infection and pathogenesis of HIV infection in gay men.

Transfusion Medicine

Darrell J. Trulzik, M.D.
Director

The Division of Transfusion Medicine supports one of the largest transfusion services in the nation, handling more than 40,000 units of red cells and 40,000 units of platelets annually for adult and pediatric patients. Research in the division includes a multi-institutional NIH study of the immunologic effects of transfused leukocytes on patients with HIV, the role of leukoreduction in these patients to prevent alloimmunization or transmission of cytomegalovirus infection to other patient populations like organ transplant and infant recipients; and blood use patterns in transplant patients, including the use of patient-specific strategies for autologous blood collection.

Hospital-Based Divisions

Magee-Womens Hospital Pathology

David J. Dabbs, M.D.
Director

This division specializes in perinatal, obstetric, neonatal, and gynecologic pathology and cytopathology; performs related diagnostic, teaching, and research activities; and provides specialized diagnostic services like flow cytometric analysis of gynecologic tumors, in situ hybridization techniques of microorganisms (particularly human papilloma virus), and immunohistochemical detection of estrogen and progesterone receptors in tumors. The division has assisted in developing new programs like Magee-Womens Hospital’s Comprehensive Breast Center and an ambulatory care program.

Pediatric Pathology—Children’s Hospital of Pittsburgh

Ronald Jaffe, M.B.B.Ch.
Director

The Division of Pediatric Pathology provides a full range of diagnostic services, including routine histo- pathology, molecular diagnostics, cytochemistry, immunohistochemistry, in situ hybridization, ultrastructural pathology, microbiology, and virology. The division also offers services in response to national and interna- tional requests for consultation on childhood disorders; pediatric solid organ neoplasia, including pediatric bone and soft tissue tumors; trans- plantation pathology involving the liver, bowel, kidney, lung, heart, and bone marrow; post-transplant lymphoproliferative disorders; bowel motility disorders, including acetylcholinesterase staining for the diagnosis of Hirschsprung’s disease; histiocytosis disorders, including Langerhans cell histiocytosis and dendritic cell disorders; and molecular diagnostics for pediatric infectious disease, including pertussis and quantitative Epstein- Barr virus analysis.

Pathology at the VA Pittsburgh Healthcare System

Moira P. McFerran, M.D.
Director

The Division of Pathology at the VA Pittsburgh Healthcare System provides comprehensive pathology and laboratory medical services to three area VA centers and provides consultation services to a fourth center in Butler County. Its specialized services include flow cytometry for hematopathology, immunohistochemistry for histology, therapeutic drug monitoring for clinical chemist- ry, and Legionella epidemiology for microbiology. This division serves as an immunopathology reference laboratory and supports VA Pittsburgh Healthcare System special patient care programs like open heart surgery and liver transplantation.

Pathology at UPMC Shadyside

Raif D. Dhir, M.D.B.B.S.
Acting Director

The Division of Pathology at UPMC Shadyside provides a complete spectrum of care, including sophisti- cated services in oncology, urology, pathology, and perinatal services, at both UPMC Shadyside and UPMC Presbyterian. Some division faculty members hold expertise in urologic and prostate pathology, areas not included in other divisions. Centers of excellence include genitourinary pathology, pathology informatics, gastrointestinal pathology, outcomes research, and dermatopathology. This division is the center for analysis of all diagnostic material generated by the department’s efforts to incorporate gene array analysis as a diagnostic tool.

Other Divisions

Community Pathology

Samuel A. Yousm, M.D.
Director

The Division of Community Pathology integrates laboratory and pathology services at these UPMC community hospitals: Horizon South Side, St. Margaret, Bedford Memorial, McKeesport, and Passavant. This collaboration helps these hospitals, which might other- wise have difficulty maintaining comprehensive pathology services, to provide all sophisticated laboratory testing required for modern practice and have access to intellectual resources through consultation with faculty members in the department.

Pathology Informatics

Anil K. Parwani, M.D., Ph.D.
Director

The Division of Pathology Informatics maintains and develops clinical infor- mation systems to support anatomic pathology, clinical pathology, and molecular diagnostics. It conducts research programs focused on the
elimination of tumor cells. The PARP, a process indicative of 48 hours and found that the agents noma cells to the omega-3 fatty acids three to six months of diagnosis. The have determined that omega-3 fatty  for 80 to 90 percent of all liver  carcinoma, which accounts in human cancer.

Selected Research Highlights

Tong Wu, M.D., Ph.D., and colleagues have determined that omega-3 fatty acids—found in fish oil, seeds, and nuts—suppress the growth of hepatocellular carcinoma, which accounts for 80 to 90 percent of all liver cancers and is normally fatal within three to six months of diagnosis. The team exposed hepatocellular carci- noma cells to the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) for 32 to 48 hours and found that the agents inhibited cell growth. In addition, DHA and EPA were shown to induce poly(ADP-Ribose) polymerase (PARP), a process indicative of apoptosis, thereby promoting the elimination of tumor cells. The omega-3 fatty acids also decreased levels of the protein beta-catenin, the overexpression of which is linked to tumor development. Together, these findings indicate that omega-3 fatty acids can work on several levels to inhibit liver cancer growth. Wu and colleagues plan to move their findings into a mouse model of hepatocellular carcinoma.

Jianhua Luo, M.D., Ph.D., and colleagues use high throughput quantitative analysis to genetically profile prostate cancer tissue. The team has identified 671 genes whose expression levels are significantly altered in prostate cancer tissue compared to disease-free tissue. Interestingly, the researchers investigated the profile of benign tissue directly adjacent to prostate cancer tissue and found gene expression in the benign tissue to be much more similar to the cancerous tissue than to disease-free tissue. Luo noted that the genetic alteration in adjacent benign tissue represented a field effect, indicating genetic changes similar to prostate cancer in a morphologically and functionally benign tissue. The expression pattern can be used to predict the tumor’s aggressiveness, with an 80 percent success rate. Because only a fraction of prostate cancers are metastatic, these findings may provide a technique to predict the aggressive, or metastatic, nature of the cancer and aid clinicians in planning treatment strategies.

Hypoxia, or oxygen depletion, arises during a variety of physiological states, including ischemia, respiratory diseases, and tumorigenesis. It can also lead to cell death just prior to reoxygenation due to tissue damage (necrosis) or apoptosis.

Reza Zarnegar, Ph.D., examines growth regulation in human cancers and has found that the growth factor (HGF) receptor c-Met forms a dimer with the apoptotic repressor Fas, preventing Fas from trimerizing and inducing cell death. However, high levels of HGF, like those that occur in fulminant hepatic failure, can actually induce apoptosis, thereby causing cell damage instead of stimulating regeneration. Zarnegar has determined that c-Met dimerization is due to a common sequence between c-Met and the Fas ligand that he has isolated and is now moving toward the drug discovery research pathway.

Alan Wells, M.D., D.Med.Sci., and colleagues study cell migration in terms of how motility processes are regulated and play a role in physio- logic and pathologic situations like wound healing and tumor invasion. Cell motility is a complex process involving a series of asymmetrical events, including lamellipodium extension, leading-edge adhesion formation, rear detachment, and cell body contraction, all of which must coordinate for successful cell move- ment. To establish a model system, Wells and colleagues explore motility signaling from the epidermal growth factor receptor (EGFR), which func- tions centrally for a wide variety of stromal and epithelial tissues. Results have shown that m-calpain, a factor activated by EGFR when adjacent to the cell membrane, produces the cell body and rear deadhesion required for cellular locomotion. In addition, m-calpain appears to be localized primarily in nonlamellipodial regions, confirming that it is key in cell-releasing regions, allowing lamellipodia to adhere in new locations and move the cell in a single direction.

Tim D. Oury, M.D., Ph.D., and his laboratory are focused on under- standing the molecular mechanisms involved in pulmonary fibrosis and acute interstitial lung disease. The group is investigating the role of extracellular oxidants in mediating physiologic and pathologic responses and has found that the enzyme extracellular superoxide dismutase (EC- SOD) can protect against pulmonary to asbestos.

Clayton A. Wiley, M.D., Ph.D., Pathology Education and Research Foundation Professor

Endowed Chairs

A.W. Demetris, M.D.

Thomas E. Starzl Professor of Transplantation Pathology

Ronald Jaffe, M.B.B.Ch.

Marjory K. Harmer Professor of Pediatric Pathology

George K. Michalopoulos, Ph.D.

Maul L. Menten Professor and Chair

Alan Wells, M.D., D.Med.Sci.

Thomas J. Gill III Professor of Clinical Pathology

Clayton A. Wiley, M.D., Ph.D., Pathology

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Maul L. Menten Professor and Chair

Alan Wells, M.D., D.Med.Sci.

Thomas J. Gill III Professor of Clinical Pathology

Clayton A. Wiley, M.D., Ph.D., Pathology Education and Research Foundation Professor

Professors

Antonina J. Amortegui, M.D.

