

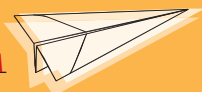
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE | FALL 2013

PITTMED



REJECTION RECONSIDERED

TOMORROW IS ANOTHER DAY FOR
TRANSPLANT IMMUNOTHERAPY.



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Medcast”)

IABC Pittsburgh Golden Triangle
Award of Honor, Magazines

2013 Press Club of Western Pennsylvania,
Golden Quill Award, Health/Science/
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(J. Miksch, “The Meaning of Life,
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MORE WOW!

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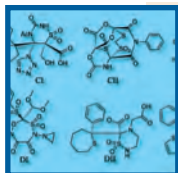
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PITTMED

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE MAGAZINE, FALL 2013

VOL. 15, ISSUE 3



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40 1/2

CONTRIBUTORS

In the early 1980s, **SALLY ANN FLECKER** ["Rejection Reconsidered," p. 12] wanted an MBA. "I went looking for a writing class to help me bone up for the graduate-level papers I expected to have to write. ... Thinking writing was writing, I signed up for 'magazine writing,' and found myself unexpectedly enthralled with the process of finding and telling a story." By the next semester, she was enrolling in classes like "strategic communications" rather than MBA fare, a choice that eventually led her to join *Pitt Magazine's* staff, serving as editor-in-chief for 11 of her 13 years there. Today, Flecker is a freelance writer/editor for college and university publications, including those at Pomona College, Sarah Lawrence, Notre Dame's Mendoza College of Business, Duke, Carnegie Mellon University, and, of course, *Pitt Med*.

ANDRE BURTON, alumni associate for the Medical Alumni Association since March, says the best part about his job is interacting with students and alums. In recent months, with philanthropic support from the School of Medicine, the MAA awarded several summer enrichment scholarships, sending eager young med students overseas for global-health work in Kenya, Mozambique, and Nigeria. "It's a great feeling, helping them out. It reminds you of why we do what we do," says Burton. In addition to supporting MAA's communications, events, and budget, he also serves as *Pitt Med's* circulation manager. Burton, who received his bachelor's in communication and media studies from Pitt in 2008, is now pursuing a master of education degree from the School of Education's higher education management program.

COVER

Turns out, organ rejection in transplantation doesn't happen for the reasons scientists had assumed. And frankly, a lot of people are going to give a damn about these findings by Pitt researchers. (Cover: Clark Gable and Vivien Leigh publicity still for *Gone With The Wind*, 1936. © Getty Images.)



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If you want to learn to swim, jump into the water. On dry land, no frame of mind is ever going to help you. —Bruce Lee

Have you heard about the Benjamin Button jellyfish? This tiny hydrozoan, *Turritopsis dohrnii*, has the uncanny ability to regenerate with such success and frequency it's been called "immortal." Not only does the jellyfish regenerate, but it seems to age backwards. (Hence the reference to Fitzgerald's Benjamin Button character.) The organism starts out as a polyp, then transforms into a medusa. If attacked or sickened, the medusa will collapse into a gelatinous ball and then, within days, become a polyp, and the cycle starts all over again. Not surprisingly, this astonishing creature's population keeps growing, swarming the oceans. Yet only a few scientists study *Turritopsis*, in hopes of learning something about the aging process; the most resolute among them aspire to discover a biological fountain of youth.

Speaking of aging and aquatics, meet the single-celled pond swimmer *Tetrahymena*. It has tons of chromosomes, the ends of which seemed less complex than those of other animals. For these reasons, in the 1970s, Elizabeth Blackburn studied *Tetrahymena's* chromosomal ends (like the caps on shoelaces) where she found an odd "stutter" of DNA sequence repeats. It turns out, these stutters, or telomeres, are shared by all eukaryotes (including us, of course), and play roles in cellular lifespan, cancer, stress, and diseases of accelerated aging. Blackburn shared a 2009 Nobel Prize for her telomere findings, which *Tetrahymena* made possible. Other scientists discovered catalytic RNAs by studying this organism (resulting in the critter's earlier Nobel triumph in 1989), as well as a host of important cellular acrobatics, including synchronized cellular division. The endlessly intriguing *Tetrahymena* happens to have two nuclei, and, believe it or not, seven different sexes—that can mate in 21 combinations. The organism "decides" which sex it will be.

Some of the fish tanks here at Pitt hold clues to another critical aspect of human biology, "innate" immunity. Like a sea sponge or a coral, the *Hydractinia symbiolongicarpus* is an ocean-dwelling colonizer. As it comes across other *Hydractinia*, the animal makes a determination of whether or not to fuse—i.e., allow the newcomer to join it or not. What *Hydractinia* does in these instances is a lot like what our frontline immune defenses do. This salty has been inspiring two scientists in our Starzl Transplantation Institute, Fadi Lakkis and Matthew Nicotra; they are using the *Hydractinia* model to address what have long seemed to be intractable issues of organ rejection.

We haven't even left the water yet, but I could tell you much more about insights that scientists are gleaning from "exotic" and "primitive" organisms. What these cases share is a willingness by some granting entity, as well as individual scientists, to value the deep and hard work of basic science and to take risks. These leaps of faith not only tell us more about the animal kingdom, of which we are members, but often they set a path to new therapies. And sometimes they shift our thinking in fields where we seem to be at a scientific dead end.

But for all we learn from animal models, be they jellyfish or mice, we still need to understand the workings of the human body—or I should say "bodies." Of late, it seems that every few weeks there's another startling finding about how complex and person-specific human biology really is. Maybe we shouldn't be so surprised. After all, our cells have evolved over 3 billion years; I doubt that even our hugely talented faculty could fully illuminate this complexity during a four-year grant cycle!

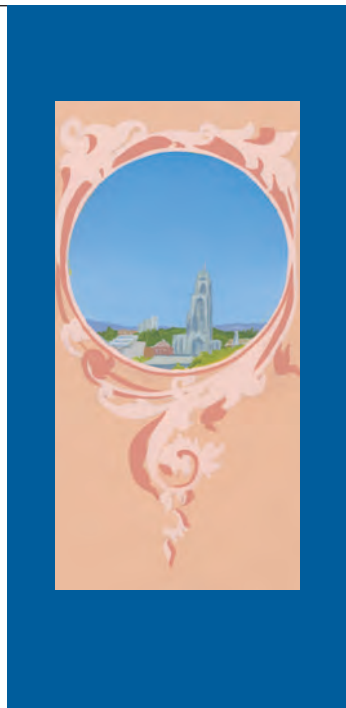


JOSHUA FRANZOS

Arthur S. Levine, MD

Senior Vice Chancellor for the Health Sciences

John and Gertrude Petersen Dean, School of Medicine



*Devoted to noteworthy happenings
at the medical school*

Opening Airways

Thanks in large part to TV advertisements, people perceive asthma to be a mild disease—a kid hops to the sidelines for a few puffs of albuterol and then dashes back into the soccer game. This image, however, does not represent the 10 to 20 percent of asthmatics who have trouble controlling symptoms despite the use of inhaled steroids and beta agonists.

Sally Wenzel, an MD professor of medicine at Pitt and director of the Pitt/UPMC Asthma Institute, recently identified a blood marker found to be elevated in a subset of patients whose asthma fails to respond to conventional treatments. A complete blood count, a test costing about \$20, can measure levels of eosinophils (a type of white blood cell), which are usually associated with allergy, asthma, and asthma exacerbation. Patients with eosinophil levels greater than 300 per microliter, Wenzel found, are responsive to a new molecularly targeted treatment called dupilumab. After four weeks, patients receiving the injections were able to taper off their inhalers. Wenzel says, “Our findings were dramatic. Nearly all patients using the injections reported improvement in symptoms, control of their asthma, and substantial improvement in lung function.” —*Katy Rank Lev*

FOOTNOTE

The rock festival Lollapalooza got its start in 1991, headlined by Jane’s Addiction. **Sciencepalooza!** at Pitt wasn’t as rockin’, but it was, doubtless, more educational. More than 200 youngsters from area YMCAs and YWCAs spent August 9 on campus learning about physics, biomagnification, and alternative energy under the aegis of **PittScienceOutreach**, a branch of the University’s Clinical and Translational Science Institute.

COURTESY MAGGIE McDONALD



Atrium of the main building on the Nazarbayev University campus. In fall 2015, that university will open Kazakhstan’s first academic medical center.

LENDING A HAND IN KAZAKHSTAN

We’ve got a darn good med school here at Pitt. Nazarbayev University (NU), in Kazakhstan’s capital city of Astana, doesn’t have one at all. But that’s about to change.

In July, the University of Pittsburgh School of Medicine agreed to advise NU in the design and development of facilities, the creation of curriculum, and the art of assembling a fine faculty.

The partnership lays the foundation for what Pitt’s Maggie McDonald, PhD associate vice chancellor for academic affairs, health sciences, describes as what will be the first real academic medical center in this country of 17 million. (UPMC is also building national oncology centers throughout Kazakhstan.)

The school is expected to open in the fall of 2015. The partnership, says Arthur S. Levine, an MD, Pitt’s senior vice chancellor for the health sciences, and Peterson Dean of Medicine, helps the University of Pittsburgh expand its presence globally. And, he says, it will give the Kazakhs “the knowledge and experience they need to institute a U.S.-style curriculum to train their republic’s new doctors and biomedical researchers.” —*Joe Miksch*



CAMI MESA

Overheard

Nursing Is Good for Mothers, Too

Eleanor Bimla Schwarz (shown above) noticed something as a new mom: “If you have a chance to look at bottled breast milk, [you’ll see] it has so much cream on the top that it can look a lot like butter.” This led her to wonder, *What does releasing milk do to the body of a new mother? And what happens to the bodies of mothers who do not breast-feed?* The MD director of Pitt’s Women’s Health Services Research Unit for the Center for Research on Health Care and associate professor of medicine, of obstetrics, gynecology, and reproductive sciences, as well as of epidemiology, has probed these questions for a decade. She now believes that moms who don’t breast-feed face a greater risk of breast cancer and heart disease, conditions on which our country spends nearly a billion dollars yearly for care.

Why is hypertension more common in women who do not breast-feed? What we’ve seen in our studies is that moms who don’t breast-feed end up with more “belly fat,” which causes diabetes and high blood pressure. The hormones that are involved in breast-feeding (oxytocin and prolactin) both have effects on blood pressure. Moms who don’t breast-feed end up with more calcium deposits in their blood vessels and are pretty dramatically more likely—like five times more likely—to have early signs of heart disease than moms who did breast-feed for at least three months after each birth.

How do your conclusions account for factors like how women who are inclined to breast-feed may also be more inclined to stay fit? Our studies controlled for many aspects of women’s lifestyles (like diet, exercise, smoking, and alcohol consumption) as well as their age, number of pregnancies, sociodemographic characteristics, and family history. This is one of those situations—like proving that parachutes work—where randomized trials aren’t really feasible, so we have to draw conclusions from the data we have.

Is there an optimal amount of time for maternal health for length of breast-feeding? I don’t have a precise answer there, but it looks like moms who breast-feed for less than nine months after their first birth have an increased risk of needing medicine for high blood pressure in the future. When we looked at diabetes, we saw pretty big differences between moms who breast-feed for one month and moms who didn’t breast-feed at all, who were at a much higher risk. So my message to new moms about breastfeeding is, “Give it a try.”

—Interview by Joe Miksch

Next Generation

Kathlene Babalola, a third-year student at the School of Medicine, is being honored with an American

Medical Association Minority Scholars Award for her work as a volunteer HIV counselor and coordinator at a women’s center and shelter in Pittsburgh, as well as for her ovarian cancer research with Pitt’s Anda Vlad (PhD ’02, Fel ’04) MD/PhD assistant professor of obstetrics, gynecology, and reproductive sciences, as well as immunology.

Before enrolling at Pitt, Babalola was a research scientist for Bristol-Myers Squibb and Wyeth/Pfizer Pharmaceuticals. She was recently selected as an Albert Schweitzer Fellow for her project in which she partnered with fellow third-year student Mildred Duvet to develop a curriculum with a local junior high school about intimate partner violence and healthy relationships.

Babalola was one of only eight medical students to receive this merit award, which includes a \$10,000 scholarship.

Michelle Rivera-Vega has won a FLARE Award (Future Leaders Advancing Research in Endocrinology) from the Endocrine Society. Rivera-Vega is a second-year fellow in pediatric endocrinology at Children’s Hospital of Pittsburgh of UPMC. She was recognized for her work evaluating type 2 diabetes and obesity. FLARE interns serve as leaders on Society-based governance committees for one year and as mentors to undergraduate students in the Minority Access Program, which is designed to encourage young people from underrepresented groups to pursue advanced degrees in the biomedical sciences.

As part of her pediatric endocrinology training, Rivera-Vega is evaluating clinical and biochemical characteristics of youth with obesity and type 2 diabetes. She’s also assessing their insulin sensitivity.

—Jeff Ihaza

Beat Depression, Live Longer and Better

Depression is tough to live with on a number of levels. A recent analysis undertaken by Pitt's Charles Reynolds III and colleagues shows that people diagnosed with late-life depression are 1.85 times more likely to develop dementia, 1.65 times more likely to develop Alzheimer's disease, and 2.5 times more likely to develop vascular dementia, in which a limited blood supply to the brain causes the death of brain cells.

The study, published in May in the *British Journal of Psychiatry*, reconfirmed the link between Alzheimer's and depression. It also was among the first, in a prospective cohort study, to confirm a stronger link to vascular dementia than to Alzheimer's dementia.

Reynolds, an MD, is the UPMC Professor of Geriatric Psychiatry and is also professor of neurology, neuroscience, and behavioral and community health at Pitt. About 15 percent of people 65 or older suffer from depression in the United States.

"We need to [help people] prevent depression by learning better coping strategies, better strategies for sleep, ... exercise, and ... nutrition," Reynolds says. He adds that doctors can also reduce risk by intervening early with talk therapy and teaching positive lifestyle changes that promote brain health and cognitive fitness. —JM

CATHERINE LAZURE



CHAMPIONS FOR KIDS

More than 1,500 children die every year as a result of abuse in this country.

A team of professionals at Children's Hospital of Pittsburgh of UPMC is looking out for area children.

Rachel Berger, an MD/MPH, is the new chief of the Division of Child Advocacy at Children's Hospital. This center is responsible for evaluating children who may be victims of physical or sexual abuse or neglect. Her team is trained to evaluate children who end up at Children's as a result of injuries. Berger and her colleagues also evaluate children referred by police, pediatricians, or child welfare agencies. The team investigated 1,826 cases of suspected abuse in 2011.

Berger, an associate professor of pediatrics at Pitt, is the principal investigator for a multicenter National Institutes of Health-funded study that seeks to develop a blood test that could indicate brain damage in young children and assist in early detection of brain trauma in children (like shaken baby syndrome). She has spent the past decade as a researcher trying to improve methods of early detection of abuse. "Parents don't come in and tell us, 'I shook my baby,'" she says.

Berger would also like to develop a program to address the secondary trauma faced by professionals who work with abused children. "We see things we wouldn't want our own children to know exist," she says. —Nick



PHOTO COURTESY RACHEL BERGER. PHOTO ILLUSTRATION: MICHAEL LOTENARO.



COURTESY CARL SNYDERMAN

FROM HERE TO SLOVENIA

In Slovenia, a man who has been suffering from vision loss from a small pituitary tumor at the base of his skull is wheeled into an operating room. His surgeons, faculty at the University of Maribor, are skilled, but they're not expert at removing such tumors through the nose via endoscope, a procedure that was developed here in Pittsburgh by Carl Snyderman (an MD/MBA and professor of otolaryngology and neurological surgery) and others at Pitt. The technique avoids disfigurement from facial incisions, limits brain and nerve trauma, and allows for shorter recovery time.

In Pittsburgh, Snyderman, shown above, who is also codirector of the UPMC Center for Cranial Base Surgery, looks up at a computer monitor to watch the Slovenians work and offer his expertise. Telementoring, he calls it. (The Slovenians came to Pitt for in-person training before any telementoring took place.)

"We help with diagnosis, the interpretation of scans," Snyderman says. "We give advice on technique, tools, reconstruction, where a nerve is. We do this for about two hours of what's usually a six-hour surgery, and we do it early in the morning here before the workday starts."

The center's codirector Paul Gardner, an MD and Pitt associate professor of neurological surgery, also consulted on the Slovenian man's case. "The surgery went fine," Snyderman reports later. "Dr. Gardner was able to provide guidance regarding extent of exposure, dissection technique, extent of resection, and reconstruction."

Snyderman and Gardner have telementored eight procedures in Slovenia. They're engaged in talks to expand the program to Russia, China, and India.

Telementoring, Snyderman says, kind of allows him to be in two places at once. "If I had to travel, I couldn't do surgeries here. And teaching someone how to fish is more valuable than giving [him] a fish." —JM

Name Dropping

When **Huda Zoghbi**, the winner of Pitt's Dickson Prize in Medicine for 2013, was a pediatrics resident at Baylor College of Medicine in the early 1980s, she saw girls with Rett syndrome. The motor skills and cognitive abilities of these young patients develop normally for about a year—then they lose the language and motor skills they've already acquired. This intrigued Zoghbi.

"This isn't a degenerative process. All the cells still seem to be there (once symptoms emerge). And it's not a developmental problem from birth, in which neural tracts are missing," she says. Since the MD's introduction to Rett, Zoghbi has teased out the syndrome's genetic basis (an error in MECP2, a gene that codes for a protein important for mature brain cells) and is hopeful that she may be able to someday "find something to substitute for the lost protein. The cells are there, waiting for something to substitute for the function of MECP2," she says.

