

Columbia Medicine

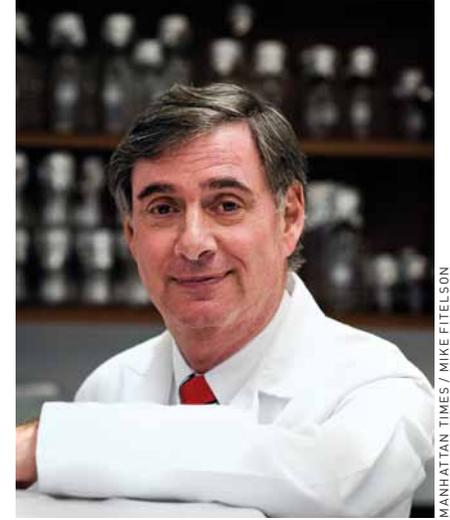
Columbia University College of Physicians & Surgeons

2014 ANNUAL REPORT

MEDICAL EDUCATION FOR THE NEXT GENERATION

TRAINING NEW LEADERS IN MEDICINE AND BIOMEDICAL SCIENCE





Great Minds at Work

On behalf of the College of Physicians & Surgeons, I am pleased to share our annual report for 2013-14. Our greatest successes, including the work described in this report, are testaments to the power of teamwork and ingenuity. The year's highlights represent diverse disciplines, but all have one thing in common: Each one is the product of great minds working together.

One example is this report's discussion of major progress made in Alzheimer's disease research, advances that are of critical importance to our aging population. Researchers with appointments in neurology, pathology, psychiatry, epidemiology, and neuroscience have worked together on a finding that has increased our understanding of the disease—as well as our hopes that we are moving closer to treatments for this formidable problem.

The work of Gerard Karsenty is another example. A profile of his two decades of research details how he identified reciprocal—and unexpected—relationships among bone and other organs. By helping to redefine bone as an endocrine organ, he has done work that has been described as single-handedly overturning the notion of the skeleton as simply a hanger for our skin. Among Dr. Karsenty's collaborators is Nobel laureate and University Professor Eric Kandel, who sees promise in the application of Dr. Karsenty's findings to research into reversing age-related memory deficits.

In the realm of cancer care, the rewards of teamwork and creativity are enormous, and we share the work of oncologist Balazs Halmos, who explains why new research into the molecular drivers of tumors gives lung cancer patients reason for optimism. Cancer patients also benefit from the new Irving Radiation Oncology Center, which opened in September. This 12,500-square-foot NewYork-Presbyterian Hospital facility is not just a modern setting for radiation therapy and diagnostic imaging; its new technology will more precisely target tumors and spare healthy cells from radiation exposure.

And as you will read in our cover story, we are revolutionizing medical education itself to prepare a new breed of physician-scientist. Our

new curriculum teaches students to not just treat patients, but also to question, review, and research patients' health care needs, drawing on different disciplines and the input of collaborators to exemplify personalized medicine at its best. We believe our graduates, who will benefit from our improved curriculum and additional educational options, will excel in their medical, biomedical, and academic medicine careers just as alumni during the previous quarter of a millennium have reinforced our reputation as a premier medical school.

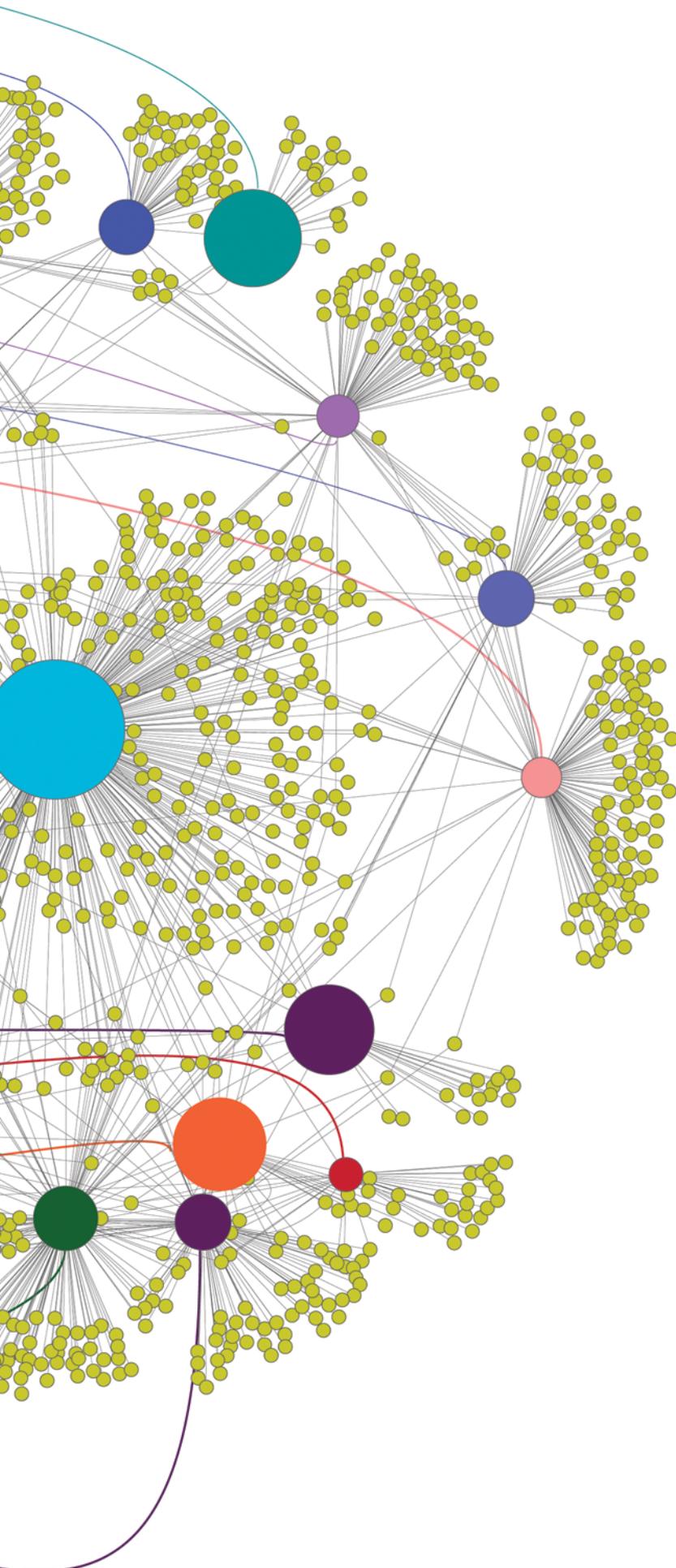
In addition to training new leaders for medicine, we also are attracting established ones. More than 120 new faculty joined us this year from the nation's top medical centers, drawn by the opportunity to teach, perform groundbreaking research, and treat patients in a unique environment where they have access to other clinicians and scientists who are leaders in their fields. We and NewYork-Presbyterian Hospital named new department chairs and chiefs of service—Lawrence Lustig in Otolaryngology and William Levine in Orthopedic Surgery—and we also have recruited distinguished senior faculty in many departments, including ophthalmology, medicine, radiology, dermatology, neurology, neuroscience, obstetrics & gynecology, and pathology.

The power of our collaborations in personalized medicine was recognized this year when Columbia President Lee Bollinger created a university-wide task force on personalized medicine, noting the "extraordinary promise" the field has for virtually every part of the university. You will see in this report how personalized medicine is integrated in all parts of our research, education, patient care, and community service missions.

I am delighted to review the progress we have made in the past year and thank you for your help toward achieving our shared goals. I hope that reading about a few of the year's notable achievements will remind you of the great work that goes on in our classrooms, laboratories, and clinical practices all year and every year.

A handwritten signature in black ink, appearing to read "Lee Goldman". The signature is fluid and cursive, with a large, sweeping "L" and "G".

Lee Goldman, MD



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On the Cover:

Whether P&S students become full-time clinicians, physician-scientists, bench researchers, teaching faculty, health care administrators, or some other variety of health care practitioner, the Columbia medical curriculum is designed to alter the way P&S graduates practice medicine in the next generation. By requiring, encouraging, and rewarding curiosity and exploration through multiple opportunities, P&S will prepare students to become leaders in a field that cannot advance without a fundamental knowledge of research methods, confidence in collaborative problem-solving, and a commitment to lifelong learning.

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Reimagining the
Research-Intensive Medical School
for the *Next Generation*



By Sharon Tregaskis

Photographs by Jörg Meyer

P&S students chart their own course and
follow their passions as they train for
medical careers in a changing world



FROM LEFT:

Taylor Nelp
Jhenette Lauder
Andre Cheng
Jonathan Kawulok
Eric Przybyszewski
Tiffany Sia
Michael Hernandez
Theodora Karagounis
Leanne Duhaney
Zachary Englander
Nina Ragaz

Paul Blackcloud
Jessica Means
Forrest Anderson
Nohemy Morones
Ekene Nwosu
Jasmine Walker
Aidin Ashoori
Christopher Gonzalez
Oz Hasbún
Billie Borden
Neil Pfister

When first-year medical student Theodora Karagounis arrived at Columbia in August 2013, she had already authored an undergraduate thesis on the microbiology of the bacterial agent behind cholera and traveled to Bangladesh to see firsthand the structural realities of health care in regions of the world where the disease runs rampant. “You can give a patient a sugar-water potion for 10 days, but hospitals there don’t have the capacity to keep patients for 10 days, so they have to give them antibiotics,” says the 23-year-old. “For me, it’s really important to work on both sides of the problem.”

By the time her name had appeared as a co-author on a peer-reviewed journal article on *Vibrio cholera*, Ms. Karagounis knew research was no passing fancy. She was just getting started. “When I got to Columbia, the need to understand how things work and why something is beneficial kept coming up,” she says. “I clearly have a lot of interests and I’m trying to explore them.”

At P&S, such curiosity and exploration are not only encouraged, they are required. “We want people to think from the beginning about research, about what questions and problems might fascinate them and drive them toward what is important in medicine,” says Jennifer Punt, VMD, PhD, associate

dean for student research at P&S and a mentor to Ms. Karagounis. Achieving that goal is easier than ever, thanks to an array of curriculum changes initiated by the P&S dean, Lee Goldman, MD. These changes require students to find their intellectual passion and pursue it, charting their own course through their training and throughout their careers.

Whatever path students choose, P&S envisions a future in which all graduates have a rich understanding of basic research techniques, the confidence to evaluate and investigate clinical questions, the capacity to collaborate with an array of other professionals to solve systemic problems in health

care, and a commitment to lifelong learning. “The field of medicine is changing too fast for medical schools to take a lock-step approach to training physician-scientists,” says Dr. Goldman, who as executive vice president and dean has presided over a metamorphosis of the school’s education programs. “We’re not just giving students lifelong habits for a successful career; we’re equipping them to create the conditions that will fuel both personal satisfaction with their professional trajectories and the kind of creative approach to problem-solving that will enhance health care for their patients.”

In 2013, P&S graduated the first class to earn MDs through an overhauled curriculum featuring a scholarly project in one of six tracks—medical education, basic science, clinical research, global health, community health, or narrative and social research. This year, the launch of Scholarly Projects Plus expanded the program, offering students even more flexibility to delve deeper into their research with up to 12 months of protected time. A new joint MD/MS degree currently in its final phases of approval will allow students to take their investigations further still. Other dual-degree options include MD/MBAs and MD/MPHs plus the option to pair an MD with a master’s degree in bioinformatics, narrative medicine, or bioethics. In a twist on the conventional MD/PhD long available to P&S applicants, the three-year PhD-to-MD program launched in 2013 recruits motivated PhD scientists to earn an MD and more fully integrate clinical considerations into their bench science.

“No profession is more personalized than medicine,” says Dr. Goldman. “By allowing students to personalize and modify their training experience to meet their individual needs and intellectual passions, we mirror the emphasis in clinical care and research on tailoring diagnosis and treatment to a patient’s unique biology. In the case of patients, that approach promotes healing. By applying that same mindset to our educational programs, we can advance the field of health care, with our graduates leading the way.”