Robert Marshall Austin, M.D., Ph.D.

Laurie Barnes Jr., M.D.

Dorethia Becker, M.D.

Harry C. Blair, M.D.

Yuan Chang, M.D.

David J. Dabbs, M.D.

Albert B. DeLoe, Ph.D.

Rene J. Duquesnoy, Ph.D.

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Anisa I. Kanbour, M.D.

Ama I. Kanbour-Shakur, M.D.

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Youhua Lu, Ph.D.

Trevor A. Macpherson, M.D.

Mona F. Meilhem, M.D.

Michael A. Nalewink, M.D.

Yuri Niloforou, M.D., Ph.D.

Stephen S. Raab, M.D.

Bruce S. Rabin, M.D., Ph.D.

Parmeet S. Randhawa, M.D.

Uma N.M. Rao, M.B.B.S.

Charles R. Rinaldo Jr., Ph.D.

Stephen C. Strom, Ph.D.

Steven H. Swordow, M.D.

Darell J. Truizli, M.D.

Mohamed A. Virji, M.D., Ph.D.

Robert M. Wadowsky, Sc.D.

Theresa L. Whiteside, Ph.D.

Chuan Yue Wu, Ph.D.

Samuel A. Housem, M.D.

Reza Zarnegar, Ph.D.

Adriana Zeevi, Ph.D.

Associate Professors

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Andrew A. Amoscato, Ph.D.

Sheldon I. Bastacky, M.D.

Gary E. Blank, Ph.D.

Robert P. Bowser, Ph.D.

Gloria Jean Carter, M.D.

Shiyuan Cheng, Ph.D.

Charles T. Chu, M.D., Ph.D.

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Fiona E. Craig, M.B.B.S.

Rajiv Dhir, M.B.B.S.

Roy A. Frye, M.D., Ph.D.

Ronald L. Hamilton, M.D.

Frank J. Jenkins, Ph.D.

Jeanne A. Jordan, Ph.D.

Skilandar L. Katyal, Ph.D.

Shih-Fan Kuan, M.D., Ph.D.

William A Laframboise, Ph.D.

Eric Lagasse, Ph.D.

Lijujuan Li, Ph.D.

Jianhua Luo, M.D., Ph.D.

Wendy M. Mars, Ph.D.

Geoffrey Howard Murdoch, M.D., Ph.D.

N. Paul Ohori, M.D.

Zoltan N. Oltvai, M.D.

Tim D. Oury, M.D., Ph.D.

Aila S. Palekar, M.D.

A. William Pasculle, Sc.D.

Robert L. Peel, M.D.

Hanna Rabiniowich, Ph.D.

Guti R. Rao, M.D.

Michael R. Shurin, M.D., Ph.D.

Urvashi S. Surti, Ph.D.

Lisa Anne Teot, M.D.

Guliana A. Trucco, M.D.

Tong Wu, M.D., Ph.D.

Xiao-Ming Yin, M.D., Ph.D.

Visiting Associate Professors

Raymond E. Feigl, M.D., Ph.D.

Wald E. Khubchandani, M.D., Ph.D.

William A. Parks Jr., M.D.

Anupama Sharma, M.B.B.S.

Research Associate Professors

Joseph T. Newsome, D.V.M.

Nikola Vlahovic, M.D., Ph.D.

Assistant Professors

Evan E. Baker, M.D.

Rohit Bhargava, M.D.

Guoping Cai, M.D.

Irina Vefmova Chilisov, M.D.

Mamatha Chivukula, M.B.B.S.

Laure Pascale Crossille, M.D., Ph.D.

Sanja Dacic, M.D., Ph.D.

Jon M. Davison, M.D.

Marie Colette Defrances, M.D., Ph.D.

Miroslav S. Djikic, M.D.

Mariany A. Donovan, Ph.D.

Jeffrely Louis Fine, M.D.

Csaba Galambos, M.D.

Christine F. Garcia, M.D.

Nick Giannopoulos, M.D.

Ain Lucian Gimita, M.D.

Nadis Fouad Habib-Bien, M.B.B.Ch.

Donald L. Kelley, M.D.

Lawrence P. Kiss, M.D.

Alyssa M. Krasnokas, M.D.

Matthew D. Krasovik, M.D., Ph.D.

Scott M. Külisch, M.D.

Bo Liu, Ph.D.

Kathryn Alice McFadden, M.D., Ph.D., Sara Antoinette Monaghan, M.D.

Sattar Khan P. Monga, M.B.B.S.

Olga Navolotskaya, M.D.

Lawrence C. Nichols, M.D.

Marina Nikoforova, M.D.

Erin Rubin Ochoa, M.D.

Scott R. Rittmaster, Ph.D.

John A. Ozolik, M.D.

Akhil K. Parwani, M.D., Ph.D.

Surenandra Patel, M.B.B.S.

Lina P. Perry, M.D.

Liron Qu, M.D., Ph.D.

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John A. Ozolek, M.D.

Akhil K. Parwani, M.D., Ph.D.

Surenandra Patel, M.B.B.S.

Lina P. Perry, M.D.
The mission of the Department of Pediatrics is to provide the best medical care for children and to advance knowledge about the pathogenesis, diagnosis, prevention, and treatment of pediatric diseases. The department’s wide-ranging program encompasses 19 divisions: Adolescent Medicine; Infectious Diseases; Cardiology; Child Advocacy and Injury Prevention; Developmental–Behavioral Pediatrics; Diagnostic Referral Service; Pediatric Emergency Medicine; Endocrinology; General Academic Pediatrics; Hematology/Oncology; Immunogenetics; Medical Genetics; Neonatology and Developmental Biology; Child Neurology; Nephrology; Pediatric Gastroenterology; Pulmonology, Allergy, and Immunology; Rheumatology; and Weight Management and Wellness.

Residency and Training Programs
The Department of Pediatrics offers three residency training programs: categorical pediatric residency, medicine–pediatric residency; and a triple-board residency covering pediatrics, psychiatry, and child psychiatry. The department also offers fellowship programs in the following 16 areas: adolescent medicine, allergy/immunology, pediatric infectious diseases, pediatric cardiology, pediatric emergency medicine, pediatric endocrinology, pediatric gastroenterology, general academic pediatrics, hematology/oncology, medical genetics, neonatology and developmental biology, nephrology, pediatric epilepsy, pulmonology, pediatric rheumatology, and developmental/behavioral pediatrics.

Infectious Diseases
Toni Darville, M.D.

Child Advocacy and Injury Prevention
Janet E. Squires, M.D.

Cardiology
Steven A. Webber, M.B.B.Ch.B.

Cardiovascular disease and the prevention of cardiovascular disease in children are a major focus of the Pediatric Cardiology Division. The Division of Cardiology provides for children and young adults with congenital heart disease and acquired heart disease, including conditions such as valvular heart disease, myocardial disease, and congenital anomalies. The Division of Cardiology also offers comprehensive clinical services from birth through adulthood for patients with congenital and acquired heart diseases. The clinical program includes ambulatory diagnostic services, a fetal cardiology program, diagnostic and interventional cardiac catheterization, medical management of cardiac dysrhythmias, inflammatory diseases, heart failure, surgical management of congenital cardiac-vascular malformations, and a dedicated pediatric cardiac intensive care unit. The division’s clinical research program focuses on optimizing outcomes following pediatric heart and heart-lung transplantation and during the management of congenital heart diseases. Basic science research focuses on the physiology and biomechanics of developing cardiovascular systems, with an emphasis on the mechanisms responsible for congenital cardiac malformations.

Developmental–Behavioral Pediatrics
Robert B. Noll, Ph.D.

The Division of Developmental–Behavioral Pediatrics provides care for children with developmental and/or behavioral problems, children at risk for such problems, and their families. The division generates and disseminates new knowledge about the prevention, identification, etiology, impact, and treatment of developmental and behavioral problems. Faculty members collaborate with community agencies and programs to improve services for these children and their families. Division research focuses on language development in various developmental disorders, autism, disability prevention through early prenatal care and education, and coping mechanisms for chronic disease.

Endocrinology
Dorothy J. Becker, M.B.B.Ch.

Clinical services provided by the Division of Endocrinology include consultations, endocrine testing, and education concerning diabetes and nutrition for patients and their families. Division research focuses on diabetes, polycystic ovary syndrome, genetic abnormalities, puberty-related development and disorders, and endocrine modulation by environmental factors.

General Academic Pediatrics
Alejandro Hoberman, M.D.