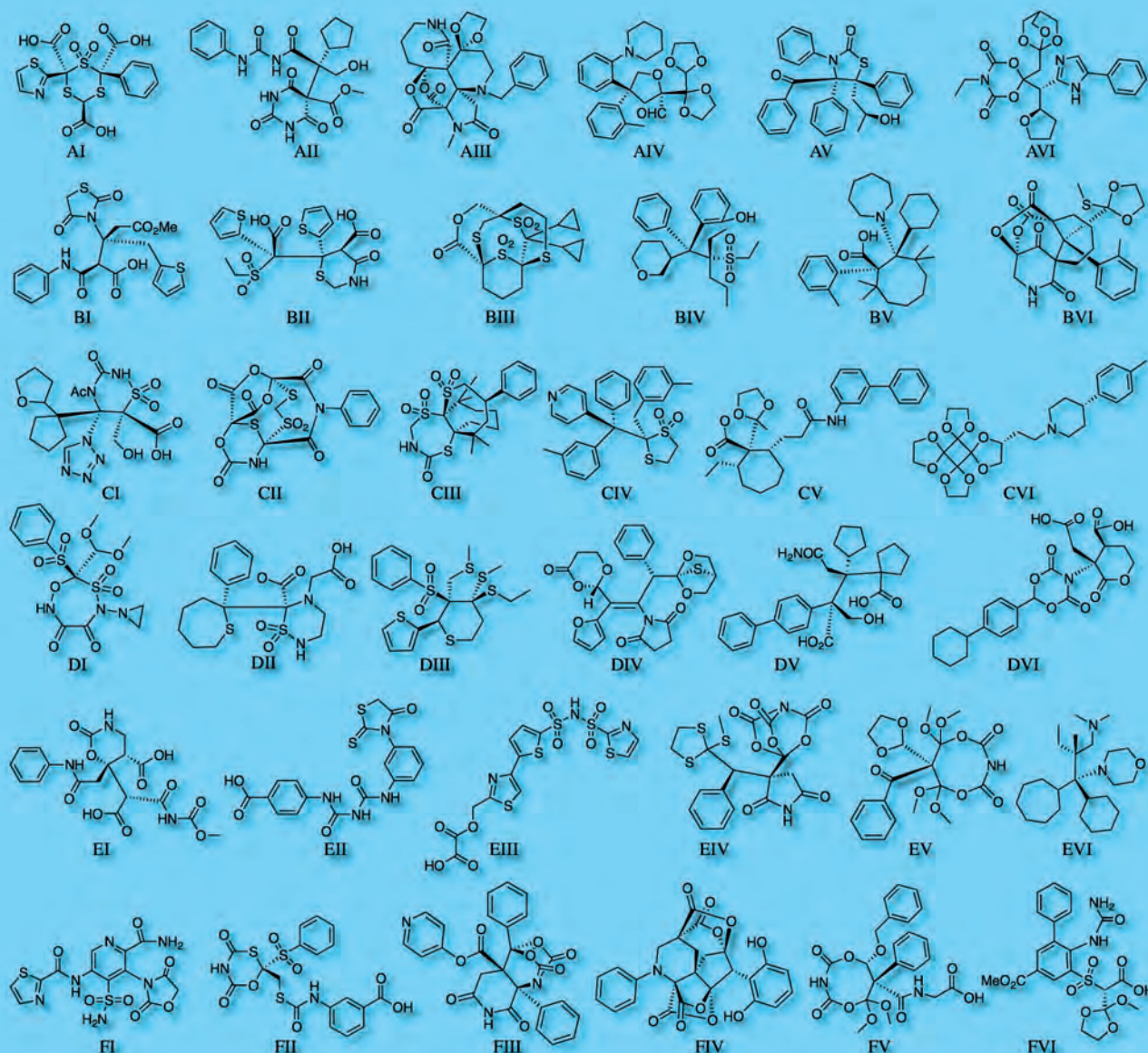
The professor of molecular and human genetics at Baylor delivered the Dickson Lecture on October 3. Her appearance was part of Pitt's Science2013—Convergence, the University's annual showcase of advances in medicine, science, engineering, and computation.

Science2013's other plenary speakers included...

Alexander Varshavsky, a PhD and the Smits Professor of Cell Biology at the California Institute of Technology. He delivered the Mellon Lecture. Varshavsky is an expert on the functions of ubiquitin, a small regulatory protein, which, as the name implies, is found throughout the body.

Napoleone Ferrara, an MD who went from Genentech to the University of California San Diego, where he is a Distinguished Professor of Pathology. Ferrara gave the Hofmann Lecture on his work exploring vascular endothelial growth factor, an effort that resulted in his winning the Lasker-DeBakey Clinical Medical Research Award.

And, from closer to home, Carnegie Mellon University's new president, **Subra Suresh**. Suresh, an ScD, directed the National Science Foundation from 2010 to 2013 after serving three years as dean of the Massachusetts Institute of Technology School of Engineering. He presented the Provost Lecture. —JM



SMALL WONDERS, BIG UNIVERSE

An invisible universe of all possible organic molecules is truly the final frontier—the exploits of the *USS Enterprise* and her crew notwithstanding—according to Pitt synthetic chemist Peter Wipf, a Distinguished University Professor who collaborates with many Pitt med people. The vast, unmapped chemical no-man's-land is as compelling to Wipf as outer space is to Captain Kirk. Discovering useful compounds that no one has seen or imagined could very well address humanity's most vexing problems, from the need for energy sources to treatments for disease.

But new compound discoverers like Wipf face daunting odds. Trying to locate a specific molecule in the vast chemical universe made up of at least 10^{60} (a novemdecillion) different compounds is akin to the *Enterprise* making a random warp jump without the benefit of specific coordinates—scientists could end up anywhere. And they do all the time. Finding specific compounds with particular properties is not simple. Enter the Small Molecule Universe Project.

Wipf and colleagues at Duke University have created an algorithm called ACSESS (Algorithm for Chemical Space Exploration with Stochastic Search) that generates a map of molecular space. The algorithm plots all known organic compounds (anything with carbon) within a range of molecular weights. Then it creates a library of novel compounds as researchers feed in parameters. If you want to improve on properties of a known molecule, the algorithm will help you discover related molecules that can be synthesized in the lab. The catch is that you need to know where you are going—and that prospect could turn traditional drug development on its head. Typically, researchers search for new drugs within the relatively small collection of molecules that we already know exists. But by feeding progressive sets of coordinates into this chemical warp drive, says Wipf, scientists can build a custom molecule, bit by bit, to perfectly address the molecular properties of a given problem.

—Jenifer Lienau Thompson
—Diagram Courtesy Wipf Lab

INVESTIGATIONS

Explorations and revelations taking place in the medical school



Tsinghua University scholars Yang Gao (left) and his roommate, Wei Li, take part in the second annual Pitt-Tsinghua scientific symposium held in April 2013. Gao is investigating the role of inflammatory-related electrophilic fatty acid derivatives in airway dysfunction related to allergic pulmonary diseases. Li is studying potential neuroprotective mechanisms of melatonin in an animal model of ischemic stroke.

“WE ARE FRIENDS.”

**TSINGHUA STUDENTS
HAVE A NEW SCIENTIFIC HOME
BY CHUCK STARESINIC
PHOTOS BY JOHN ALTDORFER**

REPRINTED WITH PERMISSION FROM *NEXT*,
THE SCHOOL'S 2013 ANNUAL REPORT.

On his way to a symposium at the University of Pittsburgh in April, Yigong Shi, a PhD, dean of Tsinghua University's School of Life Sciences, and executive vice dean of its School of Medicine, declined to fly the last leg of his trip from Beijing. Instead he elected to deplane in Chicago, visit colleagues in Illinois, then drive the 460 miles to Pittsburgh, solo.

It felt like coming home, says Shi.

He had first arrived in this country in 1990 to begin a PhD program in molecular biophysics at Johns Hopkins University and remained until 2008, when he gave up a prestigious endowed professorship at Princeton University to return to Tsinghua, his alma mater.

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

And, now, 21 Tsinghua students are making the United States a second home, too.

Shi's road trip would bring him to the second annual Joint Symposium on Medical Sciences—an unprecedented collaboration between the medical schools at Pitt and Tsinghua.

The students, who arrived at Pitt in August 2012 to begin two years of intensive biomedical research training, have been welcomed by a community eager to provide an unforgettable experience.

As the students came together to formally showcase their work for the first time at the symposium, we had a chance to see how the

program was panning out.

Lijia Cui says that she has quickly fallen in love with the unfamiliar, hilly terrain of Pittsburgh, despite the fact that it exhausts her when she bicycles around the city. She was assigned to the lab of Elodie Ghedin, a PhD, MacArthur Fellow, and associate professor of computational and systems biology. Cui was nervous at first about being in an American lab because she still has a lot to learn about conversational English. In Ghedin's lab, however, she found herself on a team with Americans, Canadians, and an Indian, so the addition of a Chinese med student wasn't out of the ordinary.

“We are friends,” Cui says now.

Ghedin's lab studies the genomics of infectious diseases. Working with her new colleagues, Cui developed an experiment using next-generation DNA sequencing to study the fungal microbiome in patients with both HIV and chronic obstructive pulmonary disease (COPD), which tend to co-occur. Her studies yielded 19 fungal genera in these patients that did not show up in healthy controls—only four of which had previously been associated with HIV and COPD in the scientific literature. Next steps for Cui include further research to determine whether fungi are driving COPD symptoms in these patients and how.

Ghedin says that having Cui in the lab has been a boost to the team. Lab staff members are supported by multiple grants, so each member has multiple areas of responsibility. But the Tsinghua students, funded by the collaborative agreement between the partner universities and the Chinese government, are able to focus on one project at a time.

“Because of limited resources, we weren't even going to do this experiment,” says Ghedin. “But now she is finding really interesting stuff that is going to lead to further research.”

Another student, Luxi Sun, says that the Pitt-Tsinghua program is exactly what she'd hoped it would be. The daughter of two developmental biologists working at the Chinese Academy of Sciences, Sun arrived with a good sense of what interests her. She was thrilled to find that Pitt has a strong and welcoming research program in DNA damage and repair mechanisms. The genome stability group, as it is called, includes multiple investigators from the medical school and the University of Pittsburgh Cancer Institute, including med school dean Arthur S. Levine, who is also senior vice chancellor for the health sciences. Sun is working with mentor Li Lan, an MD/PhD assistant professor of microbiology and molecular genetics. Sun is helping the lab team elucidate DNA-damage-response mechanisms that could have important implications for cancer and aging. Lan and others have figured out a way to induce damage in specific locations in a genome using the fluorescent protein KillerRed; they then observe DNA repair proteins as they migrate to fix the damage in live cells. Sun's contributions to the lab's work have already led to coauthorship on a forthcoming publication in *The Journal of Cell Biology*.

As for life in Pittsburgh, Sun is surprised and delighted by how easy it has been to explore American culture. She has taken in the Pittsburgh Symphony Orchestra performing Beethoven and the national tour of the musical *Chicago*; both performances were



just a short bus ride from campus. She finds Pittsburgh peaceful and says that the environment has allowed her to relax and commit completely to research.

As a driving force behind the collaboration, Levine has always had high expectations of the Tsinghua students. But after spending much of two days with them at the symposium, he declared himself in awe of the students and their work. Both Levine and Shi said at the event that they hope the Tsinghua students come to think of Pittsburgh as their alma mater.

Further cementing the bonds between these two institutions, the final day of the symposium included a gift from one longtime friend and colleague to another. When he was a grad student at Johns Hopkins, Shi was mentored by Jeremy Berg, a PhD, Pitt's associate senior vice chancellor for sci-

ence strategy and planning, health sciences, and director of the Pitt-UPMC Institute for Personalized Medicine. Berg presented Shi with a 3-D model of a protein for which Shi had determined the crystal structure. Berg also announced that Shi had learned that very day that he was among 21 foreign associates elected to the U.S. National Academy of Sciences—a rare honor.

Shi raised his gift in the air and spoke of the personal connections the students and mentors will make in their scientific careers. Some 23 years after first meeting Berg, who is scientific director of the Pitt-Tsinghua program, he is still a valued mentor, Shi said—now for the Tsinghua students.

"You are like the grandsons and granddaughters of Jeremy," he said.

The next family reunion will be in Beijing in 2014. ■

Yigong Shi (middle row, left), now dean of China's Tsinghua University School of the Life Sciences and executive vice dean of its School of Medicine, drove 22 hours from Iowa to Johns Hopkins to start his PhD work. Current Tsinghua students are traveling too—to Pittsburgh for two years of intensive biomedical research training. In April, Pitt med dean Arthur S. Levine (bottom row, left) and associate senior vice chancellor for science strategy and planning Jeremy Berg (a former Shi mentor, standing with his former mentee, middle row, right), welcomed the Tsinghua contingent to the second annual Joint Symposium on Medical Sciences, where the Chinese students presented on their first year's work in Pitt labs.

DAY 1

DAY 5

DAY 7

38 mm³211 mm³377 mm³

DAY 1

DAY 5

DAY 7

36 mm³21 mm³49 mm³

BLOWN OPEN

MICROBUBBLES BURST CANCER'S
GENETIC MATERIAL | BY DANA YATES

Villanueva has discovered a novel way to use microbubbles for cancer therapy. Here, serial 3-D images of tumors followed over the course of one week—one treated with control microbubbles (top row), the other treated with microbubbles carrying a nucleic acid that suppresses the tumor's epidermal growth factor receptor production—show tumor-growth inhibition in the latter tumor.

As scientists continue to discover promising new methods of treating cancer at the genetic level, one nagging question persists: How to administer them efficiently?

Flordeliza Villanueva, professor of medicine at Pitt and director of Noninvasive Cardiac Imaging at UPMC Presbyterian and of the Center for Ultrasound Molecular Imaging and Therapeutics (CUMIT) at UPMC's Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute, has shown that microbubbles—gas-filled globules that are smaller than red blood cells—can transport potent treatments into tumor cells. She is collaborating with Andrew Carson and Jennifer Grandis from CUMIT and the University of Pittsburgh Cancer Institute, respectively.

Microbubbles have many diagnostic applications. As Villanueva has previously shown, these tiny vesicles can be used to image blood flow to the heart. When injected into the body, microbubbles travel everywhere that red blood cells circulate, and when subjected to ultrasound, they light up inside tissue microvessels. Ultrasound causes the microbubbles to expand and contract rapidly. This activity creates a signal that can be detected by an ultrasound transducer, confirming the microbubbles' location and helping to reveal

information about blood flow to the heart.

Microbubbles also have therapeutic applications as a result of their unique vibrations in response to ultrasound—like chiseling through blood clots. Villanueva is hoping they can penetrate cancer's armor, too.

When microbubbles in the blood vessels are subjected to a particular ultrasound frequency and pressure, they pop, causing temporary leakiness of the outer membranes of blood vessels and nearby cancer cells. The effect is similar to that of a grenade on a fortress; the cancer cell may not crumble, but it will suffer holes and cracks in its protective membrane that leave it vulnerable to entry by drugs. This is where microbubbles can pull double duty.

If an anticancer agent were attached to the exterior of a microbubble and the microbubble were intravenously injected then exposed to ultrasound as it passed through a tumor, Villanueva posited, as the microbubble popped, it might not only poke holes in the cancer cell's membrane but could also release its payload drug, which could then enter the newly porous cancer cell. Importantly, only areas receiving ultrasound would receive the drug, potentially reducing side effects that typically result from drug delivery to non-tumor sites.

Villanueva's research team armed the microbubbles with a powerful cancer-inhibiting agent—a small inhibitory RNA (siRNA) directed against epidermal growth factor receptor (EGFR); the siRNA reduces EGFR production. (EGFR is overproduced by cancer cells and plays a major role in tumor growth.) “Therapeutic nucleic acids are, in general, difficult to deliver into a cancer cell,” she says. “They are fragile when injected into the bloodstream, and when injected directly into a tumor, they leak through the injection site or tumor ulcerations or are actively internalized and destroyed by cancer cells. Microbubbles are designed to get around these hurdles.” The team demonstrated the effectiveness of this siRNA-delivery method in a mouse model of head and neck cancer.

EGFR took a hit. Multiple treatments decreased tumor EGFR expression, and tumors took much longer to grow. The work gives credence to the idea of using customized microbubbles as precision delivery systems of siRNA or other gene-targeted molecules for cancer treatment. The therapy, if it acs clinical trials, may be an effective and noninvasive way to kill tumors—one that could be done at the bedside for outpatients and reduce the side effects of other treatments. ■



PARADIGMS LOST

BY SALLY ANN FLECKER

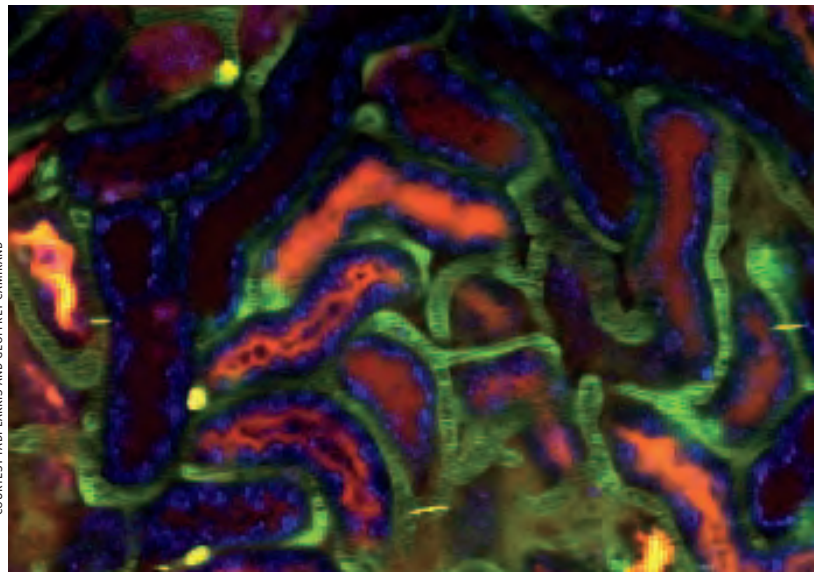
REJECTION RECONSIDERED

Fadi Lakkis, an MD and scientific director of the Thomas E. Starzl Transplantation Institute, appreciates the elegance of simplicity. He has an affinity for the simpler question. He savors a good, clean, simple answer. One summer, before he started medical school at the American University of Beirut, he spent his time reading several books on immunology. One of the books was extremely well, and simply, written, he remembers. “That attracted my attention that someone can explain things in a very simple way,” he says. “It turned out to be quite exciting.”

As the young man progressed through his medical education, the intricacies of kidney disease also captured his imagination, again for the straightforwardness of the physiology. “I found that in nephrology you can diagnose a problem just by understanding the science behind it,” he says. “Instead of having to memorize a set of symptoms and signs and then make a diagnosis, I thought, ‘Oh, if I understood how the kidney handles sodium, I [could] understand why this patient’s sodium is low and what to do to treat it.’ To me it was very appealing that you can start with a very simple thing and then make a very complex diagnosis.”

Frankly, a lot of people are going to give a damn about new findings by Fadi Lakkis and colleagues. It turns out that organ rejection in transplantation doesn’t happen for the reasons scientists had assumed.

THIS PAGE: Newly harnessed imaging technology shows that migration of T cells (bright yellow) into transplanted kidney tissue depends on the presence of what’s called a cognate antigen, rather than chemokines. Researchers can watch the process unfolding in living animals. (Blood vessels are green; epithelium is blue; urine is orange.)



COURTESY FADI LAKKIS AND GEOFFREY CAMIRAND

More recently, Lakkis (professor of surgery, immunology, and medicine, who holds the Frank and Athena Sarris Chair in Transplantation Biology at the University of Pittsburgh) asked a simple biological question about organ rejection in transplant patients. The answer surprised everyone, turned a long-held assumption on end—and just may pave the way for better, and much-hoped-for, antirejection therapies.

Finding a way to achieve tolerance is a lofty goal for many people. For transplant immunologists, it's the quest of a lifetime. Many a transplant scientist has spent a career looking for a way for the human body to accept an organ without having to resort to immunosuppressive medication.

That's not to say that contemporary immunosuppressive medication hasn't been a godsend. It's allowed for countless successful transplants, legions of lives saved. And over the years the regimen has been finessed, most notably by Pitt's Thomas E. Starzl. Starzl developed a two-pronged immunosuppressive approach that reduces the amount of drugs a transplant patient takes. Even at the minimum effective dosage, though, the side effects can be unpleasant—and a suppressed immune system lacks the basic ammunition to fight off opportunistic infections and other attacks on the body, such as malignancies.