For Ms. Karagounis, the first step to figuring out how research would fit into her medical training was enrolling in a medical scholars seminar taught by Dr. Punt and Jaime Rubin, PhD, director of research development in the Department of Medicine. “We hope the seminar helps people develop the habit of thinking creatively across disciplines,” says Dr. Punt, who designed the course to promote success in scholarly projects.

HELP FROM OUR FRIENDS

CAROL L. LUDWIG, MD

As a graduate of P&S, Carol L. Ludwig is giving back to Columbia by supporting the Scholarly Projects Program through the Sara and Arnold P. Friedman Awards, named in honor of her parents. By funding this vital aspect of our students’ education, Dr. Ludwig is ensuring current and future P&S students receive essential mentoring from faculty as well as the crucial training experience of independent scholarship. These are critical for P&S students to mature into superior Columbia physician-scientists.

Anchor Point: New Building Rises

Every two weeks over the summer, the skyline of Northern Manhattan shifted again. That was the rate at which the construction force erected another floor on Columbia's new Medical and Graduate Education Building. The glass tower at 171st Street and Haven Avenue, Northern Manhattan's new visual landmark, is visible from the nearby George Washington Bridge and Riverside Park. The building will be used by P&S students and faculty and the biomedical departments of the Graduate School of Arts and Sciences. The 14-story building is scheduled to open in August 2016.

Designed by Diller Scofidio + Renfro and Gensler, the building concept is a "study cascade," with a 14-story open staircase at its core. South-facing outdoor rooms and terraces will create a sensation of openness and access to the natural world beyond the windows. A rooftop terrace overlooking the Hudson River plus other flexible outdoor and indoor spaces will allow for quiet study, group meetings, and casual conversations.

Interior spaces include 100,000 square feet of high-tech classroom facilities, including an advanced center for immersive, simulation-based medical education, and such amenities as lounges, café, and student commons. "We're constructing a space that can be adapted as our needs change," says Ronald Drusin, MD, vice dean for education. "We're really



excited about the new building. The classrooms will be flexible, productive, and useful for a very long time."

The construction work force—35 percent of whom are minorities, women, and local trades people—is using clean building techniques, including air and dust mitigation, noise and pest monitoring, and waste management. Their efforts, combined with additional sustainable design features, are expected to qualify the project for LEED Gold certification. "The new building provides upgraded education facilities that reflect the eminence of one of the top medical schools in the world," says Lee Goldman, MD, dean of the faculties of health sciences and medicine at CUMC and Columbia's executive vice president for health and biomedical sciences. "Both the building and



MICHAEL HERNÁNDEZ '17

the newly created green space that will surround it will revitalize our campus in ways that will benefit our medical center and the entire community."

Construction is supported by a lead gift of \$50 million from P. Roy Vagelos '54 and his wife, Diana Vagelos. Philip L. and Cheryl Milstein and the Helen and Clyde Wu '56 family also made generous donations. "The formal learning space will have state-of-the-art electronics that facilitate the delivery of information to students," says Dr. Vagelos, a former chairman and CEO of Merck & Co. "Spaces where the students can informally interact and work as teams reflect our new curriculum, which emphasizes team-based learning. This building will incorporate every aspect of medical and graduate education—updated in a modern, environmentally responsible way."

"If you don't know how to ask questions, hone them, and think rigorously, you can end up being superficial." It is a principle Ms. Karagounis—who is now deciding between an MD/MS and an MD/PhD—took to heart. "I hope to have a career that combines patient care and basic research," she says. "I want my research to be useful to patients who need answers."

Dr. Punt, who has been instrumental in developing the MD/MS program, designed the medical scholars seminar to bring together students from all four classes and immerse them in multiple intellectual perspectives. "One of the beauties of medicine is its multidisciplinary nature. You have to be a linguist, an anthropologist, a sociologist, a historian, a biologist, a physicist. You can't necessarily be all of those things, but you can learn how to talk to all of those different people, to find them and ask them questions."

A commitment to the integration of disparate perspectives also infuses the Columbia-Bassett program, which graduated eight members of its inaugural class this year.

Known for both its emphasis on rural health and a systems-level approach to physician training, the program combines

traditional medical education in New York City with hospital-based outpatient and inpatient clinical education at Bassett Medical Center in Cooperstown. "This program emphasizes relationships on all levels," says Henry Weil, MD, assistant dean for education at Bassett, "relationships among students and patients, fostered by the longitudinal curriculum; among students and more senior physicians—like the preceptors assigned in their year-long clinics—and the single mentor each student is assigned upon enrolling in the program; among students and the rest of the medical staff; and, perhaps most significant, among the students themselves."

Andrew Gomez '14, enrolled in the Columbia-Bassett program intent on a career as an orthopedic surgeon. The connections he formed during his four years in New York City and Cooperstown—with preceptors and with patients—spurred a change of heart. "The curriculum exposed me to myriad statistics, scientific papers, leaders in various fields, and other evidence that clearly delineated the need for a stronger and more effective primary care system in the United States," says Dr. Gomez, who matched to a family medicine residency at the

University of Washington in Seattle. “I credit the Columbia-Bassett program for providing me with the information to make an informed decision regarding the future of primary care and my potential role in the field.”

Thirty-year-old Gloria Sheng knows something of mid-stream changes. She was in the second year of a PhD in bio-organic chemistry at the California Institute of Technology, spending 12 to 15 hours a day in the laboratory, when a close friend’s unexpected death changed her perspective. “I realized if I wanted to stay in science for the long run, I would need more interaction with people in my day-to-day work and feel less isolated in the process,” she says. While working as a volunteer caregiver on the night shift at a Los Angeles hospital, she continued to work on her dissertation to characterize the anti-inflammatory properties of a set of polysaccharide mol-

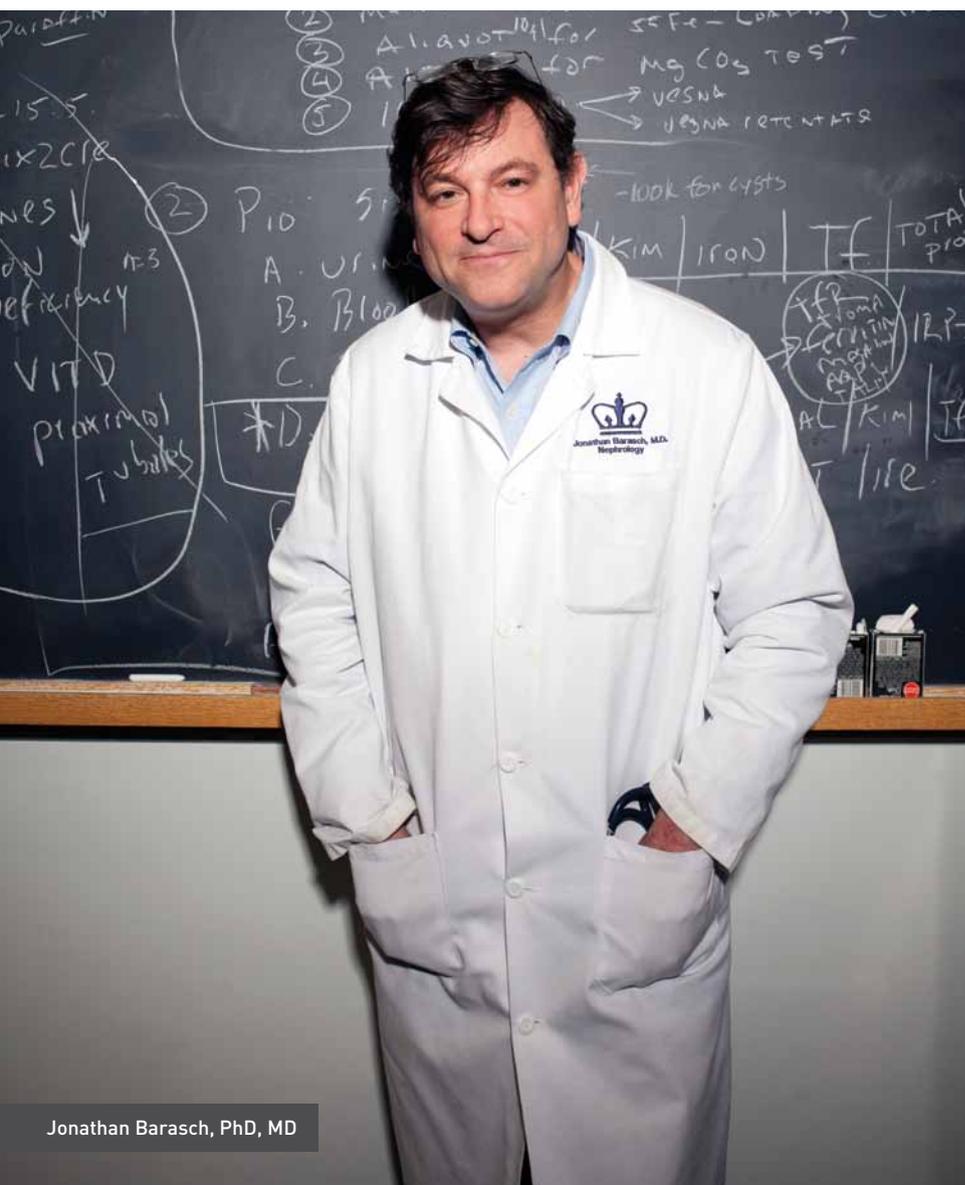
ecules that she had synthesized. “I was always aware of the clinical application of my project, but spending time in the hospital gave me so much perspective,” she says. “I could have characterized my synthetic molecules in greater detail or probed their biophysical properties, but my time in the hospital informed and affected the research questions that I really wanted to explore and pursue—which is how they could be used in the clinic.” At the end of July 2013, Dr. Sheng was awarded her PhD, and two weeks later she was living in Manhattan, diving into her first-year coursework at P&S as one of four inaugural PhD-to-MD students.

The transition from PhD-level basic science to first-year medical student has been intense, says Dr. Sheng, who credits access to the faculty team that designed the three-year PhD-to-MD program with easing the process. “I had one adviser in graduate school, and she was great for providing direct mentorship on how to become a research scientist,” she says. “At Columbia, however, I was surprised to find an entire group of faculty who were all interested in helping students build their career as physician-scientists. I think the breadth of mentorship that you encounter here is pretty unique to Columbia.”

Jonathan Barasch, PhD, MD, professor of medicine and of pathology & cell biology and associate vice chair for research in the Department of Medicine, directs the PhD-to-MD program with Nicholas H. Fiebach, MD, professor of medicine and department vice chair for graduate and continuing medical education. For the second PhD-to-MD class, Columbia received more than 100 applications and interviewed 22 people, says Dr. Barasch. “These are very advanced students with all of the intellectual tools and background information, study skills, work ethic, and creative determination to become a clinician scientist very soon. The idea of medical education for them is basically to provide the raw materials to plug into their already formed, mature, and sophisticated approaches to questions, problems, and finding solutions.”

For aspiring physicians without a PhD, the scholarly project requirement instituted as part of the 2009 P&S curriculum overhaul has created an entrée into the world of academic medicine for every Columbia medical student. Jonathan Amiel, MD, associate dean for curricular affairs, meets with all students to review their scholarly project proposals before they partner with advisers. He says beyond its benefits for students, the program is bearing unexpected fruit for the institution, as well.

A new MD/MS degree option will allow students to dig deeper into independent research, and especially motivated students can complete the dual degree in four years.



Jonathan Barasch, PhD, MD



Jonathan Amiel, MD



Lisa Mellman, MD

“All of our graduates shine according to their own strengths,” says Dr. Amiel, “and it allows us to expand the scholarly base of the medical school.”

The scholarly projects program allows both junior and senior faculty to develop deeper relationships with students, simultaneously enhancing their own research and recruiting prospective colleagues into their specialties. “They’re really getting to know students in a sustained way,” says Dr. Amiel. “Previously, faculty knew students maybe through a clinical rotation or an elective. Now, they get to know how professional students are, how invested they are; they experience their enthusiasm. It’s a very different kind of exposure.”