The Division of General Academic Pediatrics provides family-centered primary health care for infants, children, and adolescents. The division develops and disseminates new information about common childhood diseases and conditions, new approaches to treatment, best practices and standards of care, health outcomes, models of service delivery, and related issues. Comprehensive health care services in the division include regular checkups and immunizations, care for unexpected injury or illness, and special services like a question call-in line and emergency care. Current research focuses on otitis media and urinary tract infections.
Departments

Hematology/Oncology

A. Kim Ritchey, M.D.
Chief

The Division of Hematology/Oncology cares for children with blood diseases and cancers using teams of clinical specialists in general oncology, neuro-oncology, sickle cell disease, coagulation, and stem cell transplantation. The division’s clinical research includes studies as part of the Children’s Oncology Group, a nationwide clinical trials program conducting trials in stem cell transplantation as well as treatment of sickle cell disease and aplastic anemia. Basic research in the division investigates stem cell biology and molecular oncology.

Immunogenetics

Massimo M. Trucco, M.D.
Chief

The Division of Immunogenetics provides basic science support aimed at more efficiently and correctly diagnosing, treating, and possibly preventing children’s diseases. One of the division’s main interests is pediatric diabetes. Faculty members work with the University of Pittsburgh Diabetes Institute to study the etiopathogenesis of type 1 diabetes, explore possible ways to prevent the disease in genetically predisposed children, predict who will eventually convert to the disease, and investigate therapeutic approaches that are more appropriate and feasible than daily injections of recombinant insulin. Among the institute’s research goals are to generate new and more abundant insulin-secreting cells, to protect islet cells before transplanting them into recipients, and to develop recipient tolerance of donor cells to avoid the need for immunosuppressive drugs.

Medical Genetics

Girard Vockley, M.D., Ph.D.
Chief

Among its clinical services, the Division of Medical Genetics provides evaluation of children with disorders that result from genetic diseases and/or birth defects and engages the necessary specialists and support to optimize their physical treatment and mental health. Research in the division includes studies of the molecular basis of mitochondrial fatty acid oxidation defects.

Neonatology and Developmental Biology

Gary A. Silverman, M.D., Ph.D.
Chief

The Division of Neonatology and Developmental Biology provides care for high-risk neonates in the neonatal intensive care units (NICUs) at Magee-Womens Hospital of UPMC and Children’s Hospital of Pittsburgh of UPMC. Clinical activities include consultations for high-risk obstetric patients, delivery room resuscitative support, and NICU care, which encompasses care for cardiac, neuro-surgical, urological, genetic, and other complex medical problems. The division’s research program focuses on developmental lung biology, pathology of neonatal hypoxic-ischemia and kernicterus, developmental pharmacology, neonatal growth and nutrition, retinopathy of prematurity, prenatal brain metabolism and injury, mechanisms of preterm labor, and efforts to improve muscle function via gene therapy.

Pediatric Gastroenterology

Mark E. Lowe, M.D., Ph.D.
Chief

The Division of Pediatric Gastroenterology provides care and consultation for children with a variety of conditions, including abdominal pain, gastrointestinal reflux and eosinophilic esophagitis, eosinophilic esophagitis, gastroesophageal bleeding, ulcer disease, inflammatory bowel disease (Crohn’s disease and ulcerative colitis), diarrhea, poor growth, feeding disorders, intestinal failure (short bowel), meconium disorders, constipation, irritable bowel syndrome, liver diseases, liver transplantation, small bowel transplantation, acute and chronic pancreatitis, and metabolic disorders affecting the liver or intestines. Research in the division focuses on metabolic liver disease, pancreatitis, molecular regulation of fat digestion and satiety, inflammatory bowel disease, and cystic fibrosis transmembrane conductance regulation in the small intestine.

Neurology

Demetrios Ellis, M.D.
Chief

The Division of Neurology provides care and consultation for children with renal disorders, including electrolyte disturbances, hematuria, proteinuria, glomerulonephritis, urinary tract infections, end-stage renal disease, and pediatric hypertension. Clinical activities include acute and chronic dialysis, kidney transplantation for infants and children, and treatment for pediatric hypertension and acquired glomerular disorders. Research in the division includes disorders of sodium and water metabolism (central pontine myelinolysis, hyponatremic encephalopathy, and hyponatremic dehydration), the genetic basis of nephronic syndrome, viral infection after renal transplantation, and hemodialysis for children.

Pulmonology, Allergy, and Immunology

Jay K. Kohl, M.D.
Chief

The Division of Pulmonology, Allergy, and Immunology cares for children with acute or chronic pulmonary disorders, cystic fibrosis, airway lesions, sleep disorders, allergic rhinitis, anopic dermatitis, drug allergies, insect hypersensitivity, urticaria, and angioedema. The division provides clinical consultation for patients in the intensive care unit, recurrent pneumonia, bronchopulmonary dysplasia, neuromuscular disorders, airway lesions, immunodeficiencies, and other lung diseases in addition to a comprehensive sleep program for children. Division research focuses on the molecular basis of host defense at the respiratory epithelium, pathogenesis of bacterial pneumonia, cystic fibrosis, exercise physiology and respiration, environmental airway irritants, muscular dystrophy, and lung transplantation.

Rheumatology

Raphael Hirsch, M.D.
Chief

The Division of Rheumatology provides care for children with musculoskeletal and autoimmune diseases, the most common of which is juvenile rheumatoid arthritis. The division’s team of physicians also provides care and consultation for other conditions, including joint and muscle pain, systemic lupus erythematosus, dermatomyositis, vasculitis, uveitis, Raynaud’s disease, Kawasaki disease, scleroderma, and fibromyalgia. Research efforts include collaboration on clinical trials for a novel juvenile rheumatoid arthritis drug, including evaluation of patients’ quality of life. Basic research in the division focuses on T-cell function in autoimmunity and the biology of gene transfer.

Wellness Division

Silva A. Arslanian, M.D.
Chief

The Weight Management and Wellness Division cares for children with obesity and its complications. Treatment protocols include behavioral, surgical, and medical approaches. Division research focuses on pathobiology of obesity-related complications as well as methods for predicting and preventing these complications.

Selected Research Highlights

Massimo M. Trucco, M.D., and colleagues have developed a method to reverse juvenile diabetes in an animal model of the disease. Type 1 diabetes, which typically begins in childhood, is believed to occur when T cells in the body’s immune system interact with and destroy the insulin-producing beta cells of the pancreas. Using a mouse model, Trucco and his team modified the dendritic cells, thus inhibiting T-cell interactions with beta cells and giving the beta cells a chance to regenerate and resume insulin production. Halting the immune system’s destruction of pancreatic beta cells enabled the team to eliminate type 1 diabetes in the mouse model. By using a patient’s own cells, this technique would eliminate the need for immune responsive therapies. The Food and Drug Administration has approved a clinical trial that is expected to enroll at least 15 patients over the age of 18 with type 1 diabetes. Inflicted traumatic brain injury (TBI), a result of abuse, is the leading cause of TBI death in children. Misdagnosis of TBI is common because children often exhibit non-specific symptoms like vomiting and fussiness, and a physical exam can be normal. Rachel P. Berger, M.D., and colleagues are investigating biomarkers that may be able to assist in screening infants who are at high risk for TBI and whose injury might otherwise be missed. A prospective case-control study was conducted of 98 well-appearing infants who presented with nonspecific symptoms and no history of trauma. The researchers found that serum and/or cerebrospinal fluid (CSF) concentrations of neurospecific enolase (NSE) and myelin basic protein (MBP) may be useful for screening infants who are at increased risk for TBI and who may benefit from additional evaluation with a head computed tomography (CT) scan, in the ability to identify TBI that might otherwise be missed has important implications for decreasing morbidity and mortality from TBI.

Robert H. Squires Jr., M.D., and colleagues conducted a prospective, multicenter case study collecting demographic, clinical, laboratory, and short-term outcome data on children from birth to 18 years with acute liver failure (ALF). Three weeks into the study, patients were evaluated for primary outcome measures, which included death, death after transplantation, alive with native liver, and alive with transplanted organ. The researchers determined that ALF causes in children included acute acetaminophen toxicity (14 percent), metabolic disease (13 percent), acute liver disease (6 percent), non-acetaminophen drug-related hepatotoxicity (5 percent), infections (6 percent), and other diagnosed conditions (20 percent). Nearly half (49 percent)
of the causes were indeterminate. Outcomes varied among patient subgroups. Squares and colleagues determined that the causes of AEF in children differ from those in adults and noted that the high percentage of indeterminate cases warrants further investigation.

Children’s developmental impairments have often been attributed to persistent middle-ear effusion in early life. Jack L. Paradice, M.D., and colleagues previously reported that developmental outcomes up to 11 years of age. However, developmental comparisons had not been made at early ages. Paradise and colleagues enrolled 6,350 infants soon after birth and evaluated them regularly for middle-ear effusion. Before age 3, 429 children with persistent effusion were randomly assigned to have tympanostomy tubes. The research team investigated whether this approach could lead to CD4+ T cell-independent vaccine protection against a prototypic AIDS-define infection, Pneumocystis (PC) pneumonia. Zheng and colleagues used serum from mice vaccinated with PC-pulsed, CD40L-modified dendritic cells to immunoprecipitate PC antigens. They identified the antigen Kexin and used it in a similar DNA vaccine strategy, with or without CD40L pairing. CD4-deficient mice receiving DNA vaccines encoding both Kexin and CD40L showed significantly higher anti-PC immunoglobulin titers and a 3-log greater protection in a PC challenge model compared to Kexin alone. The results show promise for development of CD4-independent vaccine against HIV-related or other opportunistic pathogens.