There are some reports of patients, a handful, becoming tolerant of grafted organs on their own. In other cases, bone marrow transplants have convinced the immune system to halt the attack on the organ. "It's a little bit drastic," Lakkis says of that approach. Patients have to undergo chemotherapy or radiation to eliminate their own bone marrow, which leaves them at great risk for infection until the donor bone marrow starts to kick in. "It's a bit too much for someone coming in for a kidney transplant," says Lakkis, especially knowing that the immunosuppressive medications are a feasible, if not perfect, course of action.

So the search for tolerance continues. A few years ago, Lakkis decided to go about it from a different angle. "When something has been resistant to good solutions for so many years," he says, "you start worrying a bit that you've been missing something." He decided to question the fundamental mechanisms of rejection—starting with a paradigm that has

been accepted for the past 25 years.

"Organ rejection may seem quite complex," he says. "In reality, it's dependent on a single cell type—without that cell type, rejection will not happen. That cell is the T cell. If you take an animal or human that does not have T cells, they will not reject." The T cell is a lymphocyte, a type of white blood cell originating in the thymus (hence the "T"). It has to get activated—prepared for duty—before it can go to the transplanted organ and initiate rejection. Some T cells are memory cells; they're already primed by past infections or vaccinations to fight the foreign tissue. Other T cells are naïve and have to be turned into effector T cells before they're ready to go up against what they perceive to be the enemy—the grafted tissue.

Lakkis was interested in taking another look at exactly *how* the activated T cells got to the graft. The paradigm involved chemokines—a flexible set of small proteins that can handily fold themselves up and pass through from one side of a membrane to the other. When tissue is inflamed, certain chemokines are present in droves. And a transplanted organ will inevitably result in lots of inflammation, particularly in the delicate endothelium lining of blood vessels.

The long-held assumption was that the crowd of chemokines signaled the T cells to get their attention. An inflamed endothelium is a sticky place. The T cells would slowly roll through the endothelium to the chemokines. Once they met up, receptors on the T cells would bind to the chemokines. With the T cell firmly adhered to the chemokine, the T cells slide smoothly through the barrier of the endothelium and into the grafted tissue where the T cells can initiate the rejection process. You can see how it would follow that if you blocked the chemokines from signaling, you would stop the rejection process. However, attempts to do that had been unsuccessful.

Lakkis decided that he would put his lab to work testing that assumption about chemokines. "We, as a group, enjoy asking these very simple, fundamental questions—the wheres and whys and hows," he says. "You can come in with very little baggage—just rid yourself of all assumptions."

This is about when Jeffrey Walch showed up. Walch is an MD/PhD student in the School of Medicine who knows how to make

the most of every minute. (He fit the interview for this story into 10- and 15-minute snippets of time between exams and meetings one afternoon.) In 2007, he had been visiting labs, looking for one that would be a good fit for his doctoral work. He and Lakkis hit it off, and he was taken on. His main project for his PhD would attempt to show exactly how those little chemokines direct the migration of T cells to transplanted organs.

"Fadi had some preliminary data from previous work he had done that was suggesting a particular chemokine receptor called CXCR3 was responsible for directing the cells to the graft that would lead to rejection. When I got to the project, that's where we were," Walch says.

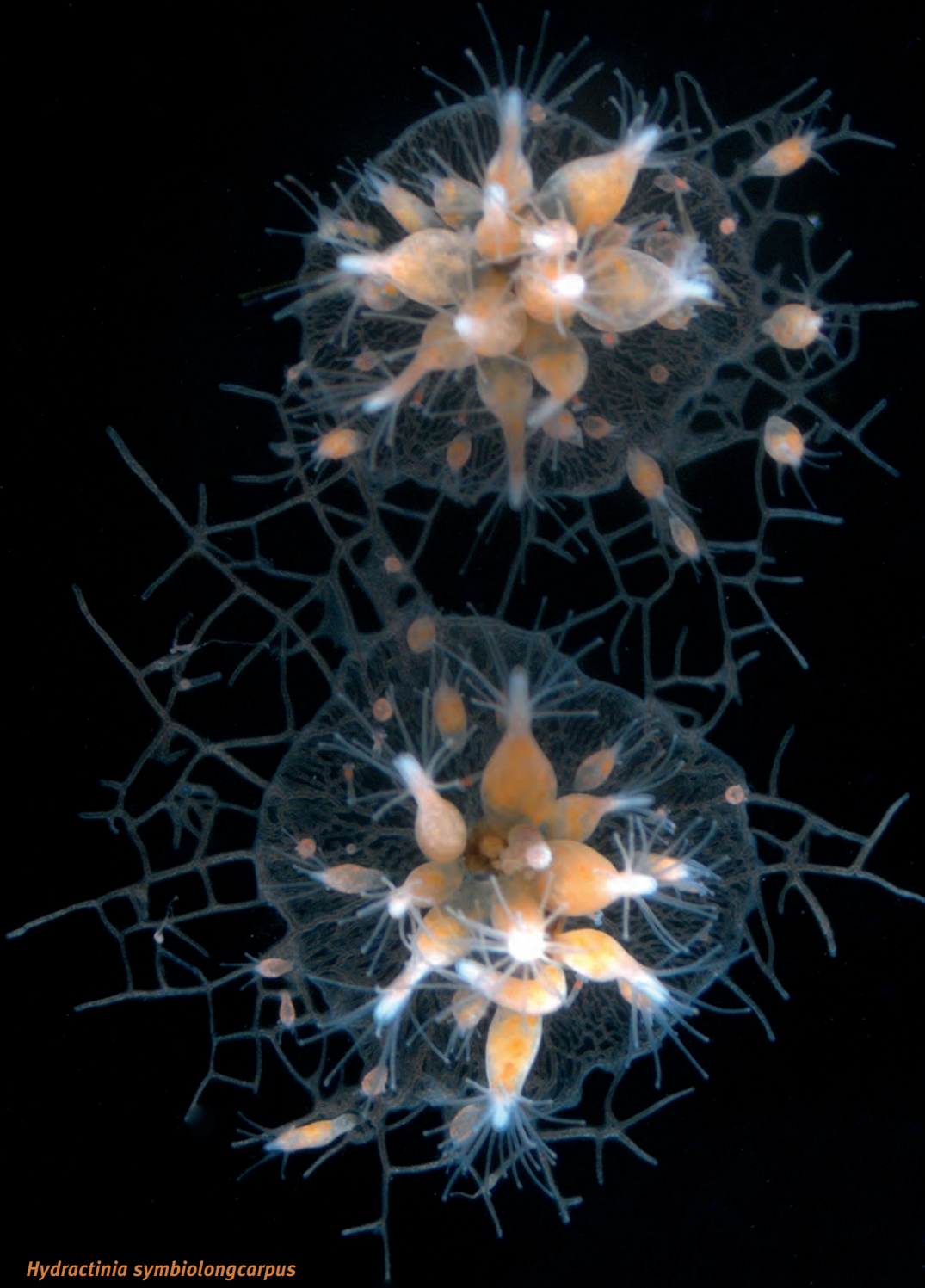
The CXCR3 receptor is highly expressed, meaning that it's found a lot on T cells that are activated. At the same time, it's not found at all on naïve T cells that have not been activated. "It made sense that that had to be the signal," says Lakkis. "We did a very simple experiment. We took cells that do not express CXCR3, put them in the animal." To everyone's surprise, the T cells were able to go in and reject the graft anyway.

Hmmm. What was wrong with this picture? The researchers scratched their heads. Maybe it's another chemokine-receptor pair? There certainly are a lot of them out there. "This is like a jungle, these chemokines. There's so many of them," says Lakkis. "We would have to spend years going through and finding out which one of them is important. And maybe it isn't a single one that is important. Maybe you knock one out and another takes over."

On the other hand, he thought, maybe we've all been wrong for the last quarter century. Maybe the whole process is completely independent of chemokines. He and Walch decided to test that idea, because it certainly was the simpler experiment. There's a toxin made by the bacterium that causes pertussis, or whooping cough. If you add pertussis toxin to cells, it blocks the chemokine receptor's signaling ability. They prepared activated T cells, some with pertussis toxin, others without. If the migration of T cells depended on any kind of chemokine receptors, the T cells treated with pertussis toxin wouldn't be able to reach the graft.

But they still did. The migration of T cells into grafted tissue was not, as had been thought for so long, dependent on chemokines. The notion was revolutionary.

"At this point, we had deviated from where



Hydractinia symbiolongicarpus

the project was initially headed,” Walch says. He changed his dissertation hypothesis regarding how T cells migrate to the grafts. “Because now we didn’t really know—what we thought was working wasn’t working.” For months, Walch pored over the literature from other fields, not just transplantation. He read about different sorts of immune disorders and the central nervous system. When he came across theories that something called a cognate antigen could direct cells, something clicked.

An antigen, of course, is a foreign molecule that revs up an immune response in the body. Experienced T cells are attracted to specific *cognate* antigens—just as a magnet is attracted to a piece of iron but won’t pick up plastic.

While the accepted paradigm had been that T cells are scattered throughout the body and migrate to different areas when chemokines signaled to them, Walch’s new hypothesis suggested a much more efficient system. “It doesn’t matter if you have a bunch of effector T cells if they can’t interact with the cell that expresses the antigen because they don’t respond to that antigen. Then they’re just sort of a bystander cell that is in the area because there’s inflammation,” says Walch. “But if they’re going where their cognate antigen is expressed,

‘ALLO. IS THAT YOU?

Could a marine organism that lives in the shallows of the North Atlantic shed light on the rejection process of transplanted organs in humans? That’s what Pitt’s Matthew Nicotra hopes.

Nicotra, assistant professor of surgery, runs the *Hydractinia* lab at the Starzl Institute. The particular species he studies, *Hydractinia symbiolongicarpus*, is a colonial saltwater animal—like a coral or sea sponge—that grows until it has covered whatever surface it’s attached to. From time to time, *Hydractinia* colonies will bump into one another. When that happens, the *Hydractinia* will either fuse with the others if it senses a good match, or it will fight. But the organism has no eyes, no ears, no nose. How does it know a good match when it doesn’t see one?

There’s an ancient mechanism at work here called *allorecognition*—the ability to distinguish between self and nonself, which has been observed in all colonial marine invertebrates. “That decision to fuse or fight is controlled, in all [of these colonizing] organisms that have been studied so far, by genetic systems that have very diverse genes as the basis for distinguishing self from nonself,” says Nicotra. “And that is sort of analogous to what happens in human transplantation. If you take an organ and put it into a recipient, there are proteins on that organ that are different between people. And those are basically what the recipient’s immune system recognizes as nonself, and that triggers the immune response.”

Nicotra wondered, does the *Hydractinia*’s mechanism of *allorecognition* share an evolutionary history with the human’s innate immune system—the first line of defense against pathogens? So far, his lab has identified the genes that encode the various proteins that are analogous to certain cell-surface molecules called the major histocompatibility complex (MHC) in humans. “Those don’t appear to be similar, but that’s not surprising because those are exactly the proteins that evolution, over at least 500 million years, has been making diverse,” Nicotra says. “Five hundred million years is probably a lowball estimate of the divergence time between *Hydractinia* and humans.” The more likely route to answer this question, he says, is to look at the signaling pathways that control *allorecognition* in the sea creature and compare those pathways to those involved in transplant rejection. Stay tuned as Nicotra’s lab continues to explore the depths of the immune response. —SF

then they're going where they need to go."

What an idea, Walch thought: Activated T cells would only go to where they needed to be.

To test the hypothesis, they put to use a new technology. In 2007, Lakkis had recruited researcher Geoffrey Camirand to the Starzl Institute. Camirand, whose own research interests include studying a subset of T cells called regulatory T cells, worked with Lakkis to set up an intravital imaging system that would be able to look at what is going on inside a living animal. The new system made use of two-photon microscopy. Although the intravital two-photon technology had been available since 2001, the bulk of the research employing it had been looking at how the immune system operates in lymph nodes. Not much had been done using it to study transplants.

To understand why everyone was so excit-

this technology."

They set about testing Walch's hypothesis: Lymphocytes, like T cells, have receptors on them that are very specific to what they are supposed to recognize. "Usually it's a virus or bacteria. But in the setting of a transplant, the antigen could be almost any foreign protein on the [transplanted tissue] that is different from the tissues of the recipient," says Lakkis. The transplanted organ expresses proteins—antigens—that are different from the recipient's because no two people's organs are alike in this way—unless they're identical twins. "We did simple experiments where the T cells are very specific to one antigen, and the transplanted organ has that antigen or it doesn't. And we found that only if the antigen is present do the T cells get in. If the antigen is not present, the T cells cannot get into the tissue of the organ and reject it." As Walch had hypothesized, the migration of T cells into the

But there was an anatomical mystery they had to solve first: How do the dendritic cells, which live in the tissue, get into the blood where the T cells reside?

The handy-dandy two-photon imaging system was able to deliver the answer. Pitt's Martin Oberbarnscheidt, a research assistant professor at the Starzl Institute, discovered that dendritic cells reach into vessels in the kidney. The dendritic cells have little leg-like projections, called dendrites, that actually stick through the blood vessels into the bloodstream.

"The blood vessel is not 100 percent lined with endothelial cells," Lakkis explains. "It's fenestrated. It has windows in it." So when the endothelium cannot present antigen to the T cells, these dendritic cells take over the job by sticking their legs into the bloodstream and presenting antigen to T cells that are going by. "Using the microscopy," Lakkis adds, "we could show that they capture T cells in the

"We've found that there is almost never a fundamental question that is not only worth visiting, but also worth revisiting."

ed about the new imaging system, you have to understand several components. First, the two-photon system was the answer to the problem of the single-photon laser, which is preferable when a higher resolution is needed, for instance, in the imaging of cell organelles. Single-photon technology can make beautiful pictures but can't penetrate deeply, because of the elevated scattering of the high-energy photons within tissues. It can also cause tissue damage. In two-photon microscopy, the photons are concentrated into a single focal point. The point where they meet with a fluorescent molecule is the only point that shines. "And it shines *brilliantly*," Lakkis says. "In that 1-micron focal plane where they meet, you can see the cell that is shining. It emits beautiful fluorescence." (See p. 13.) There's an awestruck note in his voice as he relates this. "You can study the living tissue. It's almost like four-dimensional imaging, because you can tell what it's doing [for] up to 2-and-a-half hours. This is a more definitive technology."

"It's good that we jumped on this technology a few years back," says Camirand, "because now we can apply it to a wide range of transplant-related questions. There's a huge amount of work that can be done with

organ is dependent on the cognate antigen, not the chemokines.

The third part of the work blew yet another theory out of the water. Now that they knew it was the cognate antigens that allowed the T cells to migrate to the transplanted tissue, the next question was *where?* "The thinking in the field was that the first cell in the organ that the T lymphocyte can see has to be [in the] endothelium, the inner lining of the blood vessel," says Lakkis. "That was the traditional thinking because, anatomically, that made sense." There was also evidence that the endothelium can digest foreign proteins, then present them to the T cell to activate it.

Again, back to the fundamental questions. Walch and Lakkis set out to confirm that this was really the case. "And it turned out that that's not completely true," says Lakkis. "Even though the endothelium can present the protein to the T cell, it was dispensable. There had to be another cell that's doing it." There was a likely candidate—a bone-marrow-derived cell called the dendritic cell that lives in all of our organs. Its job is to detect virus or bacteria. Then it eats the marauding particle and digests the proteins, presenting the antigen to T cells.

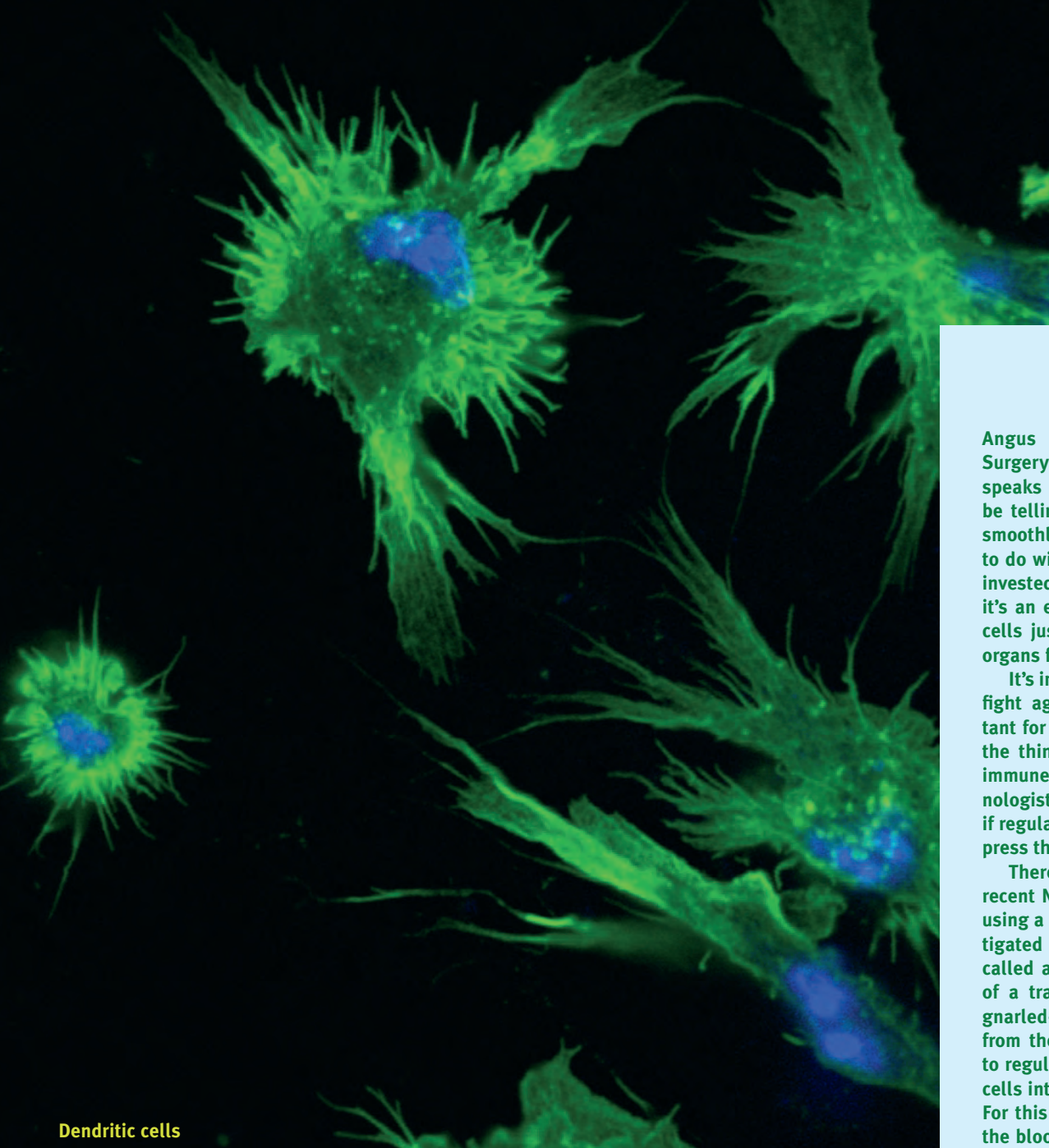
bloodstream and bring them over to the other side. That is a completely new paradigm, as well."