That exposure also has enhanced the recommendations faculty write for fourth-year students applying for residencies and has given students a richer body of material to discuss at interviews. “While the match has gotten incredibly competitive, our students are doing significantly better than the national average in terms of how many go unmatched,” says Lisa Mellman, MD, senior associate dean for student affairs. “There’s a correlation

with the new curriculum. The national average of unmatched U.S. seniors is 5.6 percent; our unmatched rate is 0.7 percent.”

In the years leading up to a class’s Match Day, students have the opportunity to take ownership of their own intellectual development. “Playing an active role in your own education begins a maturation process that involves increasing amounts of responsibility,” says Stephen Nicholas, MD, associate dean for admissions for P&S. “Students are more confident, more invested in the process and by taking responsibility for their own decisions they really internalize the process. Those are important, lifelong skills.”

For students intent on digging deeper into independent research, the new MD/MS will accommodate both a five-year track and, for a select group of especially motivated students, a four-year option. In addition to original, hypothesis-driven scholarship at a publication-worthy level, students will complete 32 credits of coursework on research methods, statistics, epidemiology, and basic and applied medical sciences. “Our new curricular emphasis on scholarship has presented us

with an opportunity to more rigorously develop the scholarly and research prowess of our best students,” says Dr. Punt. “Graduates of the MD/MS program will be uniquely poised to engage in and lead clinical research efforts; become influential participants in lay and professional discourses about medical advances; shape our health policies globally, nationally, and locally; and educate society and health professionals about best practices and advances.”

The world of medicine is changing fast, says Dr. Mellman. Physicians in some rural areas of the country may still practice in a single location, treating a small town’s array of maladies across the life span. Increasingly, however, physicians are as hyphenated as the multicultural society in which they practice. “The physician who is a policy-maker, the physician consulting to biotech, the physician who is entrepreneurial and devel-

“Our curriculum enriches students’ perception of challenges as opportunities.”

—Ron Drusin

oping a startup, the physician who is consulting in business—there are so many varieties of physician now that we need to be training physicians who can fill these various roles and provide leadership,” she says. “Having a flexible curriculum and multiple combi-

nations of degrees and pathways to careers as an MD is vital for leading institutions such as P&S.”

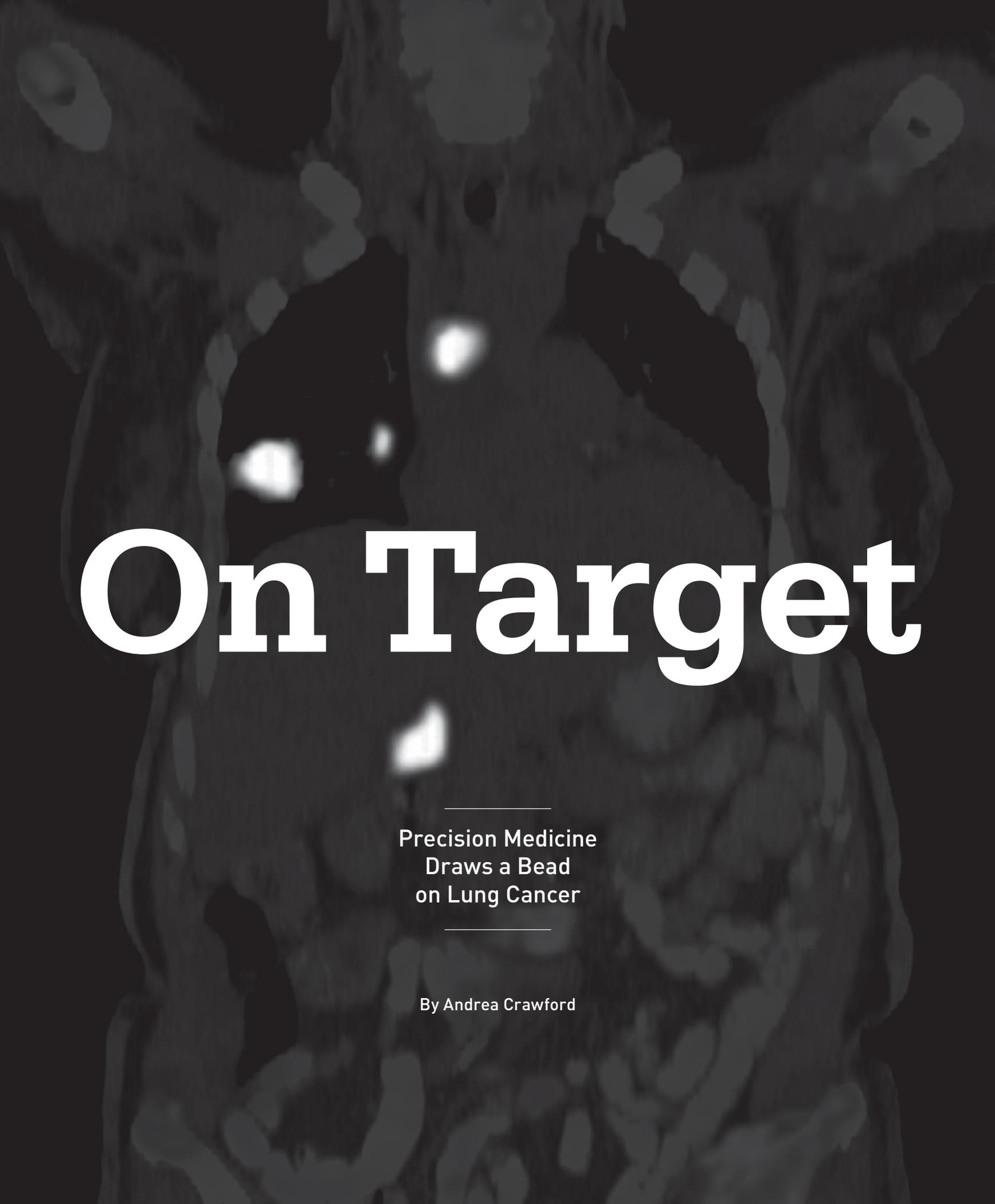
The next generation of doctors and physician-scientists also will be more diverse. P&S classes for the past four years have included at least 20 percent underrepresented minorities (24 percent of the most recent incoming class, the Class of 2018, is made up of underrepresented minorities). In recognition of the changing demographics of the medical profession, the Office of Diversity and Multicultural Affairs offers all medical center students opportunities to experience, celebrate, and appreciate the multicultural nature of their classmates, patients, and neighbors with a goal of helping students develop cultural competence. “Tomorrow’s physicians will have to be adept in their care of people from different cultures because the patients they will take care of will be of increasingly varied cultures and backgrounds,” says Hilda Hutcherson, MD, associate dean for diversity and multicultural affairs. “Our graduates will have to be good doctors to everyone.”

Students themselves hope to influence the next generation of physicians. BALSQ, the Black and Latino Student Organization, for example, created an outreach program called Young Docs that enables medical students to make monthly visits to neighborhood elementary schools, where they teach children about the human body and what it is like to become a doctor.

While the paths that students choose as they pursue their intellectual interests may vary widely, the overall effect of increased flexibility and personalization has been one of increased communication and integration between faculty and students, as well as within the student body. Such connections will only enhance the ability of P&S graduates to take fresh approaches to addressing the health system challenges guaranteed to emerge during their careers. “The new curriculum has allowed us to move forward with our plan in terms of educating students to be curious, to discover, to become outstanding physicians,” says Ronald Drusin, MD, vice dean for education. “With health care under tremendous pressure to redefine itself, our curriculum enriches students’ perception of challenges as opportunities and promotes their ability to forge connections with an array of collaborators to design new systems and address emerging problems. What our students learn at P&S will put them on a path to becoming leaders in academic medicine, which will benefit all of health care.” ❖



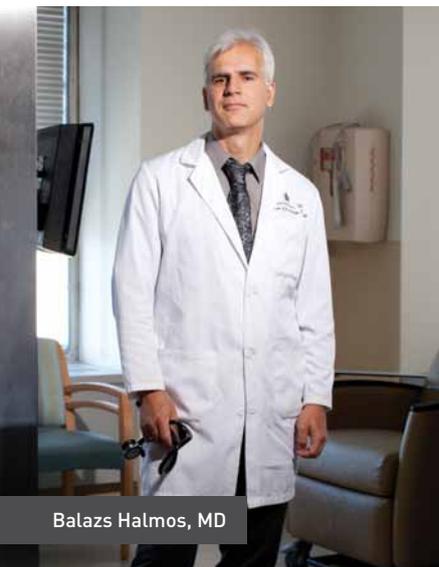
Hilda Hutcherson, MD



On Target

Precision Medicine
Draws a Bead
on Lung Cancer

By Andrea Crawford



Balazs Halmos, MD

JORG MEYER

In the clinic where Balazs Halmos, MD, treats patients twice a week, he sees firsthand the nihilism surrounding lung cancer: Individuals who have been smokers confront their diagnosis with a sense of guilt while those with advanced diagnoses believe they have been given a death sentence and think clinicians throw toxic treatments at them to no real effect.

“Now, that mindset has totally changed for me,” says Dr. Halmos, section chief of thoracic oncology. “It’s time to educate practitioners, support staff, patients, and families. We need to become more optimistic, more positive, and more proactive about lung cancer treatments.”

With lung cancer among the most lethal of cancer diagnoses—its five-year survival rate is lower than 15 percent—Dr. Halmos’ shift in attitude represents nothing short of a revolution, for the field and for Dr. Halmos himself. Only a year ago, the clinician published a moving essay in *The Oncologist*, likening his haunted feelings about caring for dying patients to the dark tale of Bluebeard in the opera written by Béla Bartók, a composer from his native Hungary. But in the past decade, the field of cancer care has been transformed by a greater understanding of the molecular drivers of tumors and propelled by an expansion of the ability to leverage that insight in the clinic.

Dr. Halmos joined P&S in 2009 to build a research effort around thoracic oncology. In the intervening five years, clinical studies involving molecular oncology—precision medicine—to treat lung cancer have gone at Columbia from zero to some 15 studies under way at any given time. “Every single patient who comes to Columbia with a lung cancer diagnosis now is triaged,” says Dr. Halmos, associate professor of medicine. “Without any delays, our pathology lab runs a very specific panel of molecular tests so that within the shortest period of time we can define the best treatment for that individual patient.” Molecular testing of biopsied lung tumors allows clinicians to identify genetic vulnerabilities within each cancer and thereby determine which combination of therapies may be most effective for a particular patient.

Dr. Halmos was a medical resident in 1997 when the first generation of targeted therapies delivered modest response. The earliest known target was the epidermal growth factor receptor (EGFR), a cell surface protein involved in cell growth and division that is overexpressed in about 10 percent of lung cancers. A few years later, as improved sequencing technologies helped identify precise mutations, Dr. Halmos was treating patients with a therapy targeted to EGFR when he noticed that in some patients, after an initial



HELP FROM OUR FRIENDS

DEBORAH AND JON KULLY

When Deborah and Jon Kully lost their father to lung disease in 2011, they were determined to prevent other families from enduring the same struggle. With a goal of transforming the outlook for lung transplant patients, the Kullys have provided major support to pulmonary research at Columbia University Medical Center.

Even though her father, Thomas, received the best possible care at CUMC, Deborah says the family came away with “some serious questions about what the standard of care for advanced-stage lung disease entailed.”

Thomas Kully faced difficult quality-of-life issues for years, even after a successful lung transplant. Transplant patients confront a number of serious challenges, including the unpleasant side effects of immunosuppressive drugs and, in Mr. Kully’s case, an ongoing battle just to breathe. “It was the most painful and frightening thing to watch, let alone what it must have been to endure,” says Deborah.