Depletion or dysfunction of CD4+ T lymphocytes greatly disrupts host defenses and impairs vaccine immunogenicity. Mingquan Zheng, M.D., Chad Steele, Ph.D., and Jay K. Kolls, M.D., have shown that plasmid DNA vaccination with a cassette encoding the antigen and a second cassette encoding a full-length CD40 ligand (CD40L), a molecule critical for T cell help function, can elicit significant titers of antigen-specific immunoglobulins in serum and CD4+ T cell responses in CD4-deficient mice. The research team investigated whether this approach could lead to CD4+ T cell-independent vaccine protection against a prototypic AIDS-defining infection, Pneumocystis (PC) pneumonia. Zheng and colleagues used serum from mice vaccinated with PC-pulsed, CD40L-modified dendritic cells to immunoprecipitate PC antigens. They identified the antigen Kexin and used it in a similar DNA vaccine strategy, with or without CD40L pairing. CD4-deficient mice receiving DNA vaccines encoding both Kexin and CD40L showed significantly higher anti-PC immunoglobulin titers and a 3-log greater protection in a PC challenge model compared to Kexin alone. The results show promise for development of CD4-independent vaccine against HIV-related or other opportunistic pathogens.
Graduate Training
Molecular pharmacology is one of the concentrations offered as part of the School of Medicine’s Interdisciplinary Biomedical Graduate Program. Biomedical research in this discipline focuses on the mechanisms of intracellular signaling using a combination of approaches (biochemical, molecular biological, biophysical, and others) as the basis for developing and testing new therapeutic agents. Applications are directed primarily at cancer pharmacology, neurotranspharmacology, and cardiovascular and endocrine pharmacology. A broad, multidisciplinary approach to training in modern molecular pharmacology is offered through formal interactions with the University of Pittsburgh Cancer Institute, the Center for Neuroscience, and the Center for Clinical Pharmacology, among other programs.

Selected Research Highlights

Bruce A. Freeman, Ph.D., studies the production, reaction, and signal transduction properties of oxidizing and free radical inflammatory mediators in eukaryotic cells. Free radicals are highly reactive molecular structures that contribute to necessary biological processes like cell signaling but can also participate in side reactions that produce cell damage. As a result, they have been implicated in atherosclerosis, symptoms of aging, and many cancers. Freeman’s laboratory examines the action of free radical species as signaling mediators under basal conditions and as pathogenic agents in inflammatory diseases. His group has elucidated the actions of numerous free radicals and their derivatives, lending new insight into cell signaling, and has revealed new therapeutic strategies for acute inflammation, metabolic syndrome, respiratory disorders, and cardiovascular diseases.

Mitogen-activated protein kinase phosphatase 1 (MKP-1) is a tyrosine phosphatase superfamily member that dephosphorylates and inactivates mitogen-activated protein kinase (MAPK) substrates. Many essential cellular processes associated with human diseases are regulated by MKP-1 and/or MKP-2.得意は、多くの研究者によって、MKP-1は細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、さまざまな細胞の発展を阻む可能性がある。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されています。MKP-1の欠損は、細胞のMAPKサブストレートを無効にし、MAPK活性を抑制するための重要な酵素であることが示されてい
of intracellular PKC, thus allowing the effectors to control PKC signaling. Her laboratory also investigates the potential regulatory role of PKC isoforms on neurotrophic and other diseases, including tumor, viral, and inflammatory responses. These studies are conducted in a mouse model to study the role of PKC signaling in cancer and other diseases.

**Research Assistant Professors**
- Paul R.S. Baker, Ph.D.
- Pamela A. Hershberger, Ph.D.
- Elena Malhina, Ph.D.
- Fernando A.P. Ribeiro Neto, M.D.
- James R. Roppolo, Ph.D.
- Francisco Jose Schopfer, Ph.D.
- Adrian Sculptoreanu, Ph.D.
- Laura A. Stabile, Ph.D.
- Andreas Vogt, Ph.D.

**Instructors**
- Palaniappa Arjunan, Ph.D.
- Daniela Galbiati, Ph.D.
- William B. Sneddon, Ph.D.
- Daniela Galbiati, Ph.D.
- Palaniappa Arjunan, Ph.D.
- Andreas Vogt, Ph.D.

**Associate Professors**
- Daniel L. Altschuler, Ph.D.
- William C. deGroat, Ph.D.
- Donald B. DeFranco, Ph.D.
- Richard M. Cyert Professor of Physical Medicine and Rehabilitation
- John S. Lazo, Ph.D.
- Bruce A. Freeman, Ph.D.
- Thomas P. Conrads, Ph.D.

**Endowed Chairs**
- Harish Srinivas, Ph.D.
- Elizabeth R. Sharlow, Ph.D.
- Dinara Mukhamat Shakiryanova, Ph.D.
- Alicia M. Palladino, Ph.D.
- Edwina C. Kinchington, Ph.D.
- Yung Kyu Kim, Ph.D.
- Melanie Sarah Flint, Ph.D.
- Andreas Vogt, Ph.D.

**Regular Faculty**
- Michael L. Boninger, M.D., Professor and Interim Chair
- Gwendolyn A. Sowa, M.D., Ph.D.
- Douglas J. Weber, Ph.D., Assistant Professor
- Paul A. Johnston, Ph.D., Assistant Professor
- Mark D. Nichols, Ph.D.
- Joseph E. de Groot, Ph.D.
- Michael J. Palladino, Ph.D.
- Michael J. Palladino, Ph.D.
- Andreas Vogt, Ph.D.

**Research Instructors**
- Melanie Sarah Flint, Ph.D.
- Yung Kyo Kim, Ph.D.
- Edwina C. Kinchington, Ph.D.
- Lynn M. Knowles, Ph.D.
- Alicia M. Palladino, Ph.D.
- Dinara Mukhamat Shakiryanova, Ph.D.
- Elizabeth R. Sharlow, Ph.D.
- Harish Srinivas, Ph.D.
- Bingyte Oestergaard Wittschien, Ph.D.
- Dong Xiao, M.D.

**Residency and Fellowship Training**
- The department's four-year residency program is designed to prepare residents to become practicing physicians. The program includes an internship year of general medicine followed by a research year focused on specific areas of interest. Residents are paired with an attending physician as a research mentor. Residents are encouraged to complete a fellowship in a specific area of interest, such as neurology, rheumatology, radiology, or oncology.

**Selected Research Highlights**
- Promising clinical evidence continues to demonstrate the effectiveness of motion-based therapies in treating low back pain. Gwendolyn A. Sowa, M.D., Ph.D., and colleagues are examining the biochemical pathways induced by mechanical force using intravital microscopy to demonstrate the effectiveness of motion-based therapies in treating low back pain.

**Physical Medicine and Rehabilitation**
- The department of Physical Medicine and Rehabilitation provides comprehensive physical therapy care for patients with limited mobility due to musculoskeletal injuries, spinal cord or traumatic brain injury, multiple sclerosis, cerebral palsy, amputations, and stroke. Services, which are offered in several UPMC hospitals and outpatient facilities, include up-to-date diagnostic options, surgical and nonsurgical treatments, and help with rehabilitative equipment. The department is committed to providing excellence in rehabilitative care through innovative research, interactive teaching, and professional personal service. Department physicians are experts in the fields of traumatic brain injury, spinal cord injury, stroke, diseases and disorders of the musculoskeletal and peripheral nervous systems, and other conditions that affect function and mobility. Research consists of lab and clinical investigations in areas like neuropsychopharmacology, neuroimaging, gene therapy, and assistive technology.

**PHARMACOLOGY**
- The department of Pharmacology focuses on the investigation of novel PKC activators and inhibitors for the therapeutic intervention of PKC signaling in cancer and other diseases. The program includes an internship year of general medicine followed by a research year focused on specific areas of interest. Residents are paired with an attending physician as a research mentor. Residents are encouraged to complete a fellowship in a specific area of interest, such as neurology, rheumatology, radiology, or oncology.

**SELECTED RESEARCH HIGHLIGHTS**
- Promising clinical evidence continues to demonstrate the effectiveness of motion-based therapies in treating low back pain. Gwendolyn A. Sowa, M.D., Ph.D., and colleagues are examining the biochemical pathways induced by mechanical force using intravital microscopy to demonstrate the effectiveness of motion-based therapies in treating low back pain.