With Walch as the lead author, the work was published this May (online, appearing in print in June) in *The Journal of Clinical Investigation*. Terry Strom, professor of medicine and surgery at Harvard Medical School and coscientific director of the Transplant Institute at Beth Israel Deaconess Medical Center, published a commentary of the work, titled, "Transplant Rejection and Paradigms Lost," in the same journal. "Dr. Lakkis' work has revolutionized our understanding of the inception of transplant rejection," he says. "Several widely held views were disproven and the work should influence attempts to prevent rejection."

While the therapeutic implications are exciting, Lakkis says he tends to be more reserved about them. It takes a long time to translate newfound biological understanding into a treatment for patients.

Walch, PhD in hand, is completing his last two years of med school. When he's done, he hopes to be a plastic surgeon, specializing in cleft lip and palate while continuing to do research in immunology.

Lakkis continues to go back to the fun-



Dendritic cells

damentals. About a decade ago, he took a sabbatical in Leo Buss' evolutionary biology lab at Yale University where he collaborated with then-doctoral student Matthew Nicotra. (See sidebar p. 15.) Lakkis was fascinated by the allorecognition response being studied on a sea creature called *Hydractinia*. (Allorecognition refers to an organism's ability to tell the difference between self and nonself cells or tissues of another member of the same species.)

"The 'primitive' organisms do not have lymphocytes, and yet they are quite good at detecting and rejecting tissues of an unrelated organism," says Lakkis. Lymphocytes are the hallmark of the adaptive immune system, which has been primed to recognize and attack foreign antigens by previous contact with them. "This told us that there must be nonself tissue recognition mechanisms in mammals that predate lymphocytes, which was not what everybody else thought." In a recently submitted paper, Lakkis and his team investigated the innate immune system of mice, which is made up of cells other than lymphocytes, and found that it indeed distinguishes tissue that is foreign from self.

Questions beget more questions: How do the innate and the adaptive immune systems work together to reject a transplanted organ? What are the earliest events that lead to graft rejection?

Notes Lakkis, "We've found that there is almost never a fundamental question that is not only worth visiting, but also worth revisiting." ■

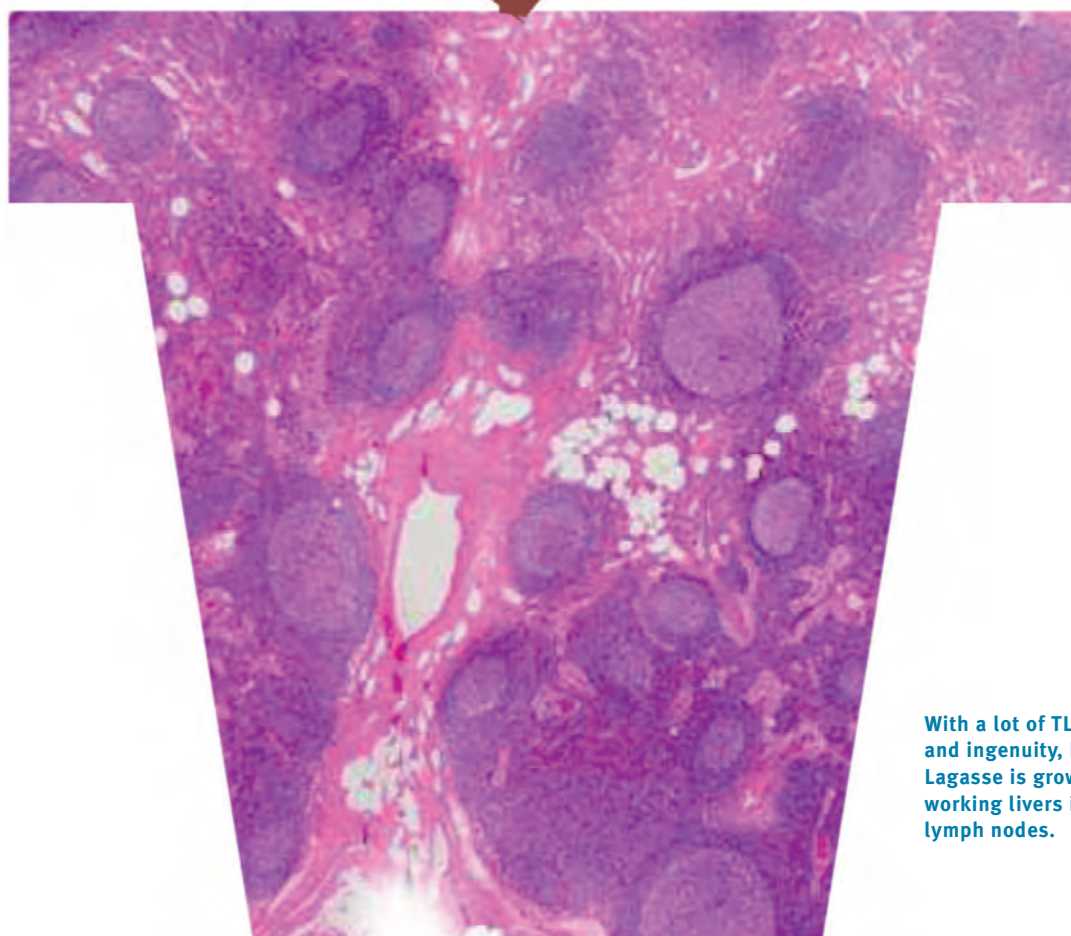
ROLES AND REGULATIONS

Angus Thomson, Distinguished Professor of Surgery and Immunology at the Starzl Institute, speaks in a soft Scottish burr. The PhD could be telling a bedtime story, his words roll out so smoothly. But the story he is relating today has to do with regulatory immune cells, which he has invested a large part of his career in studying. And it's an exciting story because regulatory immune cells just may be a key to keeping transplanted organs from going through rejection.

It's important for immune cells to fight the good fight against pathogens. But it's just as important for them to know when to stop. That's one of the things regulatory immune cells do—tell the immune system to step aside. So transplant immunologists like Thomson have long been wondering if regulatory cells could be put into service to suppress the immune response in transplantations.

There's encouraging news on that front. In a recent National Institutes of Health-funded study using a nonhuman primate model, Thomson investigated whether a certain kind of immune cell called a dendritic cell could prolong the survival of a transplanted organ. Dendritic cells have a gnarled-looking structure with appendages jutting from them like knobby tree branches. They help to regulate the immune system by either calling T cells into action or by suppressing their response. For this research, dendritic cells were taken from the blood of rhesus macaques that would later be the donors of the transplanted organ. The cells were treated to promote their ability to negatively regulate immune response and then infused into the recipient prior to the transplant. The monkeys that were not given the infusion lasted 40 days before rejecting the transplanted kidney; yet those who were given the dendritic cell infusion survived 113 days before rejection. "With the simple expediency of infusing these immune cells a week before transplant, we were able to prolong transplant survival," says Thomson. "This has never been shown before in a preclinical model. The data suggest it may well be worthwhile moving forward to design a human trial in kidney transplantation using this type of regulatory immune cell." Thomson imagines this approach might help transplant patients use less potent immunosuppressive regimens.

The study was published in this June's online edition in the *American Journal of Transplantation*. Mohamed Ezzelarab, research assistant professor of surgery, is lead author. —SF



With a lot of TLC and ingenuity, Eric Lagasse is growing working livers in lymph nodes.

A LITTLE LYMPH NODE, A LITTLE LIVER
BY ERICA LLOYD

SURROGATE ORGANS

Okay, this sounds weird: A researcher at Pitt has managed to grow working livers—and other organs—in animal lymph nodes.

The scientist's name is Eric Lagasse; he's a PhD, a PharmD, a professor of pathology at the School of Medicine, and the director of the Cancer Stem Cell Center at the Pitt-UPMC McGowan Institute for Regenerative Medicine. He's been doing fascinating studies with partners Paulo Fontes, MD associate professor of surgery who directs the machine perfusion program at the Thomas E. Starzl Transplantation Institute, Massimo Trucco, Hillman Professor of Pediatric Immunology, and, among others, Junji Komori, an MD/PhD postdoctoral fellow in the Lagasse lab who was one of the lead authors on a recent *Nature Biotechnology* paper on these breakthroughs.

Read on to learn what this team has been up to.

First, what's at stake: Each year in this country, doctors diagnose 65,000 people with end-stage liver disease; many of these people have cirrhosis. The only cure is a liver transplant, yet only 6,500 liver transplants are performed each year.

Beyond the liver, preliminary success with cells from other organs, including the pancreas and thymus, could also have dramatic implications for human health. Think help for patients with diabetes or who are immunocompromised. Lagasse's approach might even work as a way to wean transplant patients from immunosuppressive regimens.

What made Lagasse think of this? In an experimental attempt to treat liver failure in a mouse, Lagasse's team was injecting healthy hepatocytes (liver cells) into its spleen. Sometimes, the researchers inadvertently missed the spleen, and the cells were injected into the belly. They learned those cells had migrated to the lymphatic system, where they formed colonies.

So, naturally, he thought: "Maybe if we could generate a functioning liver outside of the liver, that would be an option for patients."

In fact, other researchers have been attempting to grow liver tissue (and that of other organs) elsewhere in animals using transplanted cells for some time with limited success. Some of the difficulties have involved obtaining enough donor cells, keeping the transplanted cells viable, and—in the case of liver studies—generating enough liver mass.

ILLUSTRATIONS | MICHAEL LOTENERO

What they did: Injected 100,000 to 500,000 hepatocytes into the lymph node of a mouse. Animals don't seem to get cirrhosis, and there's no animal model of the disease, so Lagasse's team used a mouse model with genetically induced liver disease. That one injection generated enough mass to rescue the animal from the disease.

The mouse grew a new, functioning liver, right there in the lymph node. Lagasse's team repeated this dozens of times. Their model in larger animals is also promising.

How does a body make enough space for a new organ? Especially something as massive as a liver? There are plenty of lymph nodes in the abdominal cavity, and there's also plenty of space for an extra liver, Lagasse assures. Also, hepatocytes don't grow out of control like cancer cells do; they only grow as needed. They innately seem to seek out equilibrium. For example, if a mouse has a liver that's functioning at about 40 percent, the new lymph-node-hosted liver will tend to be 60 percent of normal size. And when Lagasse's team removes more of the native liver, the surrogate livers in the lymph nodes grow again to make up for that loss of tissue.

As good as this sounds, Lagasse doesn't see this as a way to replace a liver. These surrogate livers have vasculature, but there's no biliary system—no bile ducts or other way to get rid of bile juice. (Which makes sense: What would the biliary system connect to?)

How he imagines these surrogate livers working, someday. As an auxiliary liver that helps the native diseased liver repair itself.

Could a surrogate organ lead to a blocked node, like what happens in lymphedema? Lagasse says, "We have not seen any lymphedema in our animal models. We believe that the ectopic organogenesis [surrogate organ growth] prevented this problem by rerouting the lymphatic drainage."

What are the chances—assuming the lymph-node-hosted organ approach proved safe in humans—that a patient might end up with a second diseased liver? "To be frank, we do not know," says Lagasse.

The technique of growing functioning organs in lymph nodes has worked in mice and, in preliminary studies, with larger animals, including pigs and a monkey.

Wouldn't it be uncomfortable to have two livers? The mice didn't show any discomfort, says Lagasse, even when the investigators injected the hepatocytes into a lymph node behind the knee.

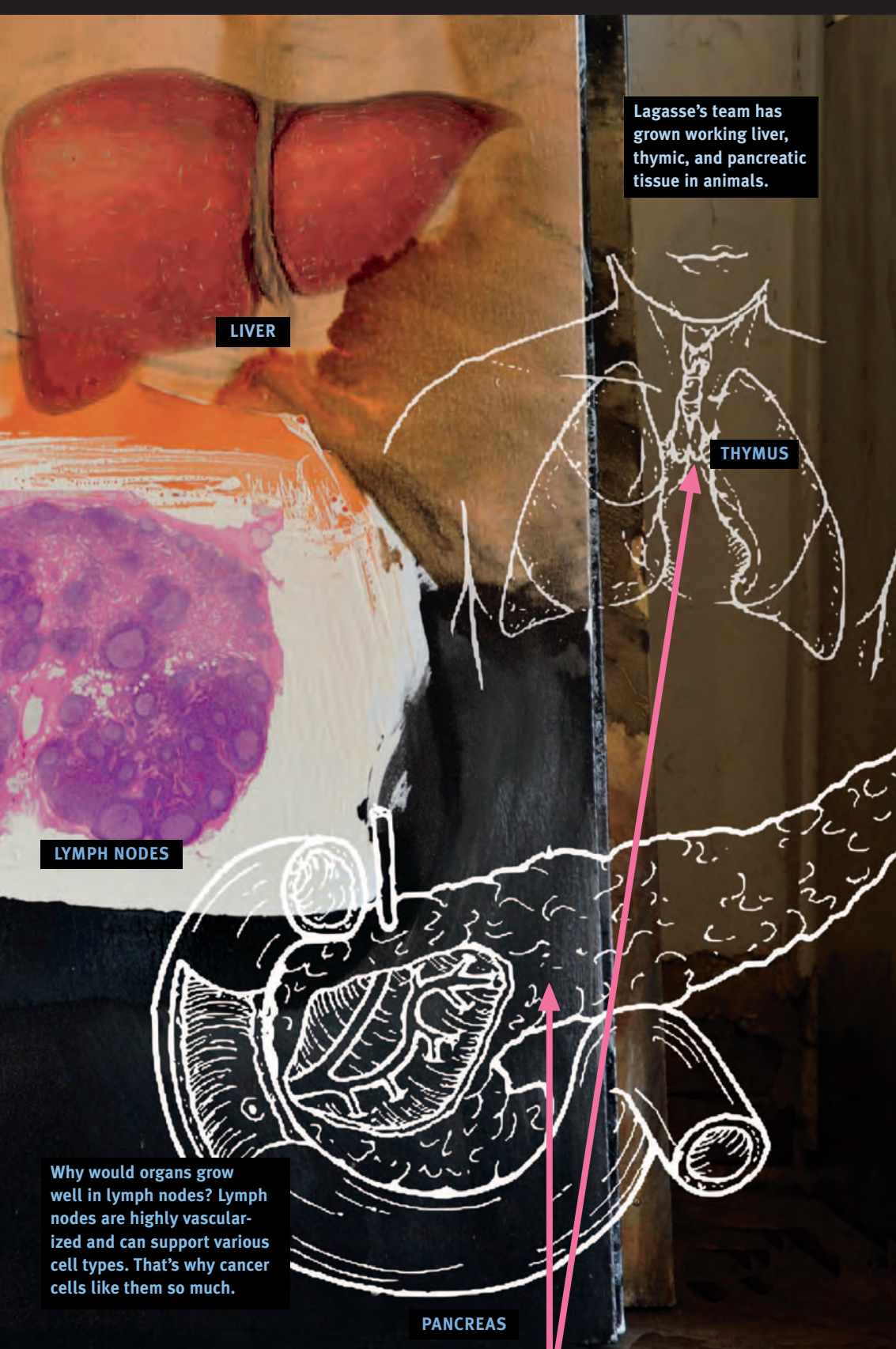
Once in the lymph node, the cells stay put—unlike cancer cells, which are infamous for migrating.

"Our hypothesis is the liver tries to regenerate, but the environment is so destroyed, there's no way that it can do so. The idea here is by transplanting cells into a lymph node, which is basically a virgin environment, we will be able to generate a functional liver."

But they won't know until they actually try it in patients.

If the lymph node is used as a bioreactor, can it still do its day job, i.e. fight off disease? The human lymphatic system has 500 to 600 lymph nodes, so using one or two for organ growth shouldn't hinder its abilities, note commentators from *Nature Biotechnology*. Lagasse's team has shown the novel approach doesn't seem to impede immunity.





Lagasse's team has grown working liver, thymic, and pancreatic tissue in animals.

LIVER

THYMUS

LYMPH NODES

PANCREAS

Why would organs grow well in lymph nodes? Lymph nodes are highly vascularized and can support various cell types. That's why cancer cells like them so much.

What about rejection? The lymphatic system is a strategic stronghold in the fight against disease, where T cells and B cells garrison to launch attacks against invaders. Wouldn't placing newly transplanted cells there be asking for trouble? Apparently not. The procedure works fine in animals when given an immunosuppressive regimen.

What's good for the liver is good for the pancreas and thymus ... A preliminary study with Massimo Trucco involved a monkey with diabetes. The animal had normal blood glucose levels after the research team transplanted islets (a type of pancreatic cell) into a lymph node. After three months, researchers detected the presence of islets in the lymph node along with insulin-producing beta cells.

If your thymus, generator of T cells, doesn't work, you become immunocompromised. When Lagasse's team transplanted thymic tissue into lymph nodes of mice born without a thymus, the mice were able to generate functional T cells that rejected tumor cells or skin grafts from other mice. (PhD postdoctoral fellows Aaron DeWard and Lindsey Boone contributed to these studies.)

An eye toward ending the rejection issue altogether. Lagasse thinks he's found a way to trick the immune system.

In addition to transplanting thymic tissue into a lymph node to treat immunocompromised people, he's experimenting with this surrogate organ technique as a way to "re-educate" the immune system so it won't reject transplanted organs.

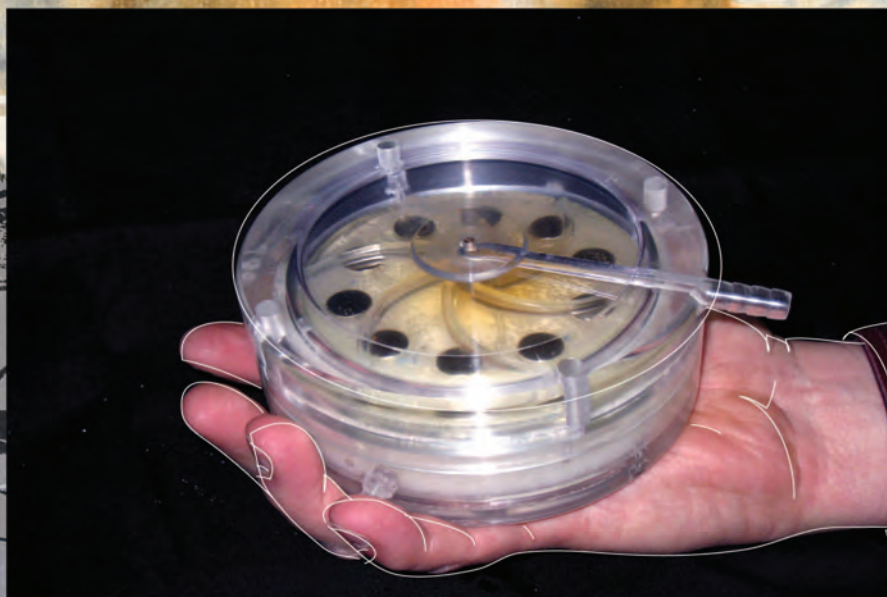
Here's the idea: Imagine you need a new liver. You are approved for a transplant. Your surgeons give you immunosuppressive drugs. They take a piece of the thymus from the liver donor and transplant it into your lymph node. At the same time, they do the liver transplant. The thymic tissue starts to function in its new habitat, and after a while, your body learns to accept the donor liver without the immunosuppressive regimen. Lagasse has not published on this yet but says that the system is working in mice.