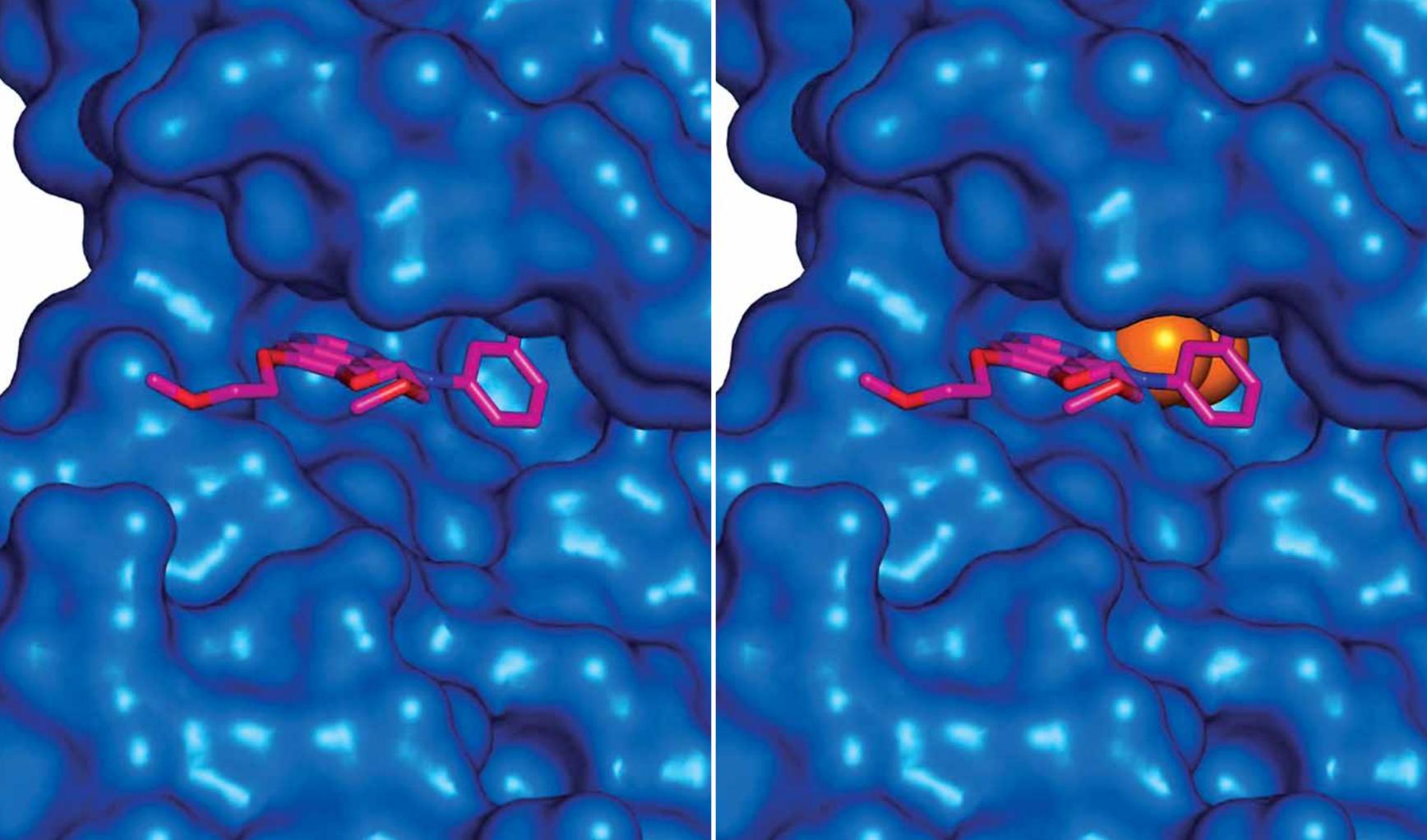
In memory of their father, Deborah and Jon established the Thomas R. Kully Pulmonary Research Initiative at CUMC to advance critical research in lung transplantation and potentially

change the landscape for lung transplant patients everywhere. The initiative supports a comprehensive approach to research in which scientific investigations of immunology and stem cells, as well as organ viability and immune tolerance, are conducted in tandem with clinical work to develop improved protocols for patients.

“We are in awe of the promising work led by Columbia faculty,” says Deborah, “and hope that some day the hardships of immunosuppression and chronic organ rejection will be distant memories and that a cure for serious lung disease will be in reach.”



Jon and Deborah Kully with P&S Dean Lee Goldman



response during which cancer growth was completely suppressed, the disease rebounded. By studying samples from these patients as tumor resistance developed, he discovered that the cause was a change in a single base pair of the cancer's DNA, research he published in 2005 in the *New England Journal of Medicine*.

Dr. Halmos likens those base pairs of DNA to the bricks used to construct a building: Shift just a single brick among the 3 billion found in human DNA, and the resulting modification in the amino acid sequence of the EGFR protein blocks a previously effective drug from fitting into the protein's binding pocket. "As a result of this little change, the medicine has no value any longer," he says. "The cancer becomes completely resistant based on just a single DNA event that occurs in one cancer cell."

Understanding that single amino acid change has propelled Dr. Halmos' quest to identify compounds that can overcome such resistance, each targeting a specific mutation while leaving the normal protein alone. "These new medications are much more successful against the mutant protein that drives the cancer and also have a lot fewer side effects," he says. While patients generally tolerate older medications that target EGFR, he explains, some people develop diarrhea and skin rashes due to the protein's role in bowel function and the growth of skin cells.

Dr. Halmos' investigation of the process by which EGFR resistance emerges has also shed light on the evolutionary pressure exerted by targeted drugs. He identified new mechanisms by which cancer cells become resistant to drugs through turning on new pathways that bypass the effect of the drug—work first reported in *Nature Genetics* in 2012—and is now collaborating with several industry partners and planning clinical trials to use this new knowledge to develop more effective combinations that can overcome and prevent such bypassing events. "The new information we gain about how the cancer changes allows us now to stay ahead of the cancer in the long term by predicting what changes could occur," he says. In this way, the future of cancer treatment resembles that of current successful HIV and tuberculosis therapies, where a combination of several agents successfully targets multiple weaknesses of the cells.

As understanding of those weaknesses continues to emerge, more patients benefit. In recent years, scientists have found targets in addition to EGFR that drive lung cancers, and Dr. Halmos' team is investigating a number of compounds to affect these genetic alterations as well. "Now, for 40 to 50 percent of all lung cancers, we can identify some genetic abnormalities where we have a clinical study for a novel drug," Dr. Halmos

Balazs Halmos discovered why lung cancer returns in some patients who initially responded well to a new drug that targets EGFR, a protein that promotes cancer growth. LEFT: When the drug, erlotinib, works well, it fits snugly into a groove in EGFR (blue), blocking the protein's cancer-causing activity. RIGHT: In patients who develop a mutation, T790M, a bulky protrusion (orange) is introduced into the groove and the drug no longer fits.

IMAGES COURTESY OF BALAZS HALMOS



Using Stem Cells to Make New Lung Cells

As a clinical hematologist performing bone marrow transplantations, Hans-Willem Snoeck, MD, PhD, felt stymied by the way older patients—“older being above age 35,” he notes—do not reconstitute T cells very well, thus lowering their chances of successful transplantation. T cells are made in the thymus, so to help his “older” patients, Dr. Snoeck set out to make a new thymus derived from stem cells.

“But, as it happens,” says Dr. Snoeck, professor of medicine (in microbiology & immunology), “the thymus, an organ that sits above the heart, is derived developmentally from an area very close to where the lung also arises.” Because of that, his effort led to a different breakthrough: Dr. Snoeck transformed human stem cells for the first time into functional lung and airway cells, setting the stage for new therapies for lung diseases and, ultimately, the ability to regenerate lung tissue.

Dr. Snoeck discovered a way to turn both human embryonic stem cells and human induced pluripotent stem cells into a primitive cell type called the anterior foregut endoderm, the cell responsible for the whole gut field, including the lung, liver, and pancreas. “We managed to coax this cell toward a very early embryonic lung dot and then differentiate those cells further into a variety of cells that we have in our lung and airways,” he says.

Building upon that work, in findings that appeared this past year in *Nature Biotechnology*, Dr. Snoeck showed functionality of the six different types of cells, including one known as type 2 alveolar epithelial. This AT2 cell makes both the lining of the airways and the alveoli, the terminal point in the respiratory system and site for gas exchange. AT2 has two vital functions. It produces a substance called surfactant, which lines the alveoli and keeps the lungs inflated. The inability to make surfactant is what causes premature infants to have severe respiratory distress; the inability also is implicated in a number of genetic disorders that result in lung failure—scientists believe some types of lung cancer derive from these cells—so the ability to generate the cells could have far-reaching clinical application, which other researchers are investigating. The other function of AT2 cells is the regeneration of the lung after injury, including minor injuries lungs sustain regularly from pollution or illness. That makes it a key target in idiopathic lung fibrosis, in which the regenerative function of AT2 cells is believed to have failed, an avenue of research that Dr. Snoeck is pursuing in collaboration with pulmonary medicine researchers David Lederer, MD, and Selim Arcasoy, MD. A lethal disease in which connective tissue, like scar tissue, surrounds the lung, IPF kills 30,000 people in the United States

every year; the only current treatment option is lung transplantation, the most difficult organ transplantation procedure and one that has the highest rates of complication and mortality. “AT2 is an extremely interesting cell to generate,” Dr. Snoeck says, “both to understand disease and to hopefully one day be able to do regenerative medicine for the lung.”

The other five cells Dr. Snoeck’s team generated hold promise, too. They include AT1 cells, the site through which oxygen and carbon dioxide exchange occurs; secretory, ciliated, and mucus-producing cells that play an important role in airway function; and, the most critical for regenerative medicine, basal cells, the stem cells that replace other cell types after an injury to the airways. Dr. Snoeck collaborates with researchers from Columbia’s biomedical engineering department to generate new lung tissue from patients’ own stem cells, using as a substrate lung connective tissue—the collagen, laminin, and so forth that acts like a scaffolding—taken from a donor.

Meanwhile, Dr. Snoeck persists with his original goal of improving the success rates for bone marrow transplantation. “We can now make to complete purity the structure from which the thymus emerges,” he says. “We have the stem just before you have a thymus, and now we’re working on what we hope will be the final step of that process.”

says. “The list is ever expanding and the percentage of patients impacted is larger and larger.”

The emerging field of immunotherapeutics may hold the key to further expansion of the portfolio of treatment options available to combat lung cancer. Although researchers long assumed that the immune system played no role in pulmonary oncology, immune cells have the ability to recognize lung cancer cells but sometimes they get outsmarted. “These cancer cells can develop ways whereby they prevent the immune system from being able to recognize and attack them,” says Dr. Halmos. “There’s a very particular pathway that the lung cancers can utilize to paralyze—basically Taser—immune cells as they patrol the body in their attempt to eradicate cells recognized as foreign, such as cancer cells.” Key to the subterfuge is a protein expressed on the cancer cell surface that engages with a protein on the surface of the immune cell, rendering it ineffective. Now new medicines are being investigated in the clinic that can disrupt this interaction, thereby turning off the Taser and allowing the immune cells to kill the cancer cells.

Lung cancers that develop among people who smoke tobacco appear to be excellent targets for immunotherapies, because smoking-related variants of the disease have many more genetic abnormalities than other types of lung cancer. “The lung cancer of a smoker has at least 200 to 300 different mutations, and many of them change the proteins of the cancer cell to the point that when it’s present on the cell surface, it looks foreign to the immune system,” he says. This too is a hopeful development; the majority of lung cancer patients fall into this category and, until now, many of the advances in targeted treatments have not been applicable to them. In collaboration with industry partners, Dr. Halmos’ team is assessing novel therapies that block the pathway most often affected in these patients.

Meanwhile, Dr. Halmos’ research team also has discovered ways to make tumors more susceptible to conventional chemotherapeutics, as he showed in a paper published in *Carcinogenesis*. “The reality is that there are still a very large number of patients who need to receive chemotherapy agents and radiation and benefit, many times greatly,” he says.

In the case of stage 3 lung cancer, for example, the current standard of care is not targeted therapy or surgery, but combined chemotherapy and radiation. That protocol has not changed in 30 years, but it works long-term in only 20 percent of patients. To better understand how tumors become resistant to this approach, Dr. Halmos has partnered with Simon K.