**PHYSICAL MEDICINE AND REHABILITATION**
- The department of Physical Medicine and Rehabilitation provides comprehensive physical therapy care for patients with limited mobility due to musculoskeletal injuries, spinal cord or traumatic brain injury, multiple sclerosis, cerebral palsy, amputations, and stroke. Services, which are offered in several UPMC hospitals and outpatient facilities, include up-to-date diagnostic options, surgical and nonsurgical treatments, and help with rehabilitative equipment. The department is committed to providing excellence in rehabilitative care through innovative research, interactive teaching, and professional personal service. Department physicians are experts in the fields of traumatic brain injury, spinal cord injury, stroke, diseases and disorders of the musculoskeletal and peripheral nervous systems, and other conditions that affect function and mobility. Research consists of lab and clinical investigations in areas like neuropsychopharmacology, neuroimaging, gene therapy, and assistive technology.
showed that the group receiving 8-OH-DPAT plus the enriched environ- ment significantly outperformed the group receiving 8-OH-DPAT alone, indicating a combination effect. However, there was no difference in performance when comparing 8-OH-DPAT versus saline in the enriched environment groups. Thus, while the study confirmed that both treatments improve recovery following traumatic brain injury, the treatment combination in this particular paradigm did not confer additional benefit. One explanation might be that the enriched environment is a high-effect treatment on its own, and the addition of 8-OH-DPAT confers no significant improvement.

### Regular Faculty

**Professor**

Michael L. Boninger, M.D.

**Associate Professors**

Michael C. Munit, M.D.

Joseph H. Ricker, Ph.D.

**Assistant Professors**

Fabrizia Ambrosio, Ph.D.

Patricia Maria Arenth, Ph.D.

Gilbert Brenas, M.D.

Lenora P. Cabacungan, M.D.

Alan W. Chu, M.D.

Megan Helen Cortazzo, M.D.

Kerry Gill Deluca, M.D.

Brad E. DiCicco, M.D.

Katharine M. Flood, M.D.

Wendy M. Heilskov, M.D.

John A. Horton III, M.D.

Beatriz Luna, Ph.D.

Judy L. Cameron, Ph.D.

Ellen Frank, Ph.D.

Katherine L. Wisner, M.D., M.S.

**Ph.D. Students**

Richard K. Voigt, Ph.D.

Kurt M. Parrott, Ph.D.

**Research Track**

David J. Kupfer, M.D., Dr. Thomas Dele Professor and Chair

**Visiting Instructor**

Cara Elizabeth Reddy, M.D.
whether the two conditions are separable or whether one precedes the other in the progression to Alzheimer's disease. The team used a new 3-D magnetic resonance imaging mapping procedure to examine specific brain areas. Results showed that the hippocampus, a key area of the brain in memory formation, is 14 percent smaller in patients with MCI-A than in normal individuals. (In Alzheimer's disease, the shrinkage is 23 percent.) However, patients with MCI-MCI showed only a 5 percent loss of hippocampal tissue. These results confirmed two distinct pathways to Alzheimer's disease and indicated that discerning pathway details could aid in developing treatments that slow or stop the progression of Alzheimer's disease. In addition, the study showed that the highly detailed imaging technique can be used to track disease rate or whether one precedes the other in the progression to Alzheimer's disease. The team used a new 3-D magnetic resonance imaging mapping procedure to examine specific brain areas. Results showed that the hippocampus, a key area of the brain in memory formation, is 14 percent smaller in patients with MCI-A than in normal individuals. (In Alzheimer's disease, the shrinkage is 23 percent.) However, patients with MCI-MCI showed only a 5 percent loss of hippocampal tissue. These results confirmed two distinct pathways to Alzheimer's disease. The team used a new 3-D magnetic resonance imaging mapping procedure to examine specific brain areas. Results showed that the hippocampus, a key area of the brain in memory formation, is 14 percent smaller in patients with MCI-A than in normal individuals. (In Alzheimer's disease, the shrinkage is 23 percent.) However, patients with MCI-MCI showed only a 5 percent loss of hippocampal tissue. These results confirmed two distinct pathways to Alzheimer's disease.
The Department of Radiation Oncology, which focuses on clinical and research activities as well as medical physics, provides radiation therapy services to 10 UPMC hospitals and oversees the treatment of approximately 6,000 new patients a year. Radiation therapy clinical programs include conventional external beam, three-dimensional conformal irradiation, intensity-modulated radiation therapy, fractionated stereotactic irradiation (Trilogy, CyberKnife®), and stereotactic radiosurgery (Gamma Knife®). In addition, the department offers a full array of brachytherapy services, including interstitial and intracavitary high-dose-rate implants, permanent radioactive implants, intraoperative brachytherapy, and minimally invasive techniques. A comprehensive clinical care program at 20 radiation oncology facilities in western Pennsylvania provides a centralized and advanced radiation treatment program for all major forms of cancer. The department's research programs in molecular biology, radiation biology, and stem cell biology are integrated with multidisciplinary research programs in molecular biology, radiation biology, and stem cell biology. Residents are also trained in the use of modern radiation therapy and brachytherapy for treatment of various cancers.

Dwight E. Heron, M.D., and Sushil Beriwal, M.D., are examining the efficacy of extended-field intensity-modulated radiation therapy (IMRT) for cervical cancer. Traditional cervical cancer radiation therapy irradiates a wide area (pelvis and abdomen), because of this, only moderate doses can be delivered. Even so, 40 percent of patients experience serious adverse side effects like pain, diarrhea, and bowel obstruction. By contrast, extended-field IMRT targets high-energy beams directly to the tumor site, passing through normal tissue without imparting damage. The convergent beams allow higher radiation doses with minimal adverse side effects. In a recent study, Heron and Beriwal treated 36 cervical cancer patients with extended-field IMRT in combination with cisplatin, a chemotherapeutic agent. Thirty-four patients responded completely to treatment and experienced minimal side effects, demonstrating reduced toxicity for this approach. While 11 of the patients developed recurrences, most appeared in distant sites, suggesting that additional systemic therapies could help to control metastasis in cervical cancer. Genes damaged by radiation exposure, environmental toxins, free radicals, and other harmful influences can lead to cancers or other diseases. Christopher J. Bakkenist, Ph.D., studies the most lethal form of DNA damage, the double-strand break (DSB). His particular focus is the ataxia telangiectasia mutated (ATM) enzyme, a nuclear protein kinase essential for cellular response to DSBs. Bakkenist and his research team have shown that inactive ATM proteins are locked into dimers, a pairing that prevents unwanted interactions with other proteins. However, in the presence of DSBs, ATM proteins separate into active monomers that trigger molecular cascades, culminating in either DNA repair or cell death. Bakkenist has determined that activated ATM monomers phosphorylate target proteins, which then signal activity further down the repair pathway and are also responsible for additional ATM dimer separation. Bakkenist’s team has found that even a small quantity of DSBs can initiate ATM response within minutes of the damage; once initiated, the response rapidly amplifies. Understanding the mechanisms of DSB repair could eventually lead to novel preventive and treatment approaches for disorders related to dysfunctional DNA repair.

Yunyun Niu, M.D., Ph.D. amplifies. Understanding the convergent separation. Bakkenist's team has identified that activated ATM monomers phosphorylate target proteins, which then signal activity further down the repair pathway and are also responsible for additional ATM dimer separation. Bakkenist’s team has found that even a small quantity of DSBs can initiate ATM response within minutes of the damage; once initiated, the response rapidly amplifies. Understanding the mechanisms of DSB repair could eventually lead to novel preventive and treatment approaches for disorders related to dysfunctional DNA repair.

Residency and Fellowship Training
The department’s residency program engages residents in intradepartmental academic and clinical efforts. Residents also are trained in the use of modern radiation therapy and brachytherapy for treatment of various cancers. The department’s research programs in molecular biology, radiation biology, and stem cell biology are integrated with multidisciplinary research programs in molecular biology, radiation biology, and stem cell biology. Residents are also trained in the use of modern radiation therapy and brachytherapy for treatment of various cancers.
Neuroradiology

William Rothbus, M.D.
Chief

The Division of Neuroradiology provides a full range of clinical services with a major focus on the treatment of thyroid diseases and thyroid cancer as well as anti- immunotherapy of lymphomas. Diagnostic procedures include PET, CT, and MR imaging, and the division focuses on the accurate and timely interpretation of chest imaging studies, including chest radiographs, thoracic CT and MR exams, cardiac MR and CT, and combined PET/CT imaging of primary thoracic abnormalities and thoracic diseases. The division interprets chest radiographs for tuberculosis screenings by the Allegheny County Health Department and for local participants in the National Cancer Institute’s Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Research being done by the division involves esophageal imaging, lung cancer screening, cardiac imaging, and characterization of growth patterns for pulmonary nodules.

Vascular and Interventional Radiology

Alberto B. Zajko, M.D.
Chief

The Division of Vascular and Interventional Radiology performs noninvasive radiographic angiographic, venographic, and interventional radiological procedures. Angiographic procedures include diagnostic problems involving the treatment of tumors or gastrointestinal bleeding. Embolization for the treatment of uterine or gastrointestinal bleeding is a useful tool.