Biggest obstacle to moving forward: It's not a question of immunology, or physiology, or anything scientific, says Lagasse, who is eager to translate his findings to the clinic. His biggest roadblock of late—diminishing funding.

What keeps these researchers inspired: The huge need—there are tens of thousands on waiting lists for new livers. And Fontes, the surgeon, adds that more than 30 percent of patients with end-stage liver disease can't even get on the transplant waiting list—they have no alternative. "This technology could be a new therapeutic option for this severely underserved patient population," he says.

"A liver transplant is an incredible operation," says Lagasse. "But most people with end-stage liver disease won't get a transplant. They will die."

"The people who are really excited about this are the surgeons who see patients, see the outcome of liver disease, and really understand what we are trying to do." ■



The Hemolung uses a rotating cylinder to disturb blood flow, facilitating the exchange of oxygen and carbon dioxide at a relatively low rate of blood flow. A wearable artificial lung under development will now use the same approach.

BREATHE EASIER

ARTIFICIAL LUNGS

ARE HELPING PATIENTS

BY NATALIE ERNECOFF

William Federspiel scoops sugar into his coffee and sits down for an interview regarding the Hemolung, an artificial lung his team has designed.

As he reaches for a coffee stirrer, he says, “You put sugar in your coffee. If you want it to dissolve faster, you stir it more vigorously. What’s unique about the Hemolung is that in the design we employ active mixing. A rotating cylindrical core disturbs the blood flow patterns. By adding that additional movement, you can increase the rate at which CO₂ moves from the bloodstream and oxygen moves into the bloodstream.”

Federspiel, a PhD, Whiteford Professor of Bioengineering with secondary appointments as professor in critical care medicine and chemical engineering, says that the Hemolung requires only a small amount of blood flow outside of the body, in contrast to previously available methods that are substantially riskier.

Since gaining approval in Europe, Australia, and Canada earlier this year, the device has helped approximately 30 patients.

The Hemolung works via a catheter that can be inserted by a physician in the intensive care unit. This access point allows blood to flow through a cartridge containing hollow, hair-like fibers. As blood runs continuously through the module, pure oxygen is pumped inside the fibers. Oxygen and carbon dioxide are exchanged using the hollow fibers, with augmentation from the rotating cylinder (recall the coffee stirring example). Federspiel notes, “That’s what enables it to remove what seem to be clinically significant levels of CO₂ at relatively low blood flow rates.”

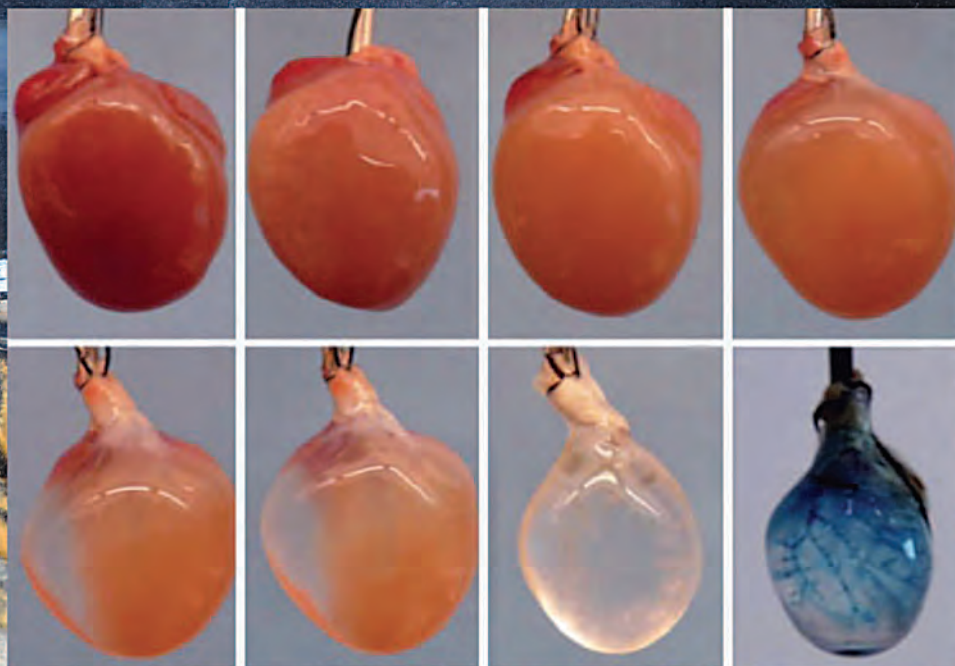
Years ago, Federspiel helped found the Pittsburgh-based ALung Technologies with the late Pitt surgeon Brack Hattler. ALung developed and manufactures Hemolung. (Federspiel is an equity holder in the company.)

Federspiel and colleagues recently received a \$3.4 million National Institutes of Health grant to develop a wearable artificial lung. Similar in function to the Hemolung, this module (Paracorporeal Ambulatory Assist Lung, or PAAL) would be contained in a single unit that could be strapped over a patient’s shoulder or around the waist.

“It would be an integrated, compact artificial lung that could be worn by the patient. That’s the goal,” says Federspiel.

Unlike existing respiratory support devices, the wearable lung would allow patients to move about relatively freely in the hospital and perhaps, eventually, in their own homes.

Though not intended to be permanent, the wearable PAAL could act as a bridge for patients waiting for a transplant. And it could help both acutely and chronically ill people increase their chances of receiving a transplant by maintaining their health in the interim. ■



Human stem cells proliferate and differentiate within the scaffold of a mouse heart that's had native cells washed away. After 20 days, the tissue started to beat without intervention from researchers.

THE LATEST HEARTTHROB

GROWN IN A LAB

BY JENIFER LIENAU THOMPSON

Be not still, spontaneously beating heart!

For the first time, researchers have used stem cells to build heart tissue that started to beat on its own, with nary a jump start. What's more, the stem cells figured out on their own what types of heart cells they needed to become.

For three years Lei Yang, assistant professor in Pitt's Department of Developmental Biology and director of the Stem Cell Core, has labored with his colleagues Tung-Ying Lu and Bo Lin to design a new process for engineering human heart tissue. But these PhD researchers are not satisfied with mere tissue—they aspire to grow whole hearts, personalized for implant in patients suffering from end-stage heart disease.

"Heart disease is the leading cause of death worldwide," says Yang. "Transplant therapy is limited by the availability of donor hearts and by problems with tissue compatibility. Our work takes a step toward engineering tissue

and whole organs specifically for each patient."

It's a big step, yet the path ahead is long. Asked when he expected that scientists would be able to build a whole human heart for implantation, 38-year-old Yang quipped, "Hopefully before I die." That said, the results of this study may find significant application sooner—perhaps to regenerate heart-tissue patches for implantation or as a model to test cardiac drug therapies.

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

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

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

Yang and his colleagues will next try to seed hearts so they produce a faster and more forceful beat. Success could send a lot of hearts racing. ■



AN EPIC TALE OF INJURY AND RENEWAL
BY ELAINE VITONE

PROMETHEAN EFFORT

Among regenerative medicine types, liver research docs, and, really, any ardent fans of tissue biology, one often-cited story is the Greek myth of Prometheus, cocreator of humankind. Prometheus so loved us that he dared to defy Zeus, stealing fire from him to give to us. To put Prometheus in his place, Zeus chained him to a mountain, where, each day, a great eagle fed from his liver. Each night, the liver grew back and, the next day, this gruesome martyrdom began anew.

In Prometheus' modern-day cheering section, one of the most vocal fans is the University of Pittsburgh's George Michalopoulos, who leads Pitt's Department of Pathology and holds the Maud L. Menten Chair in Experimental Pathology. As you might guess, if not from his name then from his accent or from the way he loves to drop Greek etymology into conversation, Michalopoulos is Greek himself. ("My daughter tells me I'm worse than the father from, you know, *My Big, Greek, Fat, what is it, Wedding?*" says Michalopoulos, chuckling. "They make fun of me.")



Michalopoulos in his hometown on the island of Samos. OPPOSITE PAGE: The Greek word for liver, *hēpar*, comes from *hēpaomai*: "to repair." In this 6th century BCE depiction, Prometheus is bound and helpless while, each day, an eagle feeds from his liver. Each night, it grows back.

One summer afternoon in 2013, sitting in his office on the fourth floor of the University's Biomedical Science Tower 3, the MD/PhD explains in his deep voice: Every tissue has its own regenerative capabilities—bone marrow, skin, intestine, and even brain and heart, we now know. But the liver leaves them all behind. You can cut away two-thirds of it, and within weeks, it will grow back to its original size. You can even cut out half of it and transplant it into someone else and, again within weeks, each half wills itself whole. The liver is the only organ that can do this.

Liver regeneration is seen in all vertebrates. Presumably, as Michalopoulos wrote in a 1997 *Science* review paper that put his favorite Greek god on the cover, this process evolved to protect animals, as liver loss has catastrophic results. The liver produces most of the blood's enzymes and all of its coagulants. It turns smithereens of food from the stomach into the soluble stuff that keeps us running. And, most famously, the liver detoxifies everything we put away, from beer to burgers to acetaminophen, as well as whatever else we might ingest. Without the liver, we truly are lost, within minutes.

In many cultures, if a person had fire in the belly, that burning center was thought to be the liver. The Zulu words for *liver* and *courage* are one and the same. In Persian, Urdu, and Hindi idioms, to “throw bits of your liver” is to give something your all. To set out and raise hell.

And the liver *is* stubborn. Block one molecular means of regeneration, and the organ will conjure up another means, then another, then another. It is a fighter. A *live-er*.

Much of what we now know about this incredible phoenix within the body, we know thanks to Michalopoulos and his team—notably, “from day one,” he says, PhD professor of pathology Reza Zarnegar. Throughout their decades-long quest to understand this process, Michalopoulos has gathered around him the strongest group in the United States for studies of liver regeneration. Pitt's “hepatomaniacs” are working to harness this force of nature to treat cancer; to develop bioartificial liver devices; to ensure better outcomes after liver-transplant surgery; and to reverse liver failure, so that fewer transplants are needed in the first place.

They continue a great tradition of hepatomance-ing at Pitt. In the 1980s, Thomas E. Starzl, Distinguished Service Professor of Surgery, performed the first successful human

liver transplants. Given Pitt's strength in this area, the hope was to cultivate a strong program in liver biology—hence Michalopoulos. And since he was recruited in 1991, Pitt's Department of Pathology has grown to one of the largest in the country, with more than 170 faculty members. They've been one of the top 10 National Institutes of Health-funded pathology departments for more than a decade.

In ancient Babylonia and neighboring countries, if you wanted to know whether the gods were on your side in battle, illness, or the whims of the weather, the place you looked for answers was the liver. Soothsayers sacrificed animals to read the scars on the organ's surface—evidence, we now know, of the liver's dogged will to survive.

Today, the liver's astounding capacity for self-healing informs regenerative medicine, transplant medicine, developmental biology, and cancer biology. The latter—regeneration's alter ego—is Michalopoulos' next challenge.

In 1971, Michalopoulos came to the United States, a newly minted MD who'd spent his teen years reading copies of *Science* and *Nature* at his local library in Athens, marveling at the impact of DNA structure on replicating cells. He began a combined pathology residency/PhD program at the University of Wisconsin, studying the effects of chemical carcinogens as part of an emerging school of thought that figured tumor growth must mimic the growth of normal tissue, but with one fatal flaw: It doesn't stop. The Wisconsin group's favorite model to study tissue growth, naturally, was the liver. Not only is it big (the largest organ in the body), soft, and easy to grind up and distill down to its proteins, but the liver is also easy to nudge into self-repair on a massive scale. Just surgically remove two-thirds of it from a rodent—partial hepatectomy, as it's called.

Well, that part was easy enough. But studying the process in cultured cells proved tricky. Out of the context of the body, these storied survivors simply give up and die. Michalopoulos spent two and a half years “trying everything under the sun” to make them grow. “That was fun, but it was frustrating,” he says. (In the late '90s, he would succeed. Working with Bill Bowen and Joe Locker, he developed a medium called hepatocyte growth medium, or HGM, which is still used in liver-research studies all over the world.)

Michalopoulos joined the faculty at Duke University in 1977, followed by Zarnegar in

the mid-1980s. In the 1970s, studies had shown that agents circulating in the blood of animals surgically divested of portions of their livers had the ability to trigger regeneration. So, they took blood from an hepatectomized animal and “fed” it to liver cells in culture. That worked. On Michalopoulos' office wall, right next to Prometheus' close-up, hangs the first photographic proof: Little black grains of radioactive thymidine tag the nuclei of these dividing crimson cells.

The two scientists moved to Pitt in 1991, where they spent six years separating out the circulating proteins and testing them one by one until they finally found what awakens the sleeping lion. Hepatocyte growth factor (HGF), which was discovered simultaneously by the Pitt duo and two other labs, subsequently opened several new fields, as it would also be found to play roles in wound healing and embryonic development, among other biological processes. As of this writing, the paper has been cited some 10,700 times.

In the early 2000s, Zarnegar's group was the first to show that HGF mutations occur in human cancer, a discovery that was made public in the *Journal of Clinical Investigation*. Zarnegar and colleagues later found that the HGF receptor system plays an important role in the regulation of hepatic glucose and fat metabolism. The findings, published in *Nature Medicine* in 2011, implicate a cross-talk between HGF receptors and their distant cousins in the insulin receptor system. This work carries implications for type 2 diabetes and fatty liver disease. “It's amazing. I'm still working on how HGF works, and what it does,” Zarnegar says.

Discovering HGF put the team on the map, but it was just the beginning.

“We had grabbed the elephant by the tail, so to speak,” Michalopoulos says.

In collaboration with Paolo Comoglio, a histology professor at University of Torino Medical School, Italy, Michalopoulos and Zarnegar helped identify the receptor for HGF in 1991.

And in a series of papers published throughout the late 1990s, the Pitt team figured out the answer to a question that had vexed liver researchers ever since their development of HGM (the medium that kept liver cells alive in culture): After a few days in the dish, the cells behaved strangely. They undifferentiated, losing their markers of liver cell-ness. The team found a solution: adding extracellular matrix to the mix. The extracellular matrix—the strong yet pliable protein “glue” that holds tissue together—has connections with receptors in the cells, Michalopoulos explains. It communicates with them.

They learned that, within an hour of liver

injury, an enzyme called urokinase is released into a rodent's bloodstream (from where, no one yet knows). Urokinase signals a breakdown of the liver's extracellular matrix, which holds abundant stores of HGF. As the extracellular matrix breaks apart, HGF is released into the bloodstream. And then, *boom*, cell division.

At the time, the only thing we knew to behave this way (step one: matrix breakdown; step two: cell division; step three: matrix resynthesis) was cancer. And, in the ensuing years, scientists would learn that every other kind of tissue regeneration begins this way, too.

To ignite liver regeneration, the Pitt team found, HGF works synergistically with another growth factor, which circulates continuously throughout the liver, whether injured or not—it's called EGF (a.k.a., epidermal growth factor). Within 30 minutes of a partial hepatectomy, both growth factors activate, prompted by the breakdown of the extracellular matrix.

When the liver suffers a bad blow, levels of protein in the blood soar, and many of these proteins have been found to act as liver-regeneration helpers. The biggest helper of all is the hormone norepinephrine. In 1986 the team found that in the presence of even the tiniest levels of HGF and EGF, norepinephrine boosts levels of both of these growth factors and, in turn, liver regeneration.

The hepatomaniacs persisted, discovering layers of redundancies in the liver's bag of tricks. They learned that, even if growth factors are nowhere to be found, the injured liver has other molecular means to press on.

Among them is Wnt/ β -catenin, a group of proteins that serve as a pathway into the cell. As a postdoc at the Department of Veterans Affairs Medical Center, Washington, D.C., and subsequently as one at Temple University Hospital's Fels Institute for Cancer Research and Molecular Biology, Satdarshan "Paul" Monga studied Wnt/ β -catenin's role in fetal liver development. The pathway had also been shown to play a role in 20 to 30 percent of liver cancers, and Monga wondered if it might also have a role in liver-regeneration. So, in 1999, he showed up on the fourth floor of Pitt's BST South, an eager emerging scientist handing out copies of his CV. He went on to prove his hypothesis correct in those very halls.

Today, Monga, an MBBS who's now a Pitt professor of pathology and its Endowed Research Professor of Experimental Pathology, is simultaneously studying Wnt/ β -catenin's potential as a target for cancer treatment, for aiding recovery from acetaminophen overdose (the largest

cause of acute liver failure), and for helping living donors for liver transplants recover more quickly.

"I've grown under George's tutelage," he says. "He's really like a father figure to me. ... I would not be where I am now without his direction, mentorship, and support."

Monga is one of many mentees who speaks of Michalopoulos with the reverence and gratitude of an adoring son. More than one young researcher told this writer that Michalopoulos is the "best thing that ever happened" to him.

At the big, international hepatomeetings, Michalopoulos, a tall guy in a blue blazer, is easy to spot. Through conference sessions, he's the earnest pupil who always sits in the front row, furiously taking notes on his iPad. In the Q&A at the end, he's the sage who steps up to the microphone, invariably asking, in his booming voice, a question so brilliant it blows everyone away. And in the session breaks, he's the unabashed aficionado of science roaming the halls like a kid in a candy store, taking in the poster presentations and chatting up young researchers: *Hey, this is wonderful. I bet you what's going on here is this. ... Have you tried it? If you need that reagent, we have it in our lab. We can give it to you.*

Michalopoulos likes to think that what goes around comes around. He often says, "Science is too big to be considered yours."

Udayan Apte (Fel '07, '08), a former Pitt postdoc twice over, says that in preparation for his leaving the nest, Michalopoulos gave him no fewer than 17 ideas to pursue in his independent research career—enough to last several researchers a lifetime. Apte is now pursuing them as an assistant professor of pharmacology, toxicology, and therapeutics at the University of Kansas. And lately, Michalopoulos has been guiding Apte's mentees, too. Students returning from conferences tell him, *Your mentor is so cool. He gave me this great idea ...*

Alphonse Sirica, PhD professor of pathology and internal medicine and chair of the division of cellular and molecular pathogenesis in the Department of Pathology at Virginia Commonwealth University and friend of Michalopoulos' from way back, says that, years ago, discussions at these meetings sometimes got a little caustic (clashes over the confound-

ing origins and behavior of liver cells). So, in 1990, the two organized a liver-regeneration summer research program for the American Society of Experimental Biology. Sirica recalls how Michalopoulos charmed everyone, fostering a respectful, collegial discussion—then corralled the herd for a fun dinner outing afterward.

"He changed the demeanor," says Sirica. "I think he coined the term *hepatomaniacs*."

Joe Locker was on the Pitt pathology faculty from 1984 to 1999, then moved to Albert Einstein College of Medicine. Last December, he came back, bringing an expertise in next-generation-DNA sequencing with him. (The professor of pathology is now developing infrastructure for the department's newly acquired, million-dollar sequencer.) Locker returned largely because of Michalopoulos, for a couple of reasons: One, he's built a department that Locker sees as the best in the country at integrating basic and clinical science. (An MD/PhD, Locker gets his kicks from both flavors or science. Pitt just launched a personalized-medicine lab for cancer earlier this year, he's pleased to add.)