JORG MEYER

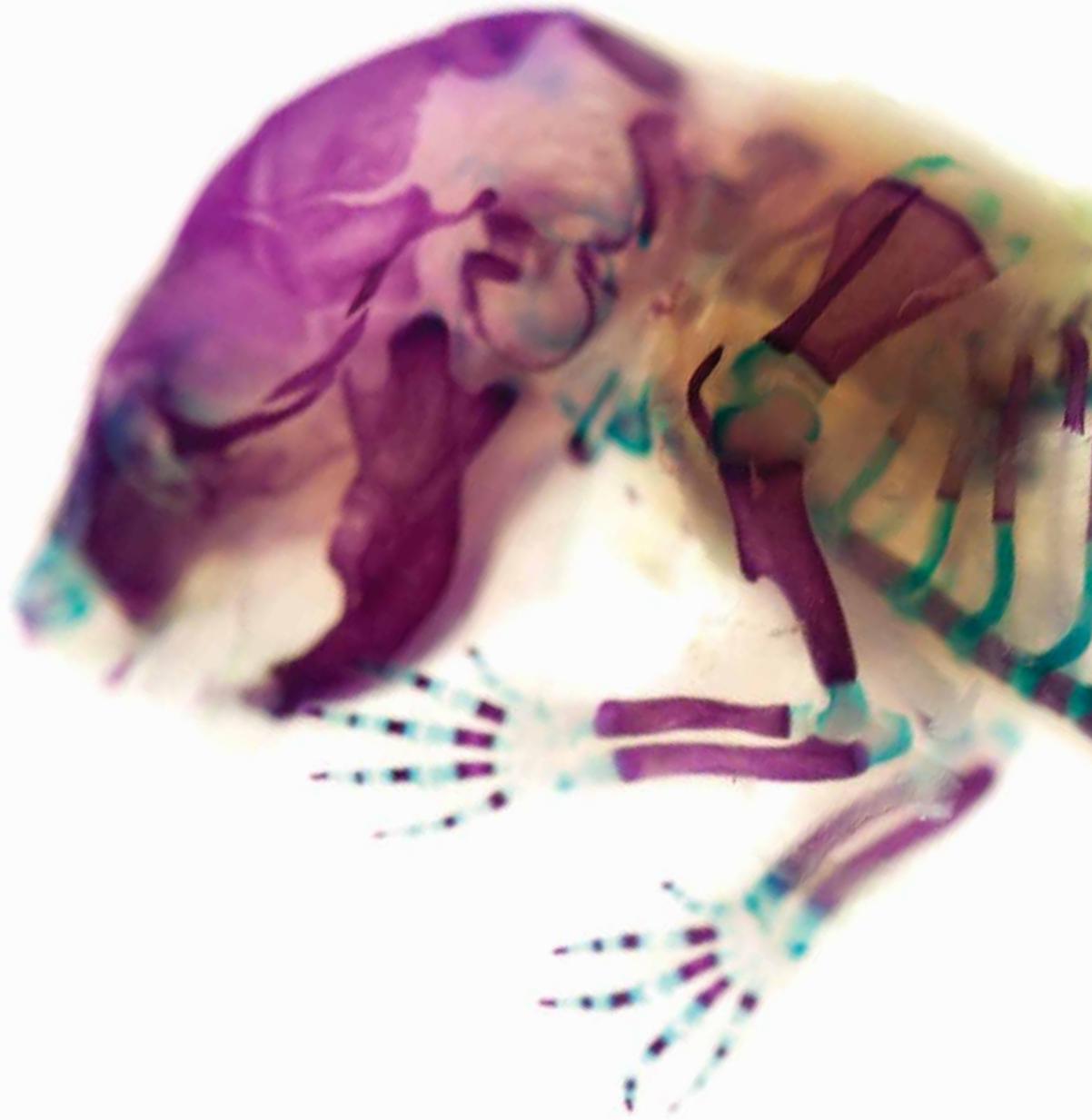
Irving Radiation Oncology Center Opens

In September, NewYork-Presbyterian Hospital/Columbia opened the Irving Radiation Oncology Center, a 12,500-square-foot clinical facility to provide radiation therapy and diagnostic imaging for children and adults with cancer. The center’s new technology offers treatments that more precisely target tumors and spare healthy cells from unnecessary radiation exposure by use of image-based target verification.

“We have an excellent radiation oncology department and that’s key for thoracic cancer patients, since the large majority of people with lung and esophageal cancer will need some form of radiation treatment as part of their curative or palliative care,” says Balazs Halmos, MD, section chief of thoracic oncology at CUMC. “The center is very sophisticated when it comes to technological advances, and we are also blessed by the fact that the center is research-oriented and active in running a number of good, strong radiation-built research studies.”

Cheng, MD, PhD, assistant professor of radiation oncology, to develop a unique, functional genomic screen that assesses every gene in the cancer cell. Says Dr. Halmos: “We can get a sense of how every single gene—depending on whether it’s under-functioning or over-functioning—might contribute to the development of resistance against these classes of agents.” This has resulted in a short list of lead candidates, including the YAP gene. “By blocking its function in the laboratory we can enhance the activity of radiation and chemotherapy quite significantly,” he says.

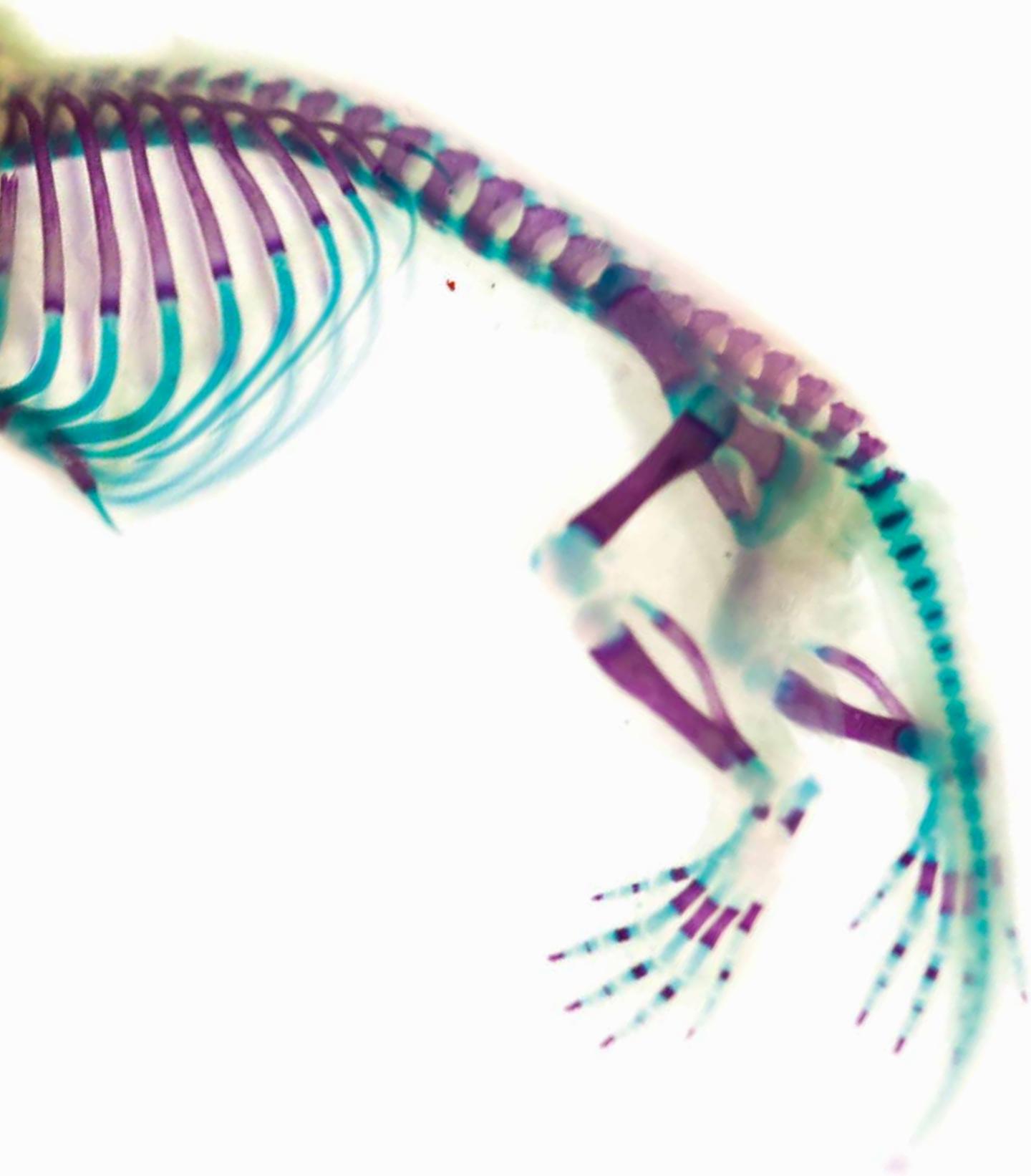
Dr. Halmos feels lucky to be working in this era of molecular revolution and in a field where patient need and research potential are equally profound. “I have had, by now, a number of patients who have gone many, many years with advanced lung cancer, going from one oral targeted agent to the next,” he says. “This is going to become more and more of a reality.” ❖



What Bone Does When It's Not Making Bone

SKELETON KEY

By Alla Katsnelson



Three years ago, when Franck Oury, PhD, put the knockout mice he was studying through a simple behavioral test, he almost could not believe the results. Normally, a mouse set loose into a new environment actively explores its surroundings. But these mice, which were missing the bone-derived hormone osteocalcin, cowered in a corner of the test cage for the full 30 minutes of the experiment—a display of intense anxiety and depression.

Dr. Oury, then a postdoc in the lab of Gerard Karsenty, MD, PhD, and now a faculty member at Paris Descartes University, immediately briefed Dr. Karsenty. To Dr. Oury's surprise Dr. Karsenty already knew about this phenotype and encouraged further study. They decided to try other behavioral screens, and what they saw was even more surprising: The animals utterly failed a classic memory test called the Morris water maze, which involves finding a submerged platform in a pool of milky water. Most mice learn over several days of training to scramble to the platform within 10 seconds, but the osteocalcin knockout mice were not able to improve their time; they could never recall, from trial to trial, where the underwater platform stood.

"The differences were so striking that we redid that experiment over and over, to make sure we were not making a mistake," says Dr. Karsenty, the Paul A. Marks Professor of Genetics and Development, professor of medicine, and chair of the Department of

really first started that with his osteocalcin work," says Thomas Clemens, PhD, director of research in orthopedic surgery at Johns Hopkins School of Medicine and a former editor in chief of the *Journal of Bone & Mineral Research*. "It's been tremendously important in the bone field."

Dr. Karsenty began his exploration of osteocalcin in the early 1990s as a junior professor at the University of Texas MD Anderson Cancer Center. After training as an endocrinologist in Paris, he launched his research career in the United States with the study of bone development and identified along the way the master regulator of bone development. Yet he had an inkling that revisiting bone physiology with modern genetics tools might be important. "I started looking at bone physiology, trying to determine whether bone is doing anything beyond bone."

He was intrigued by one observation that he saw as being the key to unraveling the relationship between bones and other organs. Throughout the vertebrate life span, the skeleton is in a constant state of destruction and renewal, with cells called osteoclasts breaking bone down and osteoblasts rebuilding it again. That made bone the only tissue in the body to contain a cell type whose only function is to destroy itself. It takes a lot of energy to commit suicide, Dr. Karsenty reasoned, and even more to replace what has been destroyed. He also kept returning to what he knew about the link between eating and bone. Anorexic children stop growing up and anorectic adults often develop osteoporosis. In other words, in absence of energy (food) intake, bone mass decreased. Could bone and energy metabolism be linked? Dr. Karsenty found the idea exciting. "I did not know if it was true," he says, "but it was completely disconnected from what everybody was doing."