Thoracic Imaging

Carl R. Fuhiman, M.D.
Chief

The Division of Thoracic Imaging focuses on the accurate and timely interpretation of chest imaging studies, including chest radiographs, thoracic CT and MR exams, cardiac MR and CT, and combined PET/CT imaging of primary chest abnormalities and thoracic diseases. The division interprets chest radiographs for tuberculosis screenings by the Allegheny County Health Department and for local participants in the National Cancer Institute’s Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Research being done by the division involves esophageal imaging, lung cancer screening, cardiac imaging, and characterization of growth patterns for pulmonary nodules.

Pediatric Radiology

Manuel P. Maza, M.D.
Chief

The Division of Pediatric Radiology is one of the nation’s oldest and largest pediatric radiology programs. The division is committed to subspecialty imaging to complement its strengths in general radiology. Faculty members’ research interests include the radiographic manifestations in organ transplantation, pediatric neuroradiology, and interventional techniques in the pediatric population. Magnetic resonance imaging in pediatric patients, pediatric stroke, imaging of traumatic speech disorders, and bone mineral density in pediatric patients receiving corticosteroids for leukemia or cancer.

Nuclear Medicine

James M. Mauzert, M.D., Ph.D.
Chief

The Division of Nuclear Medicine provides a full range of clinical services with a major focus on the treatment of thyroid diseases and thyroid cancer as well as radioimmunotherapy of lymphomas. Diagnostic procedures include PET, CT, and SPECT (single photon emission computed tomography) as well as interventional radiography for intraarterial aneurysms, arteriovenous malformations, tumors, and arteriovenous fistulae.

Radiology Imaging

David Gur, Sc.D., D.
Director

The Division of Radiology Imaging provides expertise in pediatric radiology, computer and information science, and evaluation of imaging systems. Most division activities involve digital imaging research. Other projects, which aim to improve the efficiency and efficacy of radiological imaging in the clinical environment, include the use of digital imaging and the implementation of computer-aided detection (CAD) systems.

Selected Research Highlights

David Gur, Sc.D., and colleagues have developed and tested a new multiview computer-aided detection (CAD) scheme for breast cancer. To evaluate the procedure’s sensitivity, it was applied to a patient database with images of known benign and malignant breast tissue. Gur and his team used a single-image CAD, and for each identified region, a matching region of interest on the ipsilateral breast was established. A multivariate artificial neural network scored the likelihood of the paired “matched” regions representing true-positive masses. The single-image CAD scheme achieved 74.4 percent sensitivity, where only half of the cases were detected with two single images and most false positives were detected with only one image. Applying the multiview CAD scheme, the sensitivity increased to 90.9 percent, and the false-positive detection rate was reduced by 23.7 percent.

Quantifying changes in arterial and total cerebral blood volume (CBV) and cerebral blood volume (CBV) using magnetic resonance imaging (MRI) during normal activation might provide critical vascular control mechanism information and help to identify neurovascular response in conventional cerebral blood oxygenation level-dependent (BOLD) magnetic resonance imaging (fMRI). Seong-Gi Kim, Ph.D., has quantified cerebral blood flow (CBF) as well as CBV and CBV using fMRI in isoflurane-anesthetized rats during 15-second forepaw stimulation. CBV and CBV were simultaneously determined by tissue and vessel signal modulation using arterial spin labeling. CBV was measured with a susceptibility-based contrast agent. Neural activity-induced absolute changes in CBV and CBV were statistically equivalent and independent of the size of the region analyzed, indicating that increased CBV during neural activation in this region (somatosensory cortex) originates mainly from arterial blood volume changes and implying that venous blood volume changes may be negligible in BOLD MRI.

Neuroradiology

William Rothbus, M.D.
Chief

The Division of Neuroradiology routinely uses CT angiography with three-dimensional reconstruction for noninvasive diagnosis of cerebrovascular disease and performs specialized diagnostics, including sialography, modified barium-swallowing studies, and combined PET-CT imaging of head and neck cancers. The division’s spine inter- vention service oversees discography, epidural steroid injections, selective nerve root blocks, biopsies, and vertebral augmentation (kyphoplasty and vertebroplasty). Endovascular neuroradiology, which is also part of this division, involves angiograms as well as interventional radiography for intracranial aneurysms, arteriovenous malformations, tumors, and arteriovenous fistulae.

Pediatric Radiology

Manuel P. Maza, M.D.
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Nuclear Medicine

James M. Mauzert, M.D., Ph.D.
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Radiology Imaging

David Gur, Sc.D., D.
Director

The Division of Radiology Imaging provides expertise in pediatric radiology, computer and information science, and evaluation of imaging systems. Most division activities involve digital imaging research. Other projects, which aim to improve the efficiency and efficacy of radiological imaging in the clinical environment, include the use of digital imaging and the implementation of computer-aided detection (CAD) systems.

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Tumor oxygenation plays a critical role in tumor growth, invasion, and therapy. QuanHong, Ph.D., and colleagues are developing a novel method to evaluate tumor oxygenation levels.

Clinical outcomes monitoring.

And distant metastases as well as improved detection of primary tumors. The method offers the prospect of myoglobin that has been genetically engineered into the bacterium will serve as an oxygen sensor. This method offers the prospect of improved detection of primary tumors and distant metastases as well as better therapeutic planning and clinical outcomes monitoring.

**Professors**

- Keibel V. Neshur (M.D., M.D.)
- Lorcan A. O'Tuama, M.B.B.Ch.

**Research Professors**

- Walter F. Goode, Ph.D.
- Edwin M. Nemoto, Ph.D.

**Associate Professors**

- Kathleen E. Amies, M.D.
- Walter J. Birtwistle, M.D.
- Fernando E. Boada, Ph.D.
- Barton F. Branstetter, M.D.
- Dev P. Chakraborty, Ph.D.
- James V. Ferris, M.D.
- Christiane M. Hakim, M.D.
- Jean M. Lacomis, M.D.
- Barry M. McCook, M.D.
- Fernando F. Boada, Ph.D.
- James V. Ferris, M.D.
- Christiane M. Hakim, M.D.
- Jean M. Lacomis, M.D.
- Barry M. McCook, M.D.
- Donal Padraic, D.O.
- Donald Sashin, Ph.D.
- F. Leand Thae, M.D.
- Jeffrey D. Towers, M.D.
- Mitchell E. Tubb, M.D.
- Eric C. Wiener, Ph.D.

**Visiting Associate Professors**

- Friedrich D. Knollmann, M.D.
- Charles Lee, M.D.
- Eric D. Schmitt, M.D.
- Margarita L. Zuley, M.D.

**Research Associate Professor**

- Bin Zheng, Ph.D.

**Assistant Professors**

- Gordon S. Abell, M.D.
- Hesham Mohamed Ahmed, M.B.B.Ch.
- Omar Almusa, M.D.
- Kevin M. Bassin, M.D.
- Badreddine Bencherif, M.D.
- Andrew Feldman, B.B.S.
- Todd Michael Blackett, M.D.
- David C. Buck, M.D.
- Jonathan Paul Conant, Ph.D.
- Victor J. Cataldo, M.D.
- Cathy C. Cohen, Ph.D.
- Anil Kumar Dayam, M.B.B.S.
- Christopher R. Deible, M.D., Ph.D.
- Edward Joel Escott, M.D.
- Mitsuhiro Fukuda, Ph.D.
- Maria A. Ganot, M.D.
- Sarasawati Golla, M.B.B.S.
- Kelly A. Haarer, M.D.
- Quang Ho, Ph.D.
- Keyanoosh Hosseiniehazadeh, M.D.
- Marlon Alicus Hughes, M.D.
- Tamer Selim Ibrahim, Ph.D.
- Kuop-Shyan Lin, Ph.D.
- Amy H. Lu, M.D.
- Fred M. Moselein, M.D., Ph.D.
- Asif M. Muthysharana, M.B.B.S.
- Rajesh Narendran, M.B.B.S., M.B.
- Ka-Ken Ngan, M.D.
- Kallipoli Agathangelos, M.D.
- Pasquale M. Meza, M.D.
- Philip D. Oron, D.O.
- Julie C. Price, Ph.D.
- Donald Sashin, Ph.D.
- Leand Thae, M.D.
- Jeffrey D. Towers, M.D.
- Mitchell E. Tubb, M.D.
- Eric C. Wiener, Ph.D.

**Research Assistant Professors**

- Tao Jin, Ph.D.
- Charles M. Laymon, Ph.D.
- Joseph K. Leader III, Ph.D.
- Glenn S. Martin, M.S.
- Neal Scott Mason, Ph.D.
- Claudia Regina Mello-Thoms, Ph.D.
- Chanhong Moon, Ph.D.
- Jiantao Xu, Ph.D.
- Paul A. Scherrnan, Ph.D.
- Costin Tanasa, Ph.D.
- Xiao Hui Wang, M.D., Ph.D.