And two: Michalopoulos is such a "positive force" in the field, says Locker. "He's helped people all over the world."

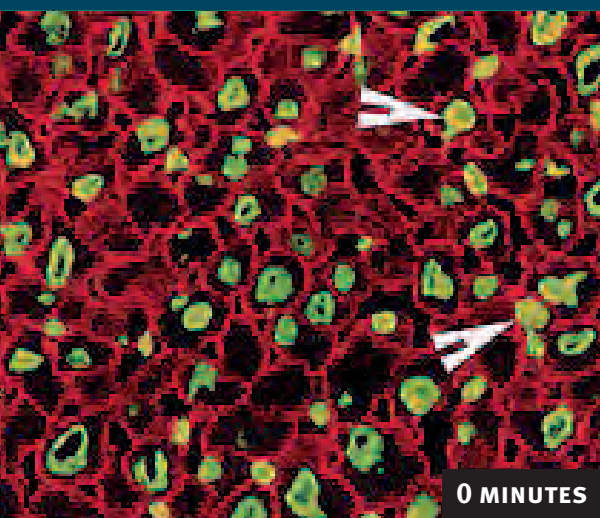
Locker studies transcription control, the cellular process of reading the genome. Previously, he focused on a gene called alpha-fetoprotein, which becomes active in development, silences in adulthood, then reawakens in liver cancer. And now he studies transcription factors in liver regeneration, as well as another type of liver growth called hyperplasia (more on that later).

Pitt's pathology department is envied for

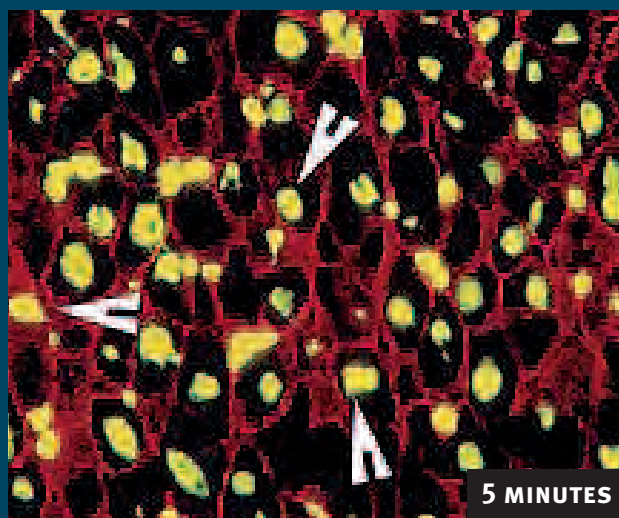
COURTESY REZA ZARNEGAR, PHOTO ILLUSTRATION MICHAEL LOTENERO



Michalopoulos and Reza Zarnegar (right) have spent decades unveiling secrets of liver regeneration.



0 MINUTES



5 MINUTES

Pitt's Paul Monga discovered that Wnt/β-catenin, a pathway involved in both embryonic development and in liver cancer, aids in liver regeneration, as well. Here, Wnt/β-catenin, seen in red, hangs out in its usual digs, the cell membrane (left). Five minutes after partial hepatectomy, Wnt/β-catenin moves inside the green nucleus, turning it yellow (right). Once inside the nucleus, Wnt/β-catenin turns on genes that initiate cell division.

HEPATOLOGY, 2001 MAY; 33(5):1098-1109. REPRINTED WITH PERMISSION.

its supportive environment. As Monga says, having a chair who is still very much an active researcher (to date, 35 years of NIH funding) means he can relate when things go south—not so in other institutions, unfortunately. “If you run out of funding, the warnings begin to pop in your e-mails. That never happens here. That’s the time when you need support. That’s when George says, ‘What can I do for you?’ I’m so used to hearing that. ‘What can I do for you? How can I help?’”

For all his skill as a leader, Michalopoulos is a scientist first. That’s clear enough when you

some kind of liver stem cells, they said—even though no one had ever been able to prove such cells existed. Michalopoulos was in a unique position to put the question to rest, thanks to the massive tissue bank he and Rajiv Dhir set up at Pitt in 2000. The samples, which are taken from patients of Pitt’s liver-transplant center, are an invaluable resource for the department, as well as to many other hepatomaniacs.

Under a microscope, using special markers, he found that these tissue samples showed “regenerative clusters,” he says. “You have bili-

no more, and no less. The organ seems to have its hand on the dial, controlling the greater bodily machine running the process—the “hepatostat,” as Michalopoulos calls it. And he wanted to know how it works.

The team turned back to the extracellular matrix. Because that’s what tells the liver cells when to start the process, they wondered: Could it be what tells them to stop, too?

And, in 2001, they found this was exactly the case. Working with Chuanyue Wu, a PhD who holds the Lombardi and Shinozuka Experimental Pathology Research Chair, they

“This is like the end of antiquity, in regards to the biological sciences. We just became capable of doing massive screening in the last 10 years. So now we’ve got to get everything defined and know what the jigsaw puzzle looks like.”

sit down and look through the microscope with him, his colleagues and friends say.

“It’s like you’re looking with a young trainee who’s experiencing it for the first time,” says Locker. “He’s just excited about it.”

In 2002, Michalopoulos’ team showed that the human liver not only has multiple molecular redundancies to incite tissue regeneration, but absent these, it can also reinvent itself at the cellular level. The two main types of liver cells—hepatocytes and biliary cells—can shape-shift like something out of mythology, turning themselves into each other as needed to fill in each other’s gaps.

Previously, a team at the National Cancer Institute had shown this happens in animal studies, but many of the world’s hepatomaniacs had remained skeptical. It must be due to

ary cells in the periphery. You go down toward the center, and you have cells that are mixed hepatic/biliary markers. And you [reach] the center, and they’re all hepatocytes.”

Having elucidated much of the process of regeneration—how it starts, how it finagles workaround after workaround, seemingly no matter what challenges you throw at it (he would write another big review paper for *Cellular Physiology* in 2007)—four years ago, Michalopoulos asked: What makes liver regeneration stop? Because when the liver stubbornly insists on growing, it doesn’t do so willy-nilly. It’s smart about it.

In pregnancy—a time when circulating blood increases by 40 percent to accommodate another kind of mythic growth—the liver doubles in size to metabolize, detoxify, coagulate, and produce critical proteins for

produced a mutant mouse that lacked an enzyme called ILK (integrin-linked kinase)—a key, shot-calling protein they’d identified within the extracellular matrix. And, without ILK, the liver cells not only undifferentiated, losing their markers of liver cell-ness, they also didn’t know when to stop growing. The livers of these mice ballooned to two-and-a-half times their normal size. Michalopoulos’ team showed that when the extracellular matrix resynthesizes, it signals to the cells that it’s time to stop growing. And not much else is known about what terminates regeneration, Michalopoulos says.

“And that got us into liver cancer.”

Three years ago, the team partnered with Jianhua Luo, a Pitt MD/PhD professor of pathology, to study the genes expressed in—and proteins produced by—liver cancer. Among these, they found one protein in particular that

liver tumors pumped out like mad: glypican 3.

And Michalopoulos, a world authority in stubborn tissue survival, had never heard of it. Which was weird. And when he looked it up in the literature, he found glypican 3 wasn't a growth stimulant, as he was expecting, but a growth suppressor. Which was even weirder.

Why would cancer cells, by nature hell-bent on growing, produce massive amounts of stuff that would prevent them from doing that very thing? To begin figuring that one out, they went back to their old, familiar model of normal tissue growth—liver regeneration after partial hepatectomy—and saw that glypican 3 was indeed produced in that setting, too. Its levels climb throughout the process, peaking at the end. Glypican 3, it seemed, is one of the brakes.

Or part of them, anyway. Luo did further tests on yeast to determine glypican 3's binding partner. And wouldn't you know, another protein Michalopoulos had never heard of popped up: CD81.

"I said, 'What the heck is CD81?!'"

Back he went to the literature, where he discovered this regenerative-medicine no-name was actually one of the two proteins that are necessary for infection of ... wait for it ... hepatitis C.

Yes, the same hepatitis C that is associated with some 95 percent of liver cancers, for reasons yet unknown. Now, the team has a hypothesis: Hep C tricks liver cells into becoming cancerous by producing a protein (dubbed E2) that suppresses the effects of glypican 3.

"This is where having a regeneration background helps you," Michalopoulos says. You can draw connections in studying cancer growth, because cancer regeneration is just like normal tissue regeneration. Both use certain pathways to make growth factors and set up shop, building blood vessels, connective tissues—everything they need to thrive as a tissue.

"Cancer is irregular, [nearly] autonomous growth of tissue. That's the definition," he notes.

A few years ago, the team began comparing liver-cancer DNA with the healthy DNA of patients and looking for the differences between them. They found 25 genes that were present in more than 10 percent of the tumors, which they published in the *American Journal of Pathology*. When Michalopoulos first looked at the genes, none of them seemed to be big players in liver regeneration. But upon closer study, he realized they were all "close cousins" of such players—proteins they interact with

during this process.

Which made a lot of sense. Cancer typically isn't the result of just one or two big, fat, molecular screw-ups, he explains. "Then, it wouldn't be a cancer cell. It would be a dead cell." But cells can afford mistakes in their critical proteins' first cousins. "Then, the configuration of the whole complex of that signaling can change. And the cell can grow faster."

In his office, Michalopoulos prints out a translation of the Prometheus myth in its earliest written form, penned by Hesiod, the Chaucer of Greece. Michalopoulos just looked up the original text last week, he explains, in preparation for a speech back home (the University of Athens awarded him an honorary doctorate in August). In his Word document, he has underlined his favorite part:

And ready-witted Prometheus he [Zeus] bound with inextricable bonds, cruel chains, and drove a shaft through his middle, and set on him a long-winged eagle, which he used to eat his immortal liver; but by night the liver grew as much again everyway as the long-winged bird devoured in the whole day.

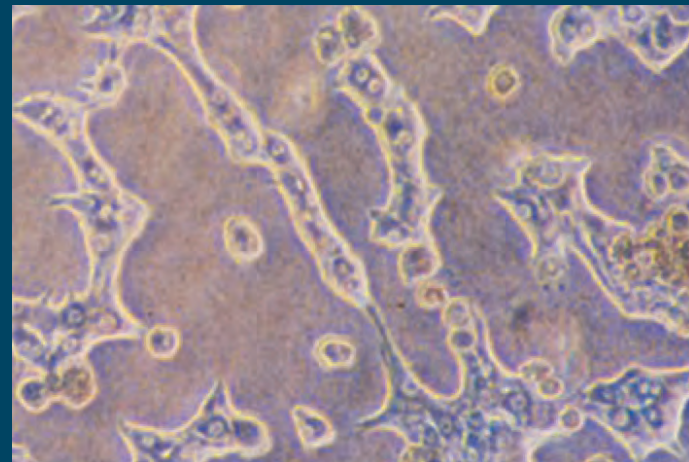
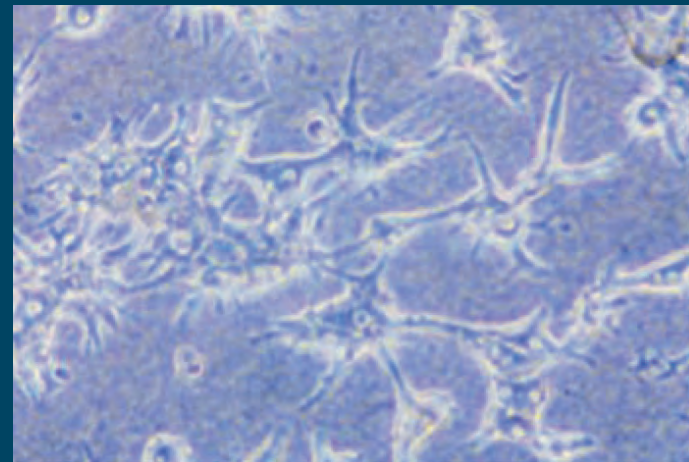
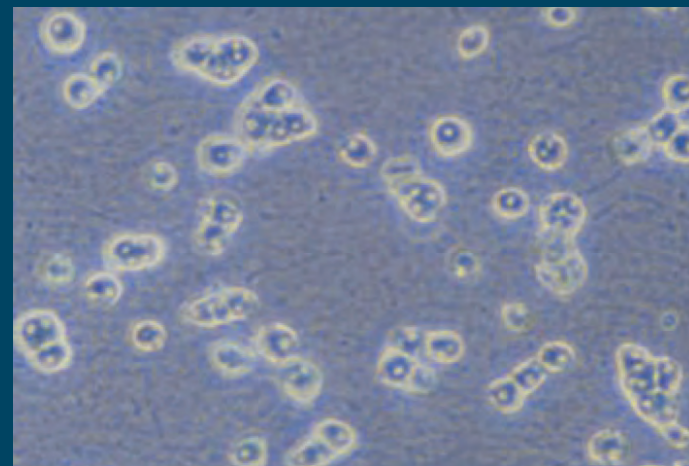
When Michalopoulos saw these poetic lines from the ancients, all but spelling out a very modern idea—the hepatostat—this scientist "freaked out."

"I said, 'My God. How did they know that?' I take no responsibility," he says, laughing.

Throughout the ages, Prometheus has been an archetype for human striving. It's a fitting backdrop for Michalopoulos' brand of selflessness: giving away ideas in the hallway, and even donating a whole lobe of his lab to give a young mentee a new start.

"I can't pursue everything I think I could possibly do. If all of us throw ideas at each other, it's conceivable some of these things might actually happen in one's lifetime. I'm 67. Will I be able to see everything? There's so much to be discovered yet.

"This is like the end of antiquity, in regards



Cells of the liver, famous for their regenerative capacity, refuse to divide in culture (top). In 1987, Michalopoulos, Zarnegar, and team discovered the missing ingredient, which circulates in the blood: HGF. Fueled by this growth factor, hepatocytes begin actively dividing within 24 hours (middle). By 72 hours, they arrange themselves into long, platelike structures, just as in normal liver tissue (bottom).

COURTESY GEORGE MICHALOPOULOS

to the biological sciences. We just became capable of doing massive screening in the last 10 years. So now we've got to get everything defined and know what the jigsaw puzzle looks like. Before, we could only see little pieces here and there and make a mechanistic hypothesis. Now it's all there. We just have to find out what it means." ■



A few years ago, then-pregnant virologist Carolyn Coyne (above, purple shirt) wondered whether work she'd been doing with viruses was safe for her developing baby. She and Elizabeth Delorme-Axford (9 months along herself, above), and Yoel Sadovsky (next page photo) went on to unravel how the placenta protects the fetus.

HOW THE PLACENTA PROTECTS THE FETUS

BY JOE MIKSCH

NOT GOING VIRAL

A grad student looking for a dissertation project. A mentor/virologist with a sudden personal interest in the fetus. Said student coincidentally sitting in on a lecture given by a man who has dedicated his research life to women's and fetal health. These are apparently the optimal preconditions for creating one of the first teams to begin sorting out how the placenta protects the fetus from viral infection.

Elizabeth Delorme-Axford (PhD '13) was the student. (She is now a postdoctoral associate in microbiology and molecular genetics here at the University of Pittsburgh.) In 2008, while rotating through labs, she alighted in that of virologist Carolyn Coyne, PhD associate professor of microbiology and molecular genetics.

"I was pregnant, and no one knew," says Coyne. "I was sitting under a tissue culture hood, purifying viruses. It was pretty early on in my pregnancy, and I thought, *Should I be doing this?*" She wondered whether the viruses she'd been working with might harm her developing baby. To Google she went.

PHOTOGRAPHY | CAMI MESA



“And there was nothing! *How is this not known?!*” Perhaps, Coyne thought, Delorme-Axford—who, it so happened, was pregnant at the time of this interview—would be interested in helping her turn the unknown into the known. And she was.

“I’m really interested in women’s health,” says Delorme-Axford, “and I know that it’s not as studied as you might think it would be. But then I finished my rotation in Carolyn’s

causes complications later on.”

A gang of pathogens known collectively as TORCH (toxoplasma, “others,” rubella, cytomegalovirus, and herpes) is responsible for various congenital defects. Also about 4 million children, who contracted HIV in utero, have died of AIDS since the epidemic began. Yet, most viruses carried by the mother are thwarted, somehow, before they can cross the placenta and invade the fetus.

tem of individual cells that allows them to fight off infection. And one of the hallmarks of cellular innate immunity is the cell’s ability to spit out antiviral factors as a means of tripping up viral invaders.

“Wouldn’t it be cool if these placental cells just happened to release certain cytokines that are antiviral?” Coyne recalls thinking.

She then came up with a way to verify her suspicion. She asked Delorme-Axford to take the

“We work with these viruses that are highly infectious. They infect many human cell types. But when we tried to infect these [primary] placental cells, there was almost zero infection.”

lab and moved on to my other graduate student rotations. On my third rotation, I was at the Eye and Ear Institute and saw a lecture given by Yoel ...”

“Yoel” is Pitt’s Yoel Sadovsky, an MD, Elsie Hilliard Hillman Professor of Women’s Health Research, professor of obstetrics, gynecology, and reproductive sciences, as well as of microbiology and molecular genetics, and director of the Magee-Womens Research Institute. Delorme-Axford knew that Sadovsky worked with primary placental cells, or trophoblasts, which play an important role in embryo implantation and interaction with the uterus. These cells, she and Coyne thought, were likely to play a vital role in keeping viruses hosted by the mother from infecting the developing fetus. Delorme-Axford had returned to the Coyne lab after finishing her rotations. She wondered whether Sadovsky would be interested in lending a hand. And some of those placental trophoblasts.

He was. “He’s such a positive personality,” says Coyne.

Sadovsky does fairly beam, even when he talks about prospective bad outcomes or things not yet understood. Not because any of it is funny, but because bad things and lingering questions afford the opportunity to ferret out the unknown. Recently, he related the story of his collaboration with Coyne’s lab, beginning with the knowns:

“Viral infections ... are one of the major insults during pregnancy. They can cause fetal death, small brains, abnormalities in the eyes, the ears, the heart. ... Babies can be too small at birth [because of such infections], which

“As Carolyn says,” Sadovsky continues, “there is very little understood about how viruses cross the placenta. Some do, and some don’t. Some infect at delivery, others throughout pregnancy, and others, none of the above.”

So, equipped with Sadovsky’s primary placental cells, Coyne and Delorme-Axford went to work. (They’d started a study with immortalized placental cells bought from a lab supplier. But, Sadovsky conjectured, placental trophoblasts cultured in his lab would be much better suited for the work because they’re more closely related to placental cells in vivo.)

“This is what really launched this project,” Coyne says. “We work with these viruses that are highly infectious. They infect many human cell types. But when we tried to infect these [primary] placental cells, there was almost zero infection.

“I remember saying to Elizabeth, ‘This is really odd. These viruses infect lots of cells, and they infected the [other] placental cell lines, but not these primary cells [from Sadovsky].’