Dr. Karsenty's lab already generated the osteocalcin knockout mice. To his disappointment, though, while these animals had some quirks—bellies overflowing with fat, for example—their skeletons did not seem all that unusual. Yet the increase in adiposity is what attracted the attention of Dr. Karsenty. In 1998 he began to look at another genetically engineered mouse with a different mutation; this one was obese because of the deletion of a gene coding for the protein leptin. Although other researchers had demonstrated leptin's ability to regulate appetite via its signaling in the brain, Dr. Karsenty suspected that it might have equally important functions. For example, flies and *Caenorhabditis elegans*—two well-studied invertebrates—have appetites but do not have the gene for leptin; evolutionarily, the protein appeared on the

"We know that osteocalcin blood levels are determined by bone formation and resorption, so we want to know if bone quality and bone health are determinants of cognition."

—GERARD KARSENTY

Genetics & Development at P&S. "In the absence of osteocalcin, mice have no memory whatsoever."

Why would osteocalcin, a protein produced by bone-forming cells, or osteoblasts, have such a profound effect on cognition? The answer to that question flows directly from nearly two decades of research in which Dr. Karsenty has woven together threads from experimental mouse studies, clinical data, and evolutionary observations to identify unexpected reciprocal relationships among bone and other organs. Along the way, colleagues say, Dr. Karsenty has singlehandedly overturned the notion of the skeleton as an inert supporting structure for the body. "The whole concept that bone is talking to other organs—it's Gerard who

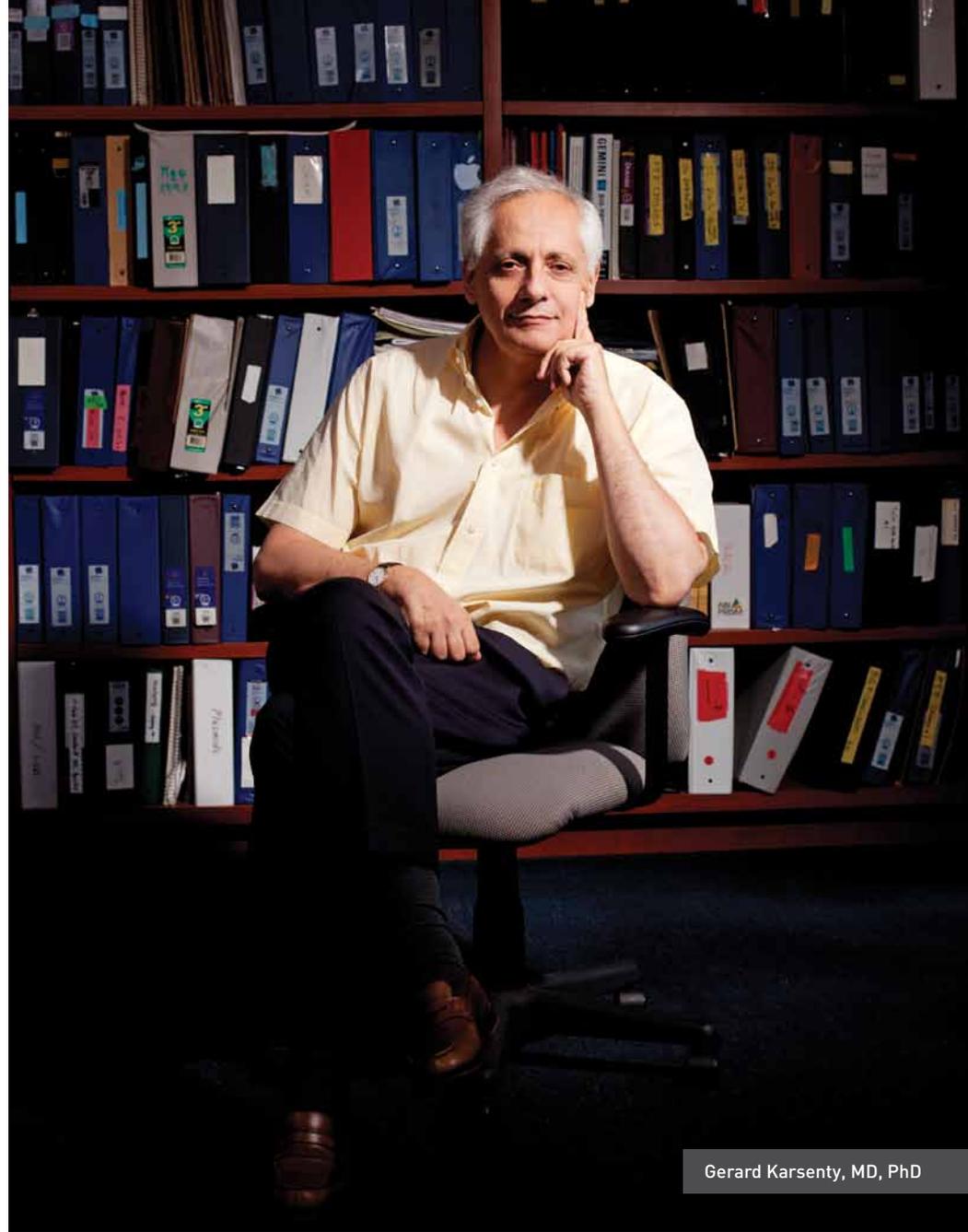
scene only with the emergence of bones. Perhaps, he hypothesized, leptin was the molecular link between bone remodeling and energy metabolism.

In the late 1990s, researchers still widely thought that bone served as little more than a hanger for skin and protection for innards. At first, many of Dr. Karsenty's students and postdocs thought his hypothesis about bone's endocrine function was off the wall; some even left the lab. To the naysayers who remained, Dr. Karsenty offered a deal: Order the mice and see. "If you are right, you buy me a beer, and if I am right, I buy you a beer," he told them. He won: In 2000, *Cell* published the group's report that leptin knockouts had 40 percent more bone mass than controls, suggesting that leptin serves as a powerful brake on bone buildup. Additional investigation showed that leptin works by inhibiting the release of the neurotransmitter serotonin in the brain stem, tying the process of bone mass regulation to a sympathetic nervous system process.

Over the next several years, the lab further delineated this signaling system, eventually bringing the story back around to osteocalcin. That belly fat in the osteocalcin knockout mice, Dr. Karsenty had long suspected, might be a sign of glucose intolerance. "If energy metabolism regulates bone," he says, "the logic of endocrinology, with its feedback loops, suggests that bone also regulates energy metabolism." With the help of additional knockout mice, the group showed that osteocalcin regulates insulin secretion, insulin sensitivity, and energy expenditure, while insulin loops back around to boost osteocalcin function. That makes bone, in effect, a regulator of energy metabolism, Dr. Karsenty says. "What is remarkable is that the two main hormones of energy metabolism"—leptin and insulin—"converge on osteocalcin but in an opposite manner."

Dr. Karsenty's reports on the skeleton's endocrine capabilities caused something of a stir among bone researchers. "The field was kind of stagnating, and he shook it up," says Dr. Clemens. But the work has not been without its critics; their most substantial concern is the translation of Dr. Karsenty's mouse studies to human biology. Mice have a much higher metabolism rate than humans, says Dr. Clemens, with a heart rate of 300 beats per minute and an appetite big enough to consume a quarter of their body weight each day. "I would bet that it's not as straightforward [in humans] as it is in the mouse," he says.

In broader terms, Dr. Karsenty reasoned that if osteocalcin is a hormone, it must have multiple functions, as most hormones do. As his group continued



Gerard Karsenty, MD, PhD

to work on the regulation of insulin secretion by osteocalcin, he pursued another hunch: Since women undergoing menopause tend to lose bone and estrogens control bone growth, fertility also must be looped into this swirl of feedback signals. Not long after arriving in Dr. Karsenty's lab in 2007, Dr. Oury took on the project of looking at the effect of osteoblasts on estrogen production in the ovaries. He began with a simple experiment: growing strips of ovaries in a petri dish with osteoblasts. He also included some dishes of testes and osteoblasts as a negative control. Unexpectedly, the osteocalcin-producing cells had no effect on the ovarian tissue, but they jacked up testosterone synthesis in the testes explants.

Dr. Oury then used the osteocalcin knockout mice, as well as mice engineered to lack the osteocalcin receptor only in specific testes cells called Leydig cells,

to show that osteocalcin was the culprit for the testosterone effects the group had observed; they published their results in 2011 in *Cell*. That report also identified a testes-specific receptor called *Gprc6a*, through which osteocalcin functions, and showed that this signaling ratchets up testosterone production in Leydig cells—a finding independently confirmed by researchers at the University of Tennessee. This time human genetics verified that, as expected, osteocalcin had the same functions in mice and in humans. The researchers identified two men who carried mutations in the corresponding human receptor, both of whom were not only infertile, but also glucose-intolerant, just like mice lacking osteocalcin. “We cannot exclude [the possibility] that there is another hormone produced by bone that also regulates female fertility, following the same feedback loop,” says Dr. Oury, first author of the 2013 report in the *Journal of Clinical Investigation*.

Even as the puzzle pieces of osteocalcin’s hormone-like actions came together, a major question remained unanswered. Leptin, the most powerful regulator of bone mass identified so far, blocks bone mass accrual. How then, in the face of this negative regulation, can bones grow? Put another way, if the brain regulates, negatively, bone mass, via brain stem-produced serotonin acting on leptin, then bone should in turn regulate the brain so that bone growth could occur.

That idea led Dr. Oury to the behavioral testing of the osteocalcin-deficient mice. Researchers working with osteocalcin knockout mice had long noticed that the animals were more docile than wildtype animals. What’s more, several bone diseases in humans have been associated with cognitive impairment; most interesting to the

team was cleidocranial dysplasia, caused by a decrease in the protein *Runx2*, a master gene of bone formation the researchers had previously identified as the major regulator of osteocalcin’s expression. Yet the team was taken aback by how powerfully the memory of the osteocalcin knockout mice was affected; their observations suggested that the molecule is a much more central player in the brain than even Dr. Karsenty’s hypothesis had predicted. “The effects of osteocalcin on memory are so profound that they call for a molecular investigation of the mechanism of action, and they also call for an investigation of other functions of osteocalcin in the brain,” Dr. Karsenty says.

Osteocalcin is not expressed in the brain, so to explore its role the group first asked whether the molecule could cross the blood-brain barrier. The researchers found that it could and that it binds to neurons in the brain stem, midbrain, and hippocampus and regulates the production of several neurotransmitters. When the researchers injected osteocalcin into the brains of adult osteocalcin knockout mice, the animals’ anxiety and depression lessened, yet their memory remained significantly impaired.

The team then looked at whether osteocalcin affects the developing brain in utero. The researchers were able to discern the molecule’s presence in fetal mice about four days before birth, and yet the osteocalcin gene is not yet expressed at that age. This led to the discovery that it is osteocalcin of the mother that, after crossing the placenta, regulates brain development of the embryos. Capitalizing on this observation, Dr. Karsenty and his colleagues could show that injections of osteocalcin to pregnant osteocalcin knockout mice normalized brain development but also rescued, to a

HELP FROM OUR FRIENDS

TONI STABILE

In the early 1990s, when Toni Stabile’s award-winning career as an investigative journalist was curtailed by osteoporosis, she met with Columbia’s Ethel Siris, MD, a leading clinician in the field. Ms. Stabile worked with Dr. Siris to develop a shared vision to design a center that would

raise osteoporosis awareness and encourage early diagnosis and treatment of women and men from all socioeconomic backgrounds. Her first gift established the Madeline C. Stabile Professorship in Medicine, held by Dr. Siris. Subsequent gifts helped open the Toni Stabile

Osteoporosis Center in 2001. Ms. Stabile died in late 2013 and bequeathed \$4.5 million in endowment to support the center, which today is the largest in the metropolitan area. It is known for its unique combination of patient care, medical research, and state-of-the-art equipment.





Eric Kandel, MD

great extent, memory in their osteocalcin-null offspring. Hence, two pools of osteocalcin exert complementary functions in the brain. During development, maternal osteocalcin favors brain development and establishment of memory. After birth, osteocalcin regulates expression of several neurotransmitters and is needed to prevent anxiety and depression and to maintain memory.