**Research Investigators**

- Denise K. Davis, B.S.
- Guang Huang, Ph.D.
- Brian J. Lopresti, B.S.
- Icctal Ocam, M.D.
- Yongxian Qian, Ph.D.

**Graduate Training**

The Molecular Biophysics and Structural Biology Graduate Program is an interdisciplinary program at the interfaces of biology, chemistry, physics, and other traditional scientific disciplines. The program, which includes faculty from Pitt’s School of Medicine and School of Arts and Sciences as well as from Carnegie Mellon University, provides a unique opportunity for students to study across traditional boundaries and to train in state-of-the-art methodologies like high field solution and solid-state nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography, cryo-electron microscopy, atomic force microscopy, mass spectrometry, infrared spectroscopy, and computational molecular biology.

**Selected Research Highlights**

- Angela M. Gronenborn, Ph.D., and colleagues study the HIV-inactivating protein Cyanovirin-N (CV-N), a cyanobacterial lectin that exhibits potent antiviral activity at nanomolar concentrations by interacting with high-mannose carbohydrates on viral glycoproteins. The researchers have investigated CV-N mutants to establish the antiviral molecular mechanisms. Gronenborn and colleagues have found that mutations, which alter the trimerization specificity in one binding site or abolish the other sugar-binding site (domain B), revealed that both carbohydrate-binding sites are essential for antiviral activity. These findings clarify that the multivalent and multisite interactions are critical and that the nanomolar antiviral potency of CV-N is related to the mannoses’ constricted and spatially crowded arrangement on viral glycoproteins and is not due to CV-N-induced virus particle clustering, making CV-N a true viral entry inhibitor.

Glycerol is a central link among the respiration, energy, sugar, and lipid metabolic processes. Joachim J. Yap, Ph.D., and colleagues have conducted detailed structural studies on soluble and membrane protein partners mediating glycerol metabolism and have revealed novel signal transduction and regulatory interactions. Sin-Glycerol 3-phosphate dehydrogenase (GPDH) is an integral membrane protein whose enzymatic activity is regulated through its interaction with the inner membrane of E. coli. The importance of these pathways is indicated by the presence of homologous systems across organisms, including humans, where some of these processes take place on the mitochondrial membrane. In the absence of lipid-enzyme interactions, the GPDH enzyme remains in an inactive conformation. Yap and colleagues have determined the structure of a fully active E. coli GPDH, revealing the unique topology of the enzyme, which exhibits a novel fold in one domain as well as protein-protein interaction surfaces whereby complex formation enhances activity. Glycerol metabolism is an important pathway in mechanisms involved in insulin signaling, and metabolic perturbations in these pathways are linked to obesity in humans. These findings illuminate how membrane-enzyme interactions regulate activity, and the similarities found in GPDH homologs across organisms show that the prokaryotic structural results can likely be applied to eukaryotic GPD enzymes to identify new means of combating conditions like diabetes and obesity.
This mutation has a much more severe and rapidly progressive (class A), but R135W causes more severe RP severity and progression rates. Whether a mutation’s location affects the pathway to RP continues to be of interest to ophthalmologists and researchers. It was recently reported that, for at least one mutation, the location of the mutation on the protein produced by the gene that causes RP has an effect on the severity of the disease. This finding suggests that understanding the role of the protein produced by the gene that causes RP in producing night blindness, tunnel vision, and, eventually, blindness. The protein rhodopsin that lead to retinitis pigmentosa is designed to provide special experiences for patients with RP. This allows patients to have a better quality of life despite the limitations imposed by the disease.

Judith H. Klein-Seetharaman, Ph.D., and colleagues study mutations in the protein rhodopsin that lead to retinitis pigmentosa (RP), a genetic disorder that produces night blindness, tunnel vision, and, eventually, blindness. The researchers have studied a number of mutations that lead to RP to determine whether a mutation’s location affects RP expression. Klein-Seetharaman and colleagues found that distinct amino acid substitutions cause different RP severity and progression rates. Specifically, both the R135L and R135W mutations (cytoplasmic end of the protein) result in diffuse, severe disease (class A), but R135W causes more severe and more rapidly progressive RP than R135L. The P180A and G189R mutations (second intradiscal loop) exhibit a mild phenotype with regional variability (class B1) and diffuse disease of moderate severity (class B2), respectively. Their study further established that rhodopsin mutations are more pronounced in the R135W mutation, perhaps explaining at the molecular level why this mutation has a much more severe phenotype.

Residency and Fellowship Training

The Department of Surgery fosters a threefold mission: to provide high quality clinical care to surgical patients, to promote state-of-the-art educational programs in all areas of clinical surgery, and to produce new information from research that will advance surgical practice. The late Henry T. Bahnson, M.D., who chaired the department from 1963 to 1987, is credited with establishing it as a leading academic surgery department. In addition, the department has pioneered a tradition for innovation and excellence at the hands of such prominent surgeons as Thomas E. Starzi, M.D., Ph.D., the world-renowned transplant specialist for whom the department’s Thomas E. Starzi Transplantation Institute is named; Richard L. Simmons, M.D., a distinguished transplanted transplant recipient; and respected mentor; and Bernard Fisher, M.D., who revolutionized residency programs leading to surgical training through the Charles Gray fellowship. The fellowship offered complete surgical training through the Charles Gray fellowship, which was developed with the insight that much surgical training must occur outside the operating room. The division’s world-leading transplant program includes three interrelated components: heart transplants, mechanical heart-lung transplants, and lung transplants. Research in the division parallels its clinical activities and focuses on clinical outcomes, immunopathology, rehabilitative and quality of life studies, clinical trials in immunosuppression and left ventricular assist devices, and basic research in organ preservation and regenerative medicine, including cellular and genetic therapies.

General Surgery

Andrew B. Pitzutz, M.D., Chief

The focus of the Division of General Surgery ranges from minimally invasive surgery to trauma surgery; it is the hub of the department’s busiest trauma program. The minimally invasive surgery section specializes in bariatric surgery and carries out NIH-sponsored outcomes research. Trauma section research includes multi-institutional clinical trials as well as investigations involving hemodynamic shock, organ dysfunction, nutrition, nitric oxide, arginine metabolism, and minimally invasive tissue perfusion measurements.

Pediatric Surgery

George K. Gittles, M.D., Chief

The Division of Pediatric Surgery, which is currently the only pediatric surgical service in western Pennsylvania, operates through Children’s Hospital of Pittsburgh of UPMC and provides clinical services through the Benedum Pediatric Trauma Program, the Pappas Trauma and Treatment Center, and the Nutritional Support Service. Division research is prolific and includes basic and clinical investigations in gut barrier failure, pediatric oncology, pediatric surgical critical care, and pediatric obesity.

Plastic Surgery

W. Andrew Lee, M.D., Chief

The Division of Plastic Surgery offers a spectrum of care for adult and pediatric patients, including surgery to correct body surface defects resulting from trauma or infection, as well as treatment for various pathologic conditions like cancer resections involving the head and neck, breast, skin, and trunk. The division also offers complete cosmetic surgery services. Through Children’s Hospital of Pittsburgh of UPMC, the division treats pediatric plastic surgical problems, congenital hand deformities, and cleft or craniofacial defects. Research in the division focuses on bone tissue engineering, including the use of bone substitutes; cranial suture biology; and skin flap design and physiology.

Surgical Oncology

David L. Bartlett, M.D., Chief

The Division of Surgical Oncology offers particular expertise in the surgical treatment of breast cancers, melanomas, sarcomas, upper gastrointestinal malignancies, pancreatic cancers, colorectal cancers, hepatobiliary cancers, and endocrine tumors. Specialized techniques available through the division include sentinel node mapping for breast cancer and melanoma, isolated limb chemoperfusion for arm or leg cancer, peritoneal mesothelioma for cancers that have advanced into the peritoneal cavity, saltine-sparing surgery for low rectal cancers, and in-transplant regional chemotheraphy infusion for liver metastases, radio frequency ablation, laparoscopic colon resection, tumor resection, and placement of brachytherapy implants for focused radiation therapy treatments. Division research is aimed at developing novel therapies for cancer and includes a wide array of clinical trials.

Thoracic and Foregut Surgery

James D. Luketich, M.D., Chief

The Division of Thoracic and Foregut Surgery offers a multidisciplinary approach to noncardiac diseases of the chest. It provides a variety of minimally invasive procedures for esophageal disorders, including gastroesophageal reflux disease, giant paraesophageal hiatal hernias, achalasia, and cancer. The division also performs video-assisted thoracic surgery and other specialized procedures like photodynamic therapy, laparoscopic Nissen fundoplication, laser light-induced fluorescence endoscopy, and laparoscopic endoscopic esophagectomy. Research in the division emphasizes clinical care by redifining options available to patients with esophageal cancer and benign esophageal disorders. Studies have focused on photodynamic therapy for esophageal cancer, minimally invasive esophagectomy, laparoscopic management of giant paraesophageal hernias, and application of molecular diagnostics to staging esophageal cancer.