“Then I said to her, ‘Elizabeth, just go to the freezer and let’s see what other viruses we have.’” (Because Coyne and Delorme-Axford were exploring viral resistance rather than pathways of infection, they didn’t start off with viruses, like those in the TORCH series, that are typically capable of infecting a fetus.)

“We found that nothing we had on hand could infect these [primary] placental cells.”

Interesting? Sure. Entirely unexpected? Not really. But—and this is the big question—why was this the case?

Coyne also has an abiding interest in innate immunity, the essential immune sys-

tem in which Sadovsky’s primary placental cells were growing (it’s called a “conditioned medium” as opposed to the fresh-out-of-the-bottle stuff), plop some cells that are very good at getting infected by viruses into it, and see what happens when these infection-prone cells are exposed to viruses.

“What we found was that just using that conditioned medium protected the recipient cells from the same panel of viruses [that the primary placental cells were subjected to]. And that’s when we knew we had something really interesting,” Coyne says.

But, Coyne says, she wasn’t sure what. As a virologist, she found the question was a bit outside her bailiwick. “And that’s when we went back to Yoel. Had he not made some suggestions pretty early on as to what to look at, I think this project would have taken a much different turn.”

Sadovsky’s advice took inspiration from another project under way in his lab. His work told him that placental cells produced all manner of vesicles (bubbly little organelles that play roles in metabolism, cellular transport, and enzyme storage, among other functions). Some of these vesicles, called exosomes, contain microRNAs, which help regulate gene expression. And, Sadovsky says, certain microRNAs are produced in great abundance only in the placentas of humans and other primates.

“We couldn’t find anything else that was unique in placental cell vesicles except for the release of these microRNAs. So we said, ‘Wow! This is an interesting candidate to potentially play a part on the effect we’re seeing,’” he says.

There’s the hypothesis. Now, the test. The group exposed the placental trophoblast medium

to sonication, a process involving sound waves (not the same type used in maternal-fetal ultrasound) that can destroy membranes, like those that are part of microRNA-carrying vesicles. When the trophoblast-conditioned medium was subjected to sonication, nonplacental cells introduced into it could no longer resist viruses. That's because sonication destroyed the microRNA-laden exosomes that target the microRNAs to the cells, eliminating the antiviral protection conferred by the conditioned medium.

"If you depleted these little microvesicles from the medium, you completely lost the antiviral effect," Coyne says. But, she adds, if you reintroduce lab-cloned microRNA to the mix, the effect is restored. These exosomes and their microRNAs, then, seemed to be the key to the placenta's defense system.

MicroRNA was discovered in 1993. This class of noncoding RNAs is commonly understood as a source of gene regulation, assisting in the vital task of keeping cells healthy. Some microRNAs also help determine a cell's fate. (A particular microRNA is responsible for turning certain cells into neurons, for example.) Benjamin tenOever, who is a PhD, professor of microbiology at Mount Sinai School of Medicine, an RNA expert, and a compatriot of Coyne's, says the Pitt team has made a significant leap forward by discovering RNAs' newfound role as an antiviral in fetal health.

"It's an amazing body of work," he says. "This is a very exciting new idea. These findings change the way in which we think about how

that digest the bad stuff.

"So," Sadovsky says, "if we take the microRNA, and we put [it] on the recipient cells, we not only cause resistance to viruses, but we also stimulate autophagy. And if we block autophagy, we block this resistance. We're not sure if this is the only [process involved] or exactly how it works, but we are pretty sure that this is true."

The resulting paper was published in the *Proceedings of the National Academy of Sciences* in July. And, before that, says Coyne, "I presented this for the first time (in 2012) to the American Society for Virology's meeting, and it was a huge hit. I think that was because, to virologists, this was something they hadn't thought about. Perhaps it required the aligning of the stars, getting the right people together at the intersection of several disciplines."

Sadovsky likes to think of the placenta project as beginning to fill in a "black hole in biology."

"I have to regretfully admit that the field of placental biology is fairly rudimentary," he says. "Most people seem to think that whatever happens in pregnancy just happens, and then life starts. Nowadays, we know that many adverse things can occur to pregnant women that have adverse effects on the child's early development and even into ... health as adults."

The Pitt team is aching to find out exactly what these very helpful microRNAs target:

sible that this collaboration will bear fruit outside the confines of the womb.

"Perhaps we can use the vesicles or the microRNAs from the placenta to bestow viral resistance outside of pregnancy. This could become a new paradigm for treating viruses in humans," Sadovsky posits.

Beyond viral resistance, Coyne notes, there is a litany of human diseases—many of which fall under the umbrella of neurodegeneration—that are caused by defects in autophagy.

"These microRNAs could prove some therapeutic benefit just by being able to robustly induce autophagy," she says.

Sara Cherry, an associate professor of microbiology at the University of Pennsylvania, says "the application of autophagy-inducers as potential therapeutics against viruses is real." (She knows Coyne from another collaboration.)

It's particularly impressive to her that the Pitt team has done this work without the aid of an animal model ("mouse placentas are very different" from humans', she says) and without much existing literature laying the groundwork. Before the researchers head down the road to novel therapeutics, they will lengthen the roster of pathogens they study. "We're adding other viruses and other nonviral pathogens that are [potentially dangerous in pregnancy]," such as *Listeria*, *E. coli*, and *Salmonella*, Coyne says.

Sadovsky is ready for that animal model.

"We're trying to create an in vivo model

The placenta project is beginning to fill in a "black hole in biology."

the body can deal with viral infection."

Yet having identified the placenta's armor isn't enough.

"We then spent a good amount of time figuring out what sort of mechanism is at work on the cell biology side," Coyne says. "And I think the credit here goes to Elizabeth. As we started going through the process of thinking about what host cell pathways are involved, ... she suggested autophagy."

Autophagy (from the Greek: *auto* "self" and *phagein* "to eat") is the process by which cells degrade unnecessary or broken parts. When the process takes place in this milieu, it destroys the virus by shuttling the viral vesicles to the cell's lysosome, which is full of enzymes

"Yoel is pursuing the target gene," Coyne says. The researchers are also identifying pathways leading to ramped up autophagy.

Along the way, they hope to find clues that will allow doctors to stymie the viruses that are able to slide past the placenta's defenses and attack the fetus.

"With most infections, the patient does not know [that she is infected]. She may have a period called viremia in which the virus is systemic in the bloodstream," Sadovsky says.

"We screen for viruses, but we don't yet understand the mechanism by which they cross the placenta and infect the fetus; nor [do we] have an effective way to stop this."

There may be more to the story. It's pos-

by putting these microRNAs into a mouse that has never had these genomic fragments," he says.

"Not having this has, to some degree, hampered our progress.

"We think what we have found is fine, but it may not be the whole picture," Sadovsky continues.

He and his colleagues would like to know what else might be in the placental vesicles that makes the microRNA so effective.

"And, from a physiological aspect, if the placenta makes these microRNAs to protect the fetus, might there be other cell types in a woman's body that are protected by these microRNAs?" ■



All in the kidney, er, family. ABOVE: Kidney chain donor Jeannette Muhl (blonde, center) stands beside her nephew/kidney recipient, James Weiss, with Weiss's wife, Sara Weiss (far right), and his mother, Margaret O'Brosky (Muhl's sister, far left), and stepfather, Robert O'Brosky (blue shirt).

THE 8TH TIME'S A CHARM

KIDNEY TRANSPLANT CHAIN PARTICIPANTS MEET
BY AMY WHIPPLE



LEFT: (Front row) recipients Eric Welch, Brooke Conley, James Weiss, Louis Sorbo. (Back row) Surgeon Amit Tevar; transplant coordinators Maureen Vekasy and Mary Beth Gorinski; Andrew Rose (whose gift of an organ started the chain); donors Allison Zacharias, Brandon Conley, Jeannette Muhl; transplant coordinator Mary Zeker; and surgeon Puneet Sood. RIGHT: Zacharias' daughter, Zoey, plays as her mom (blonde, back to camera) talks to Rose and Welch (Zoey's uncle).

Jeannette Muhl really wanted to figure this out. The kidney donors and recipients were split between two floors. Though the staff wasn't allowed to say who was who, Muhl was hopeful. Before her surgery, Muhl and her sister snuck around the hospital hallways, trying to match patients with descriptors like "sister" or "husband." They just had to know who else was part of this crazy whirlwind.

Muhl was one of eight people who participated in a kidney transplant chain undertaken over two days at UPMC Montefiore in April. Transplant chains begin when an altruistic donor offers up a kidney to someone who has a relative willing to donate, but is not a match. The relative of the recipient then donates to another patient in the same circumstance, and so on.

In accordance with privacy protocols, donors and recipients usually remain anonymous. But, in a first for UPMC, all eight participants agreed to go public with their identities and, along with their families and members of the UPMC staff, met in June—which Muhl did not know would happen when she was doing her hallway reconnaissance.

Transplant chains usually span multiple states and hospitals; this particular chain involved people from the Pittsburgh region—another first.

"It takes everyone from the OR staff to the nurses to the coordinators to the HLA [human leukocyte antigen] Lab, even the administrators," says Amit Tevar, surgical director of Kidney and Pancreas Transplantation at UPMC and associate professor of surgery. "To have four ORs reserved all day long for a transplant two days in a row is a significant amount of block time. And to make that happen, it does take a village."

To be considered for either end of a donation, potential patients go through a long series of evaluations (including standard health,

nutrition, and psychological assessments) and so much blood work that Muhl said she lost count after the 45th vial. Blood is used for discerning blood type, HLA antigens, and panel reactive antibodies. Doctors perform up to 15 tests in order to predict whether the donor kidney will be rejected by the recipient. All that work had to be done eight times over in order to bring together—and help ensure the success of—the entire chain.

Andrew Rose started the chain as the altruistic donor to Eric Welch. (Rose, more or less, woke up one morning and wondered if he could donate a kidney to someone.) Welch's sister, Allison Zacharias, donated to Brooke Conley, whose husband, Brandon, donated to James Weiss, Muhl's nephew. Muhl was the final donor, and the chain ended with Louis Sorbo, who had been on the cadaveric donor list for the previous three years.

After three years of dialysis, Sorbo received a call from a transplant coordinator that he could be the final recipient in the chain. It was two days before his 24th birthday.

"I thought she was joking, because it was April Fool's," says Sorbo. But that would have been a lousy joke.

"It was so hard to wrap my head around."

When he was 20, Sorbo came down with what presented as the flu but later was revealed to be reflux in his bladder. The backed-up urine had reduced his kidneys to the size of an infant's; suddenly, they couldn't do the work required to sustain an adult. "And then Jeannette comes along," he says.

When they were introduced at the meet-up, Muhl embraced "my little Louis," as she calls him. He refers to her as his Earth angel, and the two occasionally check in. Muhl says that when she celebrated her 50th, Sorbo wished

her a happy birthday from her kidney.

"It does touch you," says Tevar, who then adds, joking, "even ... surgeons."

Muhl was a willing donor, but not a match, for her nephew, who was 35 and had a 3-year-old boy.

"I lost a son four years ago," Muhl says. "I couldn't imagine my sister going through that." Then Muhl heard that she could donate to someone else in need and perhaps help her sister's family.

The first kidney transplant chain in the United States was performed in 2005 at Johns Hopkins; UPMC's first was in 2011. While the average chain involves six transplants, the largest—also in 2011—involved 60 people and 17 hospitals and took four months.

According to Tevar, living-donor kidneys "work longer, better, and faster." The U.S. Department of Health and Human Services reports that, as of August, more than 104,000 people are registered as potential recipients in this country; 874 of those are UPMC patients. In the first half of 2013, UPMC performed 81 kidney transplants, including 43 living-donor procedures.

As the patients from the chain—recipients and donors alike—moved on with their lives, Sorbo took his new kidney, as well as his degree in political science, and made a literal move to Connecticut. He'd landed a new job aiding in the implementation of the Affordable Care Act.

"He's a genius," says Muhl. Friends and family see a future in politics for Sorbo. Someday, says Muhl, "My kidney is going to the White House!" ■

Editor's Note: Patients in this story all gave UPMC express permission to share their identities.



CLASS NOTES

'50s

At Pitt med, **Edward W. Jew Jr.** (MD '53, Surgical Resident '62) knew his professors were class acts, but when he left for his first residency at Penn, where the Pittsburgh native was looked down on as a "boy from the hills," the contrast couldn't have been more stark. "At reunions, we always say [our faculty] were the nicest people. They treated us very well." In particular, **Bernard Fisher** (MD '43), now Pitt Distinguished Service Professor of Surgery, left a lasting impression. The two reconnected two years ago when Jew wrote to congratulate the translational scientist on a thoughtful editorial in the *Journal of the National Cancer Institute*. Jew, now four years out from bilateral knee replacements, is a walking surgical success story of another sort—make that walking, skiing, ballroom dancing, and bicycling. His most recent event was in August—Pedal Pittsburgh, a 62-mile bike trek.

'70s

George Vas (MD '70) can't take a compliment. His Pitt med classmates voted him the best physician among them, landing him at the podium for graduation—but he didn't deserve the honor, he says. SUNY Downstate Medical Center, where the neurologist has taught since 1975, gave him the Chancellor's Award for Excellence in 2011 and the Distinguished Teaching Award in 2012. He is now a Distinguished Professor and is director of neurology at the University Hospital of Brooklyn and, for years, was responsible for the electroneurophysiology fellowship program. He also served as medical editor

for the *American Journal of Electroneurophysiology Technology*. Vas has long been listed among *New York Magazine's* "Best Doctors in New York," was feted by the *New York Times* as a "Super Doctor," and was among *U.S. News & World Report's* top 1 percent of American clinicians in 2011 and 2012. In scientific circles, Vas is recognized for his expertise in interpreting electroencephalograms and evoked potentials. But all of this "is nothing major," he says warmly. "I didn't discover the polio vaccine." Vas, who escaped from Hungary in 1956, earned a BS and an MS from the Julliard School. The pianist then served on faculty there as a teaching fellow while completing his premed requirements (in secrecy) at Columbia University. He went on to enroll at Pitt med at 29, one of the oldest members of his class. "But I may not be interesting enough to write about," he insists.

'90s

In August 2012, a teenage girl lay in the recovery room at Beit Trust CURE Hospital in Blantyre, Malawi, staring at her reflection and crying tears of joy. She'd lived with a congenital deformity for her entire 17 years. Then, a quick one-hour outpatient surgery later, her cleft palate was gone.

San Francisco-based surgeon **Roy Kim's** (MD '92) one-week trip with Operation of Hope—a nonprofit that brings volunteers abroad to provide surgical and other health care services to underserved areas—was so rewarding, he opted to return to Malawi again this August. In recent years, he's performed pro bono facial reconstruction surgeries on infants, children, adolescents, and even adults. A few dozen procedures is a drop in the bucket, he concedes, but for individual patients, "it's life changing."

In 1999, **Bryon Petersen** (Pathology PhD '96), a

PhD professor and director of pediatric stem cell research and hepatic disorders at the University of Florida, authored a seminal paper in *Science*, showing that bone marrow-derived cells could become functioning liver cells. Today, he investigates the mechanisms of this process in the liver, as well as the potential of stem cell therapy for metabolic diseases. He's also working toward a bio-artificial liver device. Petersen has Pitt's George Michalopoulos to thank for talking him into getting his PhD, he says. Petersen first met Michalopoulos as a research technician at Duke University and followed his mentor here when Michalopoulos was recruited to lead Pitt's pathology department in 1991. (For more on Michalopoulos, see story p. 24.) "George taught me how to stand up for my research," says Petersen.

As a pediatric and developmental pathologist, **Gail Deutsch** (Pathology Resident '97)—associate professor of pathology at the University of Washington and director of Seattle Children's Pathology Core and Cancer Biorepository, as well as its fetal autopsy service—has evaluated lung samples from around the world. In her research life, she aims to understand normal lung development and the molecular mechanisms underlying neonatal lung disease. She's also studying the potential of certain neuropeptides that might be used as biomarkers. She has designed protocols for the Global Alliance to Prevent Prematurity and Stillbirth, a multicenter study. And since 2009, Deutsch has served as chair of pathology for the Children's Interstitial Lung Disease Research Network, which supports research and provides support for families affected by these rare, life-altering lung diseases.

'00s

In a crisis, like a medical emergency, or a stressful situation that could put children at risk, not all parents have the support they need to keep their children safe. This is the problem that Jeremiah's Place, a 24/7 Crisis Nursery to be located in East Liberty, aims to address. Founded by **Tammy Murdock** (MD '98) and **Lynne Williams** (MD '02, Internal Medicine, Pediatric Resident '06), this nursery, which will offer sanctuary for young children for up to three days, will be the first of its kind in Pittsburgh. Social workers and child-care providers who are trained in trauma care will work alongside family advocates to help parents alleviate the crisis at hand, and also work to educate the community. The hope is that with this combination of resources, "the whole family will be better," says Murdock. They plan to expand to the North and South sides of town in coming years.

A Pitt team that includes MD assistant professors of



Deutsch



Murdock (left) and Williams (right) with board member Bob Cicco (Pediatrics Resident '76, Neonatology Fellow '80) at a 5K fundraiser in Pittsburgh last April

radiology **Saeed Fakhran** (Diagnostic Radiology Resident '09) and **Lea Alhilali** with **Karl Yeager** (MD '10, who is now in UPMC's diagnostic radiology residency program) has reported that the white matter of teenagers who've suffered from mild traumatic brain injury looks a lot like that of people with early Alzheimer's dementia.

"The brains look normal under MR," says Fakhran. "But with diffusion-tensor imaging [which can reveal tissue architecture by tracking water dissemination], when you look at the white matter, it looks more like that of someone's grandma who doesn't remember names." Doctors already knew that certain symptoms common among people with Alzheimer's—like difficulties with sleeping and with filtering out white noise—were also classic signs of concussions. Now they have a picture of the damage done. "The big take-home message we have is to take your injuries seriously," says Fakhran. "Get checked out."

Since receiving her PhD, **Vanja Lazarevic** (Molecular Virology and Microbiology PhD '04) has completed an immunology fellowship at Harvard and now runs her own lab as an immunologist at the National Cancer Institute, where she studies the pathogenesis of multiple sclerosis, an autoimmune disease. Currently, her lab is working in a mouse model of MS to understand how DNA transcription factors such as T-bet can affect disease outcome. T-bet turns on (or off) a wide variety of genes that could potentially affect the onset and severity of disease. By studying the regulation of such genes by T-bet, Lazarevic hopes to improve our understanding of how MS is triggered.

'10 With colleagues from his residency at Johns Hopkins, **Devin Coon** (MD '10) has developed EchoSure, a system implanted during transplants, as well as reconstructive and vascular surgeries, to allow medical personnel to monitor blood flow postoperatively. Because it's easily read by nurses with little to no ultrasound training, EchoSure makes it possible to spot a clot at the bedside—before it has a chance to break down the blood vessel and undo the surgeon's work. This innovation won a \$10,000 cash prize in the 15th annual Biomedical Engineering Innovations, Design, and Entrepreneurship Award contest. To date, the prototype has performed well in trials of large animals.