“No one has ever found an effect like this,” says Eric Kandel, MD, University Professor and Kavli Professor of Brain Science at Columbia. “It’s a wonderful finding and it has completely come from Gerard Karsenty’s lab.” Dr. Karsenty asked Dr. Kandel, who won a Nobel Prize for his work on the biological basis of memory, to confirm the Karsenty team’s behavioral observations before *Cell* published the work in September 2013. If the findings can be extended to humans, Dr. Kandel says, the implications may be great. “As we age, we have loss of bone mass; therefore, in principle, we release less osteocalcin. It’s possible that age-related memory deficits may in part be due to insufficiencies in osteocalcin and that by giving osteocalcin, we might reverse it.”

Much remains to be learned about osteocalcin’s role in the brain. Teasing apart how the molecule exerts its effect on cognition has become a central project in the Karsenty lab. One key effort, therefore, is identifying the receptor for osteocalcin in the brain—which is different from its receptor in other tissues. The group is also investigating whether the hormone can improve

cognition in older animals and, if so, whether it binds to the same neurons in mice and in humans. If the answers are yes, Dr. Karsenty says, testing osteocalcin’s ability to fight cognitive decline in aging will be warranted.

“The notion that arises from this work is that bone may be a gatekeeper preventing aging of the organism, as long as bone mass and osteocalcin secretion

“My own belief is that osteocalcin has a lot of functions in the brain and that age-related memory loss is due to a number of different contributing factors.” —ERIC KANDEL

are maintained at high levels,” Dr. Karsenty says. “We know that osteocalcin blood levels are determined by bone formation and resorption, so we want to know if bone quality and bone health are determinants of cognition.” The group is also extending its work on the protein’s involvement in development; perhaps an osteocalcin-based treatment might prove effective for children born to malnourished mothers.

The Karsenty and Kandel labs are now collaborating to test osteocalcin’s potential to treat memory loss in aging. “My own belief is that osteocalcin has a lot of functions in the brain and that age-related memory loss is due to a number of different contributing factors,” says Dr. Kandel. “The overlap will be fascinating to explore.” ❖



Going Retro

Obscure Protein
Complex Furnishes
Fresh Clues for
Alzheimer's
Investigators

By Andrea Crawford

Illustration by
Davide Bonazzi

Columbia neurologist Scott Small, MD, was hot on the trail of a relatively unknown cellular component known as retromer and sure he was on to something big—the molecular engine underlying the pathologies at the core of Alzheimer's devastating symptoms—when a journalist investigating the root causes of dementia visited the Small lab in 2006. “I think that if you come back here in five years,” he told the reporter, “we'll have drugs for retromer dysfunction.”

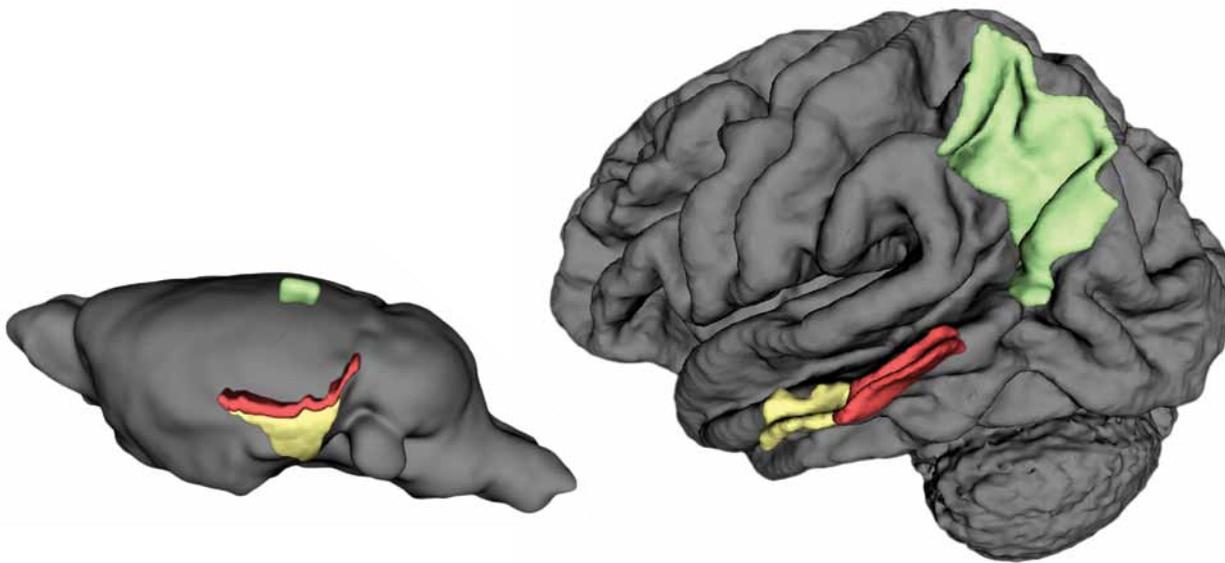
Though he did not quite make the five-year prediction, in an April 2014 paper in *Nature Chemical Biology* Dr. Small revealed a “pharmaceutical chaperone” for retromer, an obscure complex of proteins that acts as a clearinghouse during intracellular transport. The finding, which resulted from a decade-long collaboration, offers the potential for targeted therapy for Alzheimer's disease as well as Parkinson's disease. In its report of the breakthrough, *Science* magazine noted that, while Dr. Small's published work has thus far been carried out only in cells, “the new results have nonetheless impressed some veterans of the Alzheimer's field.”

It's an exciting lead for Columbia researchers—and one that has emerged from two directions. Richard Mayeux, MD, founding co-director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, has spent more than a decade compiling the genetic records of families with Alzheimer's. Dr. Mayeux is part of an international team that has identified about 25 genes that play a role in late-onset Alzheimer's; many are involved in retromer function as well. It is also an exciting lead for anyone touched by the intractable disease, which affects some 5 million Americans. That number is growing sharply as the population ages; last year the disease represented \$210 billion in health care costs.

The retromer breakthrough comes at a time when the mood among researchers and the public alike has darkened, as a number of large-scale drug failures around the country have raised questions about the basic hypothesis of what causes Alzheimer's disease. But that dark mood is not universal. Investigations by Taub scientists have uncovered where the disease begins, how it spreads, and what genes are associated with it. This year, the drug discovery program for retromer entered the preclinical stage by testing for efficacy and safety in animal models. In sum, P&S researchers are bringing an altogether new level of understanding to the disease and raising expectations that treatments may be within sight.

In 1906, in the autopsied brain of a woman who had suffered from severe dementia, the German physician Alois Alzheimer saw how amyloid-beta peptide—a-beta to the scientists investigating it—forms around neurons in dense clumps known as plaques and how neurofibrillary tangles, the pathological twisting of tau protein, builds up within nerve cells. In the 1980s, scientists discovered that a-beta is a byproduct of amyloid precursor protein (APP), which, like tau, is an important protein for tissue stability and cell biology and thus essential to human health. As Michael Shelanski, MD, PhD, the Delafield Professor of Pathology & Cell Biology, chair of pathology & cell biology, and founding co-director of the Taub Institute, puts it: “It turns out that in Alzheimer's disease, as best we know, a number of proteins that are good friends of ours have taken on evil roles. The first question is ‘Why?’ The second is, ‘What can we do to return them to normal function?’”

The leading theory to address Dr. Shelanski's first question emerged in the 1990s, when scientists identified a genetic mutation that triggers



Alzheimer's disease starts in the entorhinal cortex (shown in yellow in a mouse brain, left, and a human brain, right). Using fMRI, the researchers show how the disease spreads from the entorhinal cortex to other cortical regions: the perirhinal cortex (shown in red) and the posterior parietal cortex (shown in green).

IMAGE COURTESY OF SCOTT A. SMALL

early-onset Alzheimer's, a rare form of the disease. The mutation causes APP to be overproduced. Based on that finding, in 1992 scientists formulated the amyloid hypothesis: The accumulation of amyloid plaques lies at the root of the disorder.

"There are a lot of reasons why the amyloid hypothesis is taking body blows," says Dr. Small, the Boris and Rose Katz Professor of Neurology and director of Columbia's Alzheimer's Disease Research Center. "The reasonable ones involve a couple of observations." First is the failure of hundreds of drugs that were designed to clear the plaque; second is that the area of the brain with the highest density of plaques in Alzheimer's is not the area with the highest dysfunction.

Nevertheless, the hypothesis is legitimate, if imperfect, he says. When APP is misprocessed, it is ultimately broken into multiple fragments, the final fragment of which is a-beta. It is becoming clear that keeping APP from breaking into these fragments is key. "There's growing evidence that the intermediate fragments could be just as toxic," Dr. Small says. In that case, if you clear only the amyloid plaques, "You've cleared the smoke, but the fire's still burning."

The burning fire appears to be in the endosome, an organelle within the cell that acts as the trafficking hub, directing proteins on their itineraries among cellular destinations. The two primary routes are toward the secretory pathway and the degradation pathway. Proteins can be recycled back to the cell surface, via the Golgi, where they are secreted outside the cell or sent to the lysosome—the garbage can of the cell—to be degraded.

Retromer is a key component of the endosome-to-Golgi pathway, packaging the cell's cargo of proteins and lipids and thus playing a role in how proteins are sorted and transported to the cell surface. When Dr. Small first found retromer a decade ago, he says, "I knew absolutely nothing about it. But it was not that difficult to read everything because there wasn't much to read." Retromer had been discovered in yeast in 1998 by a Cambridge University scientist and confirmed in mammalian cells just a year before Dr. Small encountered it in 2004.

At the time, Dr. Small's research was focused on determining where Alzheimer's begins. Using newly developed fMRI techniques to image the brains of living patients, he confirmed what was first suggested postmortem—that the entorhinal cortex is the site where the disease originates. "You probably could have intuited that from postmortem studies," says Dr. Small, who in a December 2013 paper in *Nature Neuroscience* described more precisely where in the entorhinal cortex the damage begins, why it starts there, and how it spreads.

"What turned out to be more important is identifying a neighboring area that was relatively unaffected by Alzheimer's," he says. What made that adjacent, unaffected area different were its higher levels of retromer.

Once Dr. Small had found those low levels of retromer in the area of the brain where Alzheimer's originates, he hypothesized that when the protein complex malfunctions, it slows the movement of APP through the endosome—often enlarged in Alzheimer's disease—where it is then broken down into the harmful amyloid-beta. "APP processing happens in the endosome, so the goal is to keep APP flowing quickly," Dr. Small says. "When you have defects in the retromer-related proteins, APP remains longer than it should in the endosome—even milliseconds too long—and it's there that it meets the enzyme that starts to cleave it."

Dr. Small and a team of P&S collaborators took that insight to the lab, where they delved deeper. With Tae-Wan Kim, PhD, associate professor of pathology & cell biology (in the Taub Institute), he demonstrated retromer's role in the APP-endosome process in cell culture. With



HELP FROM OUR FRIENDS

CHARLES ADLER

As a member of the advisory board of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Charles Adler knows just how prevalent these diagnoses are—and how devastating they can be. He also sees firsthand the extraordinary promise in the tireless efforts of Taub investigators and how the work of Columbia faculty provide hope where little or none existed even just a few years ago.

To ensure that the work of the brightest investigators in the field is nurtured early in their careers, Mr. Adler established the Adler Assistant/Associate Professorship

at the Taub Institute. The Adler Professorship recognizes the outstanding contributions of a young physician-scientist working on neurodegenerative disorders and provides the faculty member with crucial support to take advantage of every opportunity to translate new knowledge into better and more effective treatments for patients. Nurturing the early careers of pioneering scientists is a core element of the mission of the Taub Institute, and the vision and generosity of friends such as Charles Adler help make that possible.