Transplantation Surgery

Armando Marcos, M.D., Chief

The Division of Transplantation Surgery, which operates through the Thomas E. Starzl Transplantation Institute, has built a worldwide reputation for innovation and excellence in organ transplantation. Much of modern transplant technology was pioneered in Pittsburgh, and this program remains at the forefront not only in liver, intestine, pancreas, and kidney transplants but also in unmatched transplant procedures involving pediatric patients. In addition, the institute has done groundbreaking work in pancreatic islet cell transplants and xenotransplantation and has established an innovative procedure to optimize intestinal transplantation. Recent advances have focused on immunosuppressive drug protocols, organ preservation, surgical techniques, pre- and postoperative care, and transplant immunology. Division research covers a wide range of issues, including studies on tolerance, immunotherapy, chimerism, gene therapy, molecular virology, growth factor biology, and bioengineering.

Vascular Surgery

Michel S. Makaroun, M.D., Chief

The Division of Vascular Surgery provides comprehensive and surgical intervention for the treatment of aneurysms, atherosclerotic occlusive disease, cerebrovascular disease, thoracic outlet syndrome, and
Lee and colleagues concluded that TRAIL works via cellular mito-
overexpression suppressed the studies revealed that BCL-2 protein production. Additional cancers.
protein production. The researchers inoculated mice with ovarian cancer cells and treated them with cytosine deaminase-encoded vaccinia virus immediately or at 30 or 60 days post-inoculation. The control group was inoculated with cancer cells and received no gene therapy. Bartlett and colleagues observed that immediate gene therapy completely suppressed tumor growth and that therapy provided at 30 and 60 days post-inoculation produced significant tumor inhibition. Mice not receiving gene therapy died from the cancer or its complications. Bartlett and colleagues hope that vaccinia virus-based gene therapy will prove effective in humans because current treatments for ovarian cancer do not provide tumor selectivity and are harsh for patients.

Women who undergo surgery and subsequent radiation treatment for breast cancer often experience breast deformities that require surgical correction. Howard D. Edington, M.D., and colleagues have developed a method to encapsulate the chemotherapeutic agent doxorubicin into biodegradable polymer microspheres, which depletes both T and B cells. In a trial of the protocol, all patients were given the standard antirejection drug tacrolimus following transplant, but none received steroid supple-
mantion. At 120 days post-surgery, tacrolimus tapering was initiated. While 43 percent of patients exhibited some level of rejection before tacrolimus weaning, the rejection was not chronic. Patients who received alemtuzumab before surgery did slightly better than those treated with thymoglobulin; however, both drugs improved rejection outcomes. The ability to reduce antirejection drug use for immunosuppressive regimens also provides evidence that a reduction protocol is feasible for other abdominal and thoracic transplant procedures.

The gene therapy is designed to improve the response in second-line chemotherapy, which has a current success rate of only 15 to 20 percent. The best treatment for patients with liver cancer, overall, is surgical removal of the tumor tissue and possible transplant. However, in 75 percent of cases, the liver cancer is inoperable at the time of diagnosis. Geller and colleagues hope gene therapy will significantly improve treatment responses when combined with traditional chemotherapy. Because the intestine is especially prone to infection and rejection, patients are normally given several antirejection drugs following intestinal transplants.

Bartlett and colleagues observed that at least 12 hours of aspirin pretreatment was required to promote TRAIL-induced apoptosis. Western blot analysis showed that aspirin pretreatment followed by TRAIL activated caspases and cleaved poly(ADP-ribose) polymerase in tumor cells, confirming that the treatment did, in fact, stimulate apoptosis in these cells. The researchers found that at least 12 hours of aspirin pretreatment was required to promote TRAIL-induced apoptosis and also appeared to down-regulate BCL-2 protein production. Additional studies revealed that BCL-2 protein overexpression suppressed the protective effect of aspirin on TRAIL-
induced apoptosis, suggesting that TRAIL works via cellular mito-
chondria. Based on these results, Lee and colleagues concluded that aspirin promotes TRAIL cytoxicity may provide a new therapeutic angle for treating particularly aggressive cancers.

Selected Research Highlights

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has demonstrated selective apoptosis induction in cancer cells with minimal toxicity to normal tissues, but not all cancers are sensitive to TRAIL-mediated apoptosis. Yvon Jung Lee, Ph.D., and colleagues have observed that pancreatic cancer with acetylsalicylic acid (aspirin) augments TRAIL-induced apoptosis in human prostate adenocarcinoma and human colorectal carcinoma cells. Western blot analysis showed that aspirin pretreatment followed by TRAIL activated caspases and cleaved poly(ADP-ribose) polymerase in tumor cells, confirming that the treatment did, in fact, stimulate apoptosis in these cells. The researchers found that at least 12 hours of aspirin pretreatment was required to promote TRAIL-induced apoptosis and also appeared to down-regulate BCL-2 protein production. Additional studies revealed that BCL-2 protein overexpression suppressed the protective effect of aspirin on TRAIL-induced apoptosis, suggesting that TRAIL works via cellular mito-
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Various venous and visceral vascular problems. The division works closely with interventional radiology to manage vascular endoluminal imaging for treatment of aneurysms and occlusions. Basic research in the division involves vascular tissue engineering, the effects of nitric oxide on vascular endothelium, biomechanical forces on vascular biology, and pathology using organ culture. Recent clinical investigations have focused on abdominal aortic aneurysms, endografts, and gene therapy.
The Department of Urology aims to become a premier center for urologic care and research through outstanding patient care, scientific inquiry, and discovery. Clinical faculty members specialize in prostate cancer, benign prostatic hyperplasia, renal cancer, female urology, and kidney stones. Members of the department also collaborate with colleagues at the University of Pittsburgh Cancer Institute to develop innovative protocols for cancer management. The department's state-of-the-art research facility at Shadyside Hospital houses research laboratories for neurourolgy, oncology, transgenic mouse models, tumor biomarkers, gene therapy, and tissue engineering.

Residency and Fellowship Training Residencies are available in all aspects of adult and pediatric urology, including urologic oncology, general urology, urodynamics, female urology, reconstructive surgery, endourology, laparoscopy, stone disease, and sexual dysfunction. The department also has a training program for physicians, residents, and scientists in applied basic science relevant to urologic disease. The overall focus of the training program is on the molecular biology of neuroepithelial development, cancer, function, and inflammation.

Selected Research Highlights Benign prostatic hyperplasia (BHP), also known as enlarged prostate, affects more than half of men older than 60 and 80 percent of men older than 80. Fifty percent of those with BHP exhibit symptoms, including urologic oncology, general urology, urodynamics, female urology, reconstructive surgery, endourology, laparoscopy, stone disease, and sexual dysfunction. The department also has a training program for physicians, residents, and scientists in applied basic science relevant to urologic disease. The overall focus of the training program is on the molecular biology of neuroepithelial development, cancer, function, and inflammation.

The researchers determined that tumor cells expressing PMSA (LNCaP) experience a growth advantage when cultured in a low folate environment with polyglutamated folates. No such advantage was observed in non PMSA prostate tumor cells (DU-145). In addition, the PMSA-specific folate hydratase inhibitor 2-(phosphonomethyl)-pentanedioic acid (2-PMPA) attenuated the increased growth in LNCaP cells but had no effect on DU-145 cells. Baci and colleagues plan to extend their studies to investigate the role of folate consumption in prostate cancer. Research laboratories for neurourolgy, oncology, transgenic mouse models, tumor biomarkers, gene therapy, and tissue engineering.

Zhou Wang, Ph.D., is characterizing androgen receptor (AR) intracellular trafficking in androgen-refractory prostate cancer cells, which are classified by ligand-independent AR internalization. Initial prostate cancer development is dependent on androgen; however, following androgen ablation therapy, androgen-refractory prostate cancer cells remain active, necessitating alternative therapeutic interventions. Because AR nuclear localization is a prerequisite for transcriptional activation, Wang, in collaboration with researchers at the Feinberg School of Medicine at Northwestern University, examined this mechanism in androgen-refractory prostate cancer. The researchers used a green fluorescent protein (GFP)-tagged AR to first confirm that AR internalization in these cells is truly androgen-independent. Then, they observed that the heat shock protein 90 (hsp90) inhibitor, 17-allylamino-17-demethoxygeldanamycin (17-AAG), inhibited basal prostate specific antigen expression and disrupted ligand-independent AR nuclear localization. These findings demonstrate that hsp90 is a key regulator of ligand-independent nuclear localization and may provide an appropriate theraeutic target for androgen-refractory prostate cancer cells.

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