Claudia Ramirez (MD '11), a physical medicine and rehabilitation resident at University of Rochester Medical Center, was selected for a one-week medical mission that treated and educated more than 1,500 patients in the Dominican Republic this June. Ramirez further honed her teaching skills by instructing premed undergrad volunteers, as well. For her service work, she has been nominated for the 2013 Circulo Latino Community Leadership Award. Ramirez also developed a patient registry, to record patient demographics and clinical concerns. Her hope is that the tool will assist in providing targeted care on subsequent trips. —Natalie Ernecoff, Erica Lloyd, Rachel Puralewski, and Elaine Vitone

FREEZE!

LEW KAPLAN HAS A STETHOSCOPE!

Last year when the North Haven/North Branford SWAT Team served a high-risk arrest warrant, **Lewis Kaplan** (Critical Care Fellow '97), an associate professor of surgery and trauma at Yale University at the time, was right there with them. But instead of a firearm, he packed a rucksack full of medical supplies. As tactical police surgeon and director of tactical medicine—an unpaid, volunteer position—Kaplan gave on-site, emergency care to anyone who needed it. (He recently became chief of surgical critical care at the Philadelphia VA Medical Center and an associate professor of surgery at the University of Pennsylvania. He'll continue his "police" work with the Philadelphia branch of the FBI's SWAT team.)

Usually, if someone is injured in the midst of a police operation, there's no time to call for a medic. "If they go down, they go down hard, and no one's gonna come get them until it's all over," he says. Kaplan adds it's been especially gratifying providing emergency care for this unique breed of public servant, as well as the innocent bystanders he's encountered on the scene, many of whom are uninsured.

In addition to having joined the North Haven/North Branford SWAT team for call-outs (about once a month), Kaplan covered much more "mundane" medical needs for some of New Haven County's finest: He designed physical fitness standards, taught medical-emergency response, and provided medical referrals for officers and their "mother's brother twice removed."

In January, Kaplan was part of a SWAT team effort to train detectives and other police officers, as well as firefighters, in how to respond to an active shooter. "Because the first responders to these things are patrol. The SWAT team will take an hour to assemble.

"Everybody turns to [officers], but we do very little for them," says Kaplan. "This is something I can do for them. I like that." —EV



Trauma surgeon Kaplan also works with SWAT teams.

WISH YOU WERE HERE

There must be 50 ways to leave your med school. You can go your own way, ride a horse with no name, or take a midnight train to Georgia. Tell us what you've been up to: career advancements, honors, appointments, volunteer work, publications. And we love to hear old Pitt memories, like: What's going on with this scene we found in Pitt's 1975 edition of *The Owl*? Let us know. Send a message in a bottle (or via medmag@pitt.edu), ring our bell (412-624-4152), or friend us on Facebook at www.pitt-medfb.pitt.edu/.



MAA SAYS, “GOOD SHOW!”

This spring, a small pilot study made a big splash for **Ian Pollack** (Neurosurgery Resident '91), who is the **Medical Alumni Association's (MAA)** pick for the 2013 William S. McEllroy Award for distinguished residency alumnus, codirector of the Brain Tumor Program at the University of Pittsburgh Cancer Institute, chief of pediatric neurosurgery at Children's Hospital of Pittsburgh of UPMC, and Walter Dandy Professor of Neurological Surgery at Pitt. In a preliminary trial, Pollack found that children with gliomas, the most common type of brain tumor, may respond positively to treatment with peptide vaccines—perhaps with an even more effective immune response than adults. The paper, presented in 2012, won him the Mahaley Clinical Research Award from the National Brain Tumor Society.

“The fact that we’ve seen tumor shrinkage in children with very high-risk tumors has been extremely encouraging and gratifying,” he says. The research team is continuing the study and has received funding to evaluate the vaccines in children with other brain tumors; a multicenter study is also on the horizon.

In honor of Pollack's many achievements, on October 16, the MAA will host a ceremony and, for the first time in the award's history, a Grand Rounds Lectureship and dinner (see the calendar inside our back cover for details). The idea is to give this award the “prestige, fanfare, and attention” it deserves, says MAA director **Pat Carver**.

Fanfare has been a running theme in MAA's doings of late. The White Coat Ceremony in Scaife Hall this August drew a standing-room-only crowd of more than 500—so many, they had to stream video of the ceremony into the adjacent lecture hall. “I'd like to grow this program and take it to the Petersen Events Center next year,” says Carver. (Jumbotron closeup, anyone?)

In September, the MAA executive board amended its bylaws to invite more people to join the party, expanding membership and encouraging more active involvement from alums from across the country. One goal is “to maintain a member from each graduating class,” says **Brian Klatt** (MD '97, Res '02), board president. The board also opened full, voting board membership to current Pitt med faculty—regardless of whether they are Pitt alums. And students are now encouraged to take on committee roles, “so they can understand all that the MAA offers” them, Klatt says.

To nominate candidates for next year's Hench and McEllroy awards, or to volunteer for the executive board (telecommuters welcome!), contact Carver at cpat@pitt.edu or Klatt at klattbrian@hotmail.com. —EV

MEDICAL ALUMNI ASSOCIATION
WWW.MAA.PITT.EDU



First-year students receive their white coats, proudly donated by the Medical Alumni Association, in August.

KENNETH GARVER

MARCH 22, 1923–MARCH 21, 2013



Garver

In the late 1960s, Kenneth Garver (MD '46, Pediatrics Resident '53) was a beloved pediatrician who made house calls long after they had gone out of fashion. Having lost a son in infancy, he developed an interest in congenital disorders and became his colleagues' go-to consult for these cases. “I think he could empathize with the loss of the dream of a healthy child,” says daughter Kathy Garver Lamb (MD '79). After practicing in Penn Hills for nearly two decades, he shuttered his office to go back to school and begin a new career, receiving his PhD in human genetics from Pitt's Graduate School of Public Health in 1975.

Garver, who went on to become one of the founders of modern medical genetics, died at his home in March.

In the 1970s, genetic counselors worked solely in pediatric settings. Garver made Magee-Womens Hospital one of the first to bring these services to obstetrics patients when he founded the medical genetics department. “That showed foresight,” says Allen Hogge, Milton Lawrence McCall Professor and chair of obstetrics, gynecology, and reproductive sciences at Pitt. Garver also directed Pitt's genetics counseling program at Pitt Public Health and later created the genetics program at West Penn Hospital.

Garver was proud of his seminal research in neural tube-defect prevention, notes Lamb, which led to the recommendation of prophylactic folic acid supplements to reduce these risks in pregnancy, still a standard of care today.

It was Garver who first brought prenatal screening for chromosomal abnormalities, PKU disease, and spina bifida to Pittsburgh. He also recruited and worked with biomedical geneticist Edwin Naylor to supplement Pennsylvania's then-scant requirements for newborn testing. Their program was later adopted at the state and, eventually, federal levels; it's the basis of the Uniform Screening Panel of the U.S. Department of Health and Human Services.

Garver was exemplary in his practice and advocacy of nondirective counseling throughout his genetics career, says Hogge. “He would spend hours with those families,” recalls Lamb. —EV

IN MEMORIAM

'40s

JOSEPH S. LIDDELL
MD '41
APRIL 15, 2013

FRANK N. TETLOW
MD '42
AUG. 10, 2013

ROBERT G. MONSOUR
MD '43A
APRIL 23, 2013

LUTHER W. SPOEHR
MD '43A
JULY 11, 2013

GOMER P. EVANS JR.
MD '47
JUNE 25, 2012

'50s

WILLIAM COLANTONI
MD '51
MAY 3, 2013

DAVID B. GOODMAN
MD '54
MAY 25, 2013

TOM B. JONES
MD '59
SEPT. 5, 2013

'60s

LEE C. DOBLER
MD '63
AUG. 3, 2013

'70s

RICHARD BROADHEAD
MD '74
AUG. 12, 2013

DISEASE SEEN MORE CLEARLY SEDDON TAKES ON MACULAR DEGENERATION

BY AMY WHIPPLE

The problem starts small. Words on the page start to blur, and reading light becomes a problem. As the retinal damage worsens, the center of your visual field can become crooked or hazy. In its advanced stages, age-related macular degeneration, the most common cause of vision loss for people older than 60, can rob people of their independence.

"The largest motivator is my patients who have lost their central vision; they tell me that their biggest problem is they can't see the faces of the people they love," says Johanna Seddon (MD '74), professor of ophthalmology at Tufts University and founding director of the Ophthalmic Epidemiology and Genetics Service of Tufts Medical Center. These patients most inspire her to pursue her goal—to better understand the disease "so we can find better therapies and ways to prevent it for future generations."

Seddon grew up outside of Pittsburgh in Bethel Park with three older brothers and parents who encouraged her interests in the sciences and medicine. She completed a Bachelor of Science degree with a major in chemistry and a minor in physics. After earning her undergraduate degree and finishing her first year of medical school at Pitt, Seddon spent two summers as a "scrub nurse" in the operating room at UPMC Mercy. The OR experience exposed Seddon to a whole new world. She assisted an ophthalmologist performing cataract surgery. "She encouraged me, and said she was very happy with her choice of a career," says Seddon. "So she inspired me to consider the field of ophthalmology." In the mid-'70s, women were underrepresented in the field. The year she finished med school, the annual meeting of Women in Ophthalmology (WIO), a subset of the American Academy

of Ophthalmology, drew only 25 members. Today, Seddon is one of 435. This August, she received the WIO's Honorary Award and lectureship.

She earned a Master of Science degree in epidemiology at Harvard School of Public Health and then completed her ophthalmology residency at Tufts, followed by fellowships in ophthalmic pathology and retina-vitreous diseases at Harvard. There, she started one of the initial programs on epidemiologic research of eye diseases in the country. She also began what was probably the first systematic study of nutrition and eye diseases, launching the Age-Related Macular Degeneration Dietary Study in the mid-1980s, demonstrating that lutein and zeaxanthin found in dark green leafy vegetables and omega-3 fatty acids found in fish and nuts help prevent the disease. Her team also found that exercise reduced risk and that smoking, as well as overall and abdominal adiposity, increase risk of progression of the disease. These behavioral and lifestyle findings remain central to clinical recommendations for prevention of the disease.

Despite grant reviews that said the disease was not genetic, Seddon began studying twins in 1988 to determine how much disease risk is genetic and what part is environmental. She surveyed 12,000 twins in the World War II twin registry, and enrolled 1,000 twins who had macular degeneration and their co-

twins. Doctors across the country worked with Seddon using her protocols. Her hypothesis was correct: Macular degeneration is highly heritable, with a heritable component of up to 71 percent.

Of the 20 common genetic factors known to be related to macular degeneration, Seddon's team discovered 10. She and her team also found the first rare genetic variant, which is the strongest genetic factor related to macular degeneration to date, and they just published (in *Nature Genetics*) additional new rare genetic variants in three genes that impact risk.

She also published some of the first prediction models for this disease and its progression, which combine the environmental and genetic factors. "Healthy habits are important if you're genetically susceptible," says Seddon.

In May 2013, Pitt's Medical Alumni Association recognized Seddon with the Philip S. Hench Award for her accomplishments as a distinguished alumna of the School of Medicine.

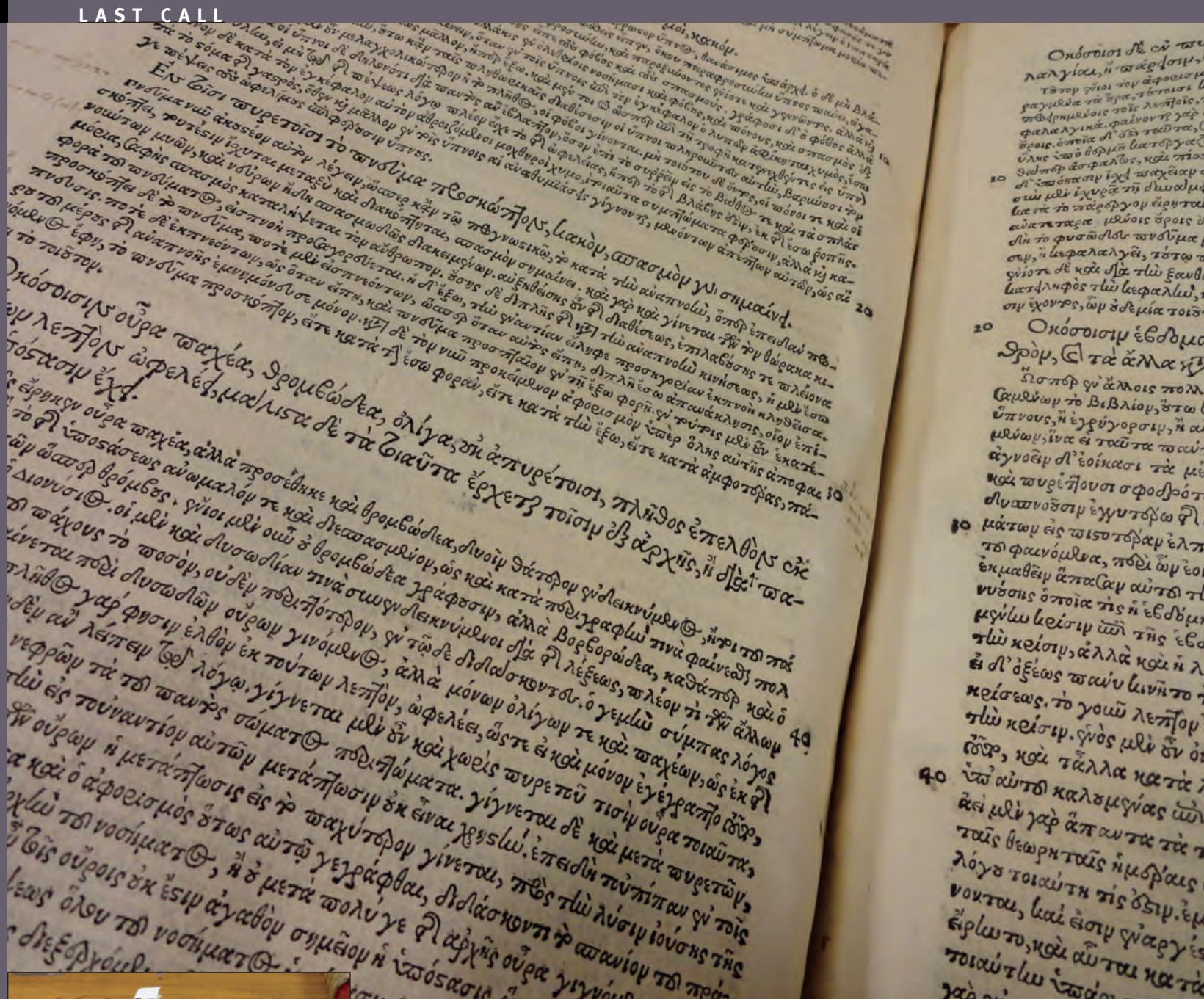
She was also awarded the University's Distinguished Alumni Fellow Award in February 2013.

"We've come a long way," says Seddon. "Our research has been translated into patient management and recommendations for how patients can delay the progression of the disease." Her gene discoveries have also shed light on targets for future therapies. ■

Of the 20 genes known to be related to macular degeneration, Seddon's team discovered 10.

PHOTO COURTESY JOHANNA SEDDON; PHOTO ILLUSTRATION MICHAEL LOTENERO.





The Falk Library's 1538 CE edition of *Galenī Librorum Pars Quinta*, the fifth volume of Galen's works, in original Greek, with an introduction in Latin.

MYTHNOMER

The liver is the only organ in the body that can regenerate on a massive scale. Did the ancient Greeks—penners of the myth of Prometheus and his “immortal” liver—know this? Hard to imagine how, say medical historians. Human dissection in the ancient Greek world was strictly taboo. Hepatoscopy, the animal-sacrificing/soothsaying tradition practiced in Mesopotamia in that era, focused on the shape and surface of the liver to predict the future, not its innards. And on the battlefield, liver injuries were deadly.

Besides, consider the crowd Prometheus ran with. Athena sprang from Zeus’ head. Dionysus, once shredded to bits by the Titans, completely rebuilt himself around his heart. It only makes sense that Prometheus’ liver was immortal. So was he!

The unparalleled regenerative capacity of the liver was not documented until the late 19th century. (And only in the past few decades has George Michalopoulos’ team begun to reveal how it does so. See p. 24 for that epic tale.) Really, until the 1800s, no one even knew what the liver was for. Humorism—a theory conceived by physician/philosopher Galen of Pergamon (131-215 CE) in the second century, popularized in the fifth century, and then favored for hundreds of years—held that the liver was the source of our lifeblood and, thusly, our courage. (The proper balance of our bodily fluids was key to maintaining our health as well as our emotions, Galen wrote.) Traces of this hepato-misnomer remain in our language even today. Just ask Yosemite Sam. Or are ya too lily-livered? —By Elaine Vitone, Photo by Rachel Puralowski

CALENDAR

FOR ALUMNI & FRIENDS

WILLIAM S. McCELLROY AWARD PRESENTATION OCTOBER 16

4 p.m.

UPMC Presbyterian—Suite B-400

Recipient—Ian Pollack, MD

Pitt chief of pediatric neurosurgery

EVENING WITH THE DEAN NOVEMBER 3

5:30 p.m.

Philadelphia Marriott Downtown

Philadelphia, Pa.

MEDICAL ALUMNI ASSOCIATION PHONATHON NOVEMBER 5-7

6 p.m.

Forbes Tower, 8th floor

For information:

Andre Burton, 412-648-9090

aab86@pitt.edu

HEALTH SCIENCES ALUMNI RECEPTION FEBRUARY 19, 2014

Palm Beach, Fla.

WINTER ACADEMY FEBRUARY 21, 2014

Naples, Fla.

Unless otherwise noted, for more information:

Pat Carver, 412-648-9059, cpat@pitt.edu.

To find out what else is happening at the medical school, visit health.pitt.edu and maa.pitt.edu.

Kids have more trouble sweating, and cooling down, than grown-ups.

CORBIS



FOR REAL! TWEEN SCIENCE.

Preseason training is killer—sometimes literally. Heat stroke is the third-leading cause of death in high school athletes. Kids are especially vulnerable to heat stroke. Why? Well, they generate a lot of body heat when exerting themselves. And one way the body cools itself is by sweating—water in sweat evaporates from skin and takes heat into the surrounding air with it. Maybe you've noticed that grown-ups perspire more than younger people. Kids have a higher temperature threshold for a sweat response—meaning they have to get *really* hot before they start sweating.

More bad news: On steamy days, when the body's ability to regulate temperature may already be out of whack, kids can have other problems cooling down. Compared to adults, they have more surface area (mostly skin) than body mass (innards and the whole shebang). In other words, more of a kid's body is exposed to the environment. Conversely, on frigid days, kids are more prone to getting dangerously cold. (Listen to your mom and put a coat on!)

So if you find yourself running around in beastly weather, beware. Heat stroke can start with cramps, clammy skin, tiredness, or dizziness. These symptoms mean you're in the danger zone. Head for shade; get some help; and cool down with an ice bath or packs, ASAP. —*Jenifer Lienau Thompson*

Pitt med prof Tanya Hagen (a chill sports medicine doctor) filled us in on this hot topic. For more kid-friendly science, visit How Science Works at www.howscienceworks.pitt.edu

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