Trying Dietary Interventions to Improve Memory

The anatomical investigations that led to Dr. Small's discovery of the role of retromer also yielded insights that help distinguish Alzheimer's disease from the memory loss associated with normal aging. Dr. Small has identified a specific molecular pathway in an area of the hippocampus, the dentate gyrus, long associated with age-related memory loss; in this case, a gene stops producing a key protein involved in memory formation. In a collaborative effort with University Professor and Kavli Professor of Brain Science Eric Kandel, MD, whose lab generated a genetically modified animal model based on this molecular observation, this molecular pathway has been shown to play a causal role in age-related memory loss in mice, whose hippocampus is very similar to humans. Indeed, a recent genetic study by Dr. Mayeux's group has suggested that this molecular pathway plays a causal role in humans.

"It's a very different pathway from what we found in Alzheimer's, which further supports that Alzheimer's and aging are two different processes," says Dr. Small. "They're different at the anatomical level and at the molecular level." He and his team have since launched a clinical trial to test dietary interventions to reactivate the dentate gyrus; they expect to publish their findings later this year.

"Should we be fixing a normal process? The answer is yes, if it's safe and available for everyone," says Dr. Small, who likens such an intervention to a prescription for reading glasses. "Memory loss is still the chief complaint of many of my patients—because we're all living longer, and we all want to stay cognitively engaged."

Karen Duff, PhD, professor of pathology & cell biology (in psychiatry and in the Taub Institute), and Brian McCabe, PhD, assistant professor of pathology & cell biology and of neuroscience, he documented the pathway in animal models. Then, in what Dr. Small calls "the most powerful experiment, Mother Nature's experiment," Dr. Mayeux identified genetic variants in SORL1, which codes for the transport of APP through the cell by regulating retromer, in patients with Alzheimer's disease. "I think the field now is comfortable in concluding that the retromer pathway plays a pathogenic role in late-onset Alzheimer's," says Dr. Small.

About a decade ago, Dr. Mayeux started collecting data from families throughout the United States who had multiple members with late-onset Alzheimer's. Scientists had already identified the risk factor genes for early-onset forms of the disease, which account for just 1 percent of patients. "With a common disease, there could be more than one gene involved, so you have to have a large enough sample to detect all of the genes, even though they might have small effects," says Dr. Mayeux, the Gertrude H. Sergievsky Professor of Neurology, Psychiatry, and Epidemiology (in the Sergievsky Center and the Taub Institute), chair of neurology, and director of the Sergievsky Center. Partnering with other institutions, he collected DNA data on 1,600 families and from the beginning gave any qualified scientist access to the data. Subsequently, the federal government asked Dr. Mayeux and others with data on families to devise a project, now known as the Alzheimer's Disease Sequencing Project, to sequence a large number of individuals, with the hope that by identifying the genetic substructure of the disease, the scientists could start to see how DNA fits into the picture.

"The limitation of that approach is that you basically get a signal near the gene, but it may not tell you what's wrong with the gene," Dr. Mayeux says. A group of Taub scientists is now doing targeted sequencing of the 25 known genes in an attempt to identify mutations. "I can't imagine that each of them is causal," he says. "My guess is that they work in collaborative pathways, and so far it looks like there are probably three major pathways." In addition to the genes associated with retromer function, another likely culprit is the pathway involved in a localized inflammatory process in the brain. A third has to do with lipid transport.

"It is thought that some of these mutations just don't give you enough SORL protein for retromer to actually perform its task, but there must be a half dozen genes that are all part of that family, and they all act about the same way," Dr. Mayeux says. "Why do you need a half dozen? No one knows yet, but it's a very interesting story and once we start defining these things, we'll have a much better idea of how to treat the condition."

The work of the Taub researchers "seems to come together like a jigsaw," Dr. Small says. "Basically, what it said to us was that if the endosome is the problem, let's start thinking about developing drugs to fix it." In the *Nature Chemical Biology* paper, Dr. Small and his co-authors showed that the pharmacological "chaperone" they had developed increases levels of retromer proteins, shifts APP away from endosomes, and decreases the transformation of APP into amyloid-beta.

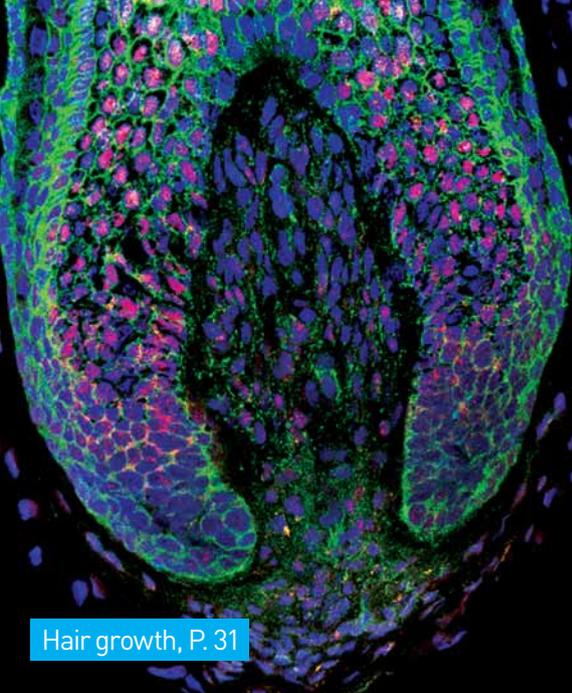
The elucidation of protein-processing functions in Alzheimer's disease has been important in refining the long-held assumption that amyloid-beta is a key driver of the disease. "It's a known fact that people with early-onset mutations produce way too much amyloid," says Dr. Mayeux. Stopping overproduction "is important in early-onset disease. It may also be important in late-onset

disease, although in late-onset disease none of these genes produces too much amyloid. But they don't clear it, and over time that can be just as bad."

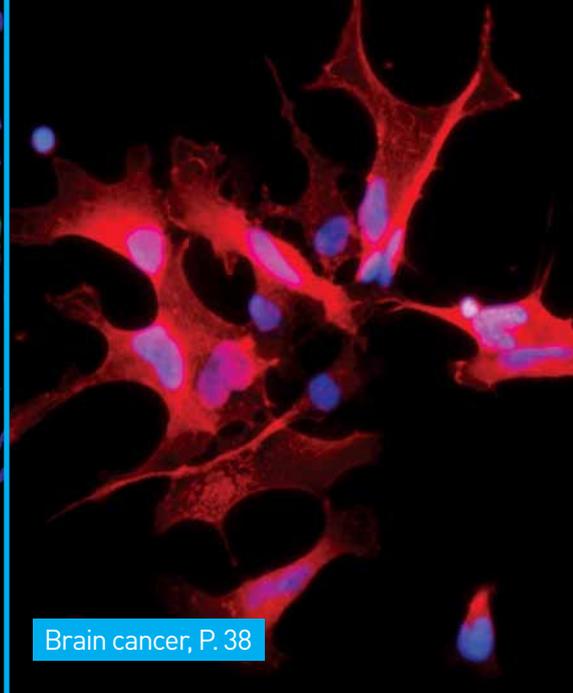
A new study on gene profiling at P&S will investigate the differences between early- and late-onset forms of the disease. Columbia is one of 18 centers around the world taking part in the Dominantly Inherited Alzheimer Network—DIAN—study to identify people with early-onset mutations who are unaffected. The team has just finished a study on biomarkers and has begun a clinical trial to vaccinate these patients or give them an infusion that prevents amyloid from depositing in their brain. Another study involves people who have evidence of disease based on PET scans that reveal amyloid deposition but who are asymptomatic; they will be randomized for the vaccine.

"We know, based on studies done here and elsewhere, that people have pathological changes in their brain starting as much as 10 to 15 years before they show any symptoms," says Dr. Mayeux. In this way, Alzheimer's disease is not unlike other chronic diseases, such as atherosclerosis, in which the process that leads to the stroke or cardiac event develops over an extended period of time. Late-onset Alzheimer's doesn't typically occur until a person reaches his or her 80s, so to catch the disease early and slow its progress by even a few years would be transformational, he says. "If you could give people another five to 10 years of good quality life, that would be a good outcome."

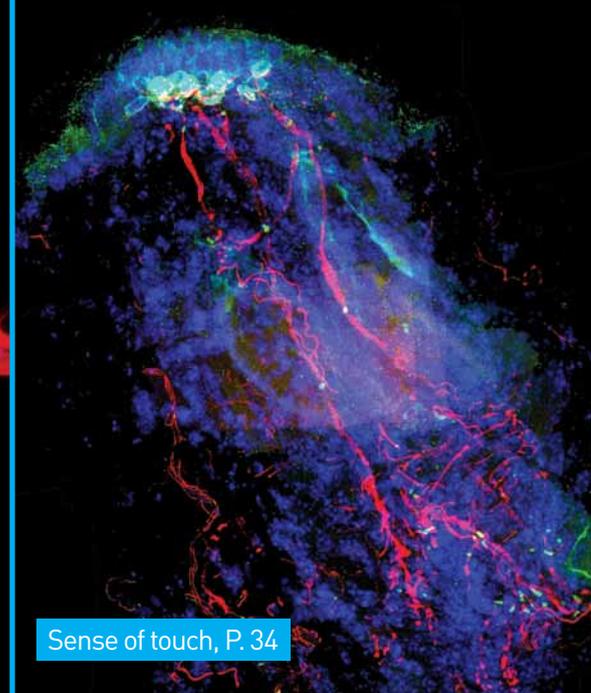
How close are experts to being able to offer something like that to patients? Dr. Small and his colleagues believe they are quite close: "We are where we want to be now," he says. Over the past 15 years, "the goal was to understand the disorder to the point where we could develop novel therapies. We have our novel therapies, and now we need to see if they work." ❖



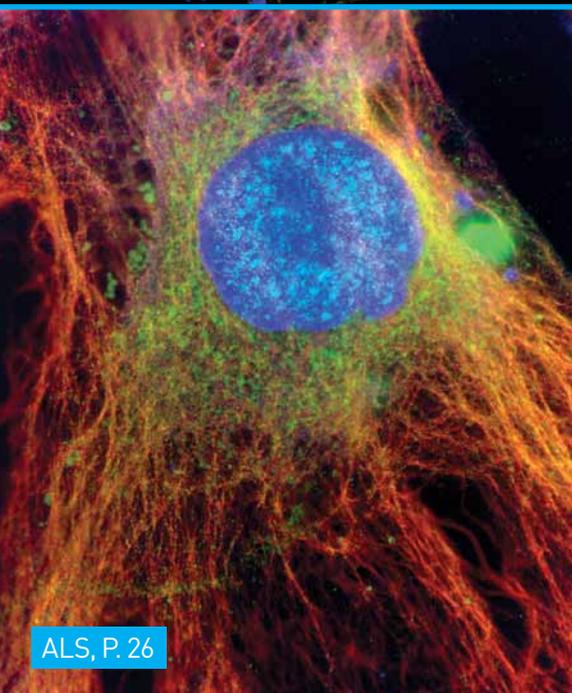
Hair growth, P. 31



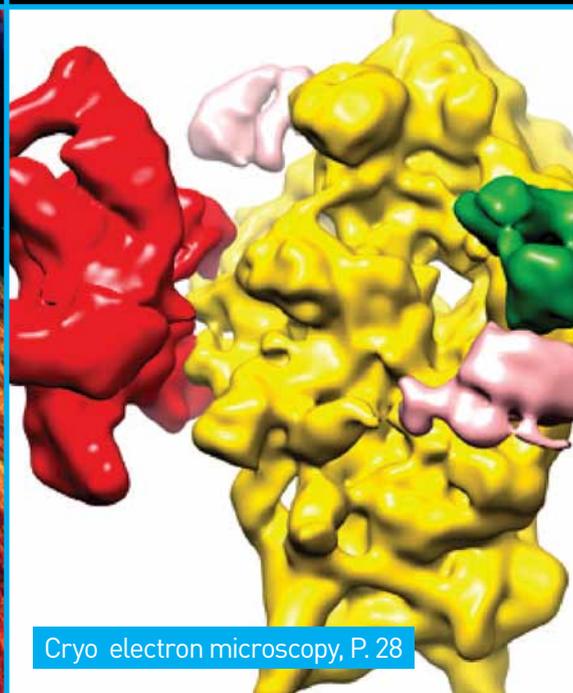
Brain cancer, P. 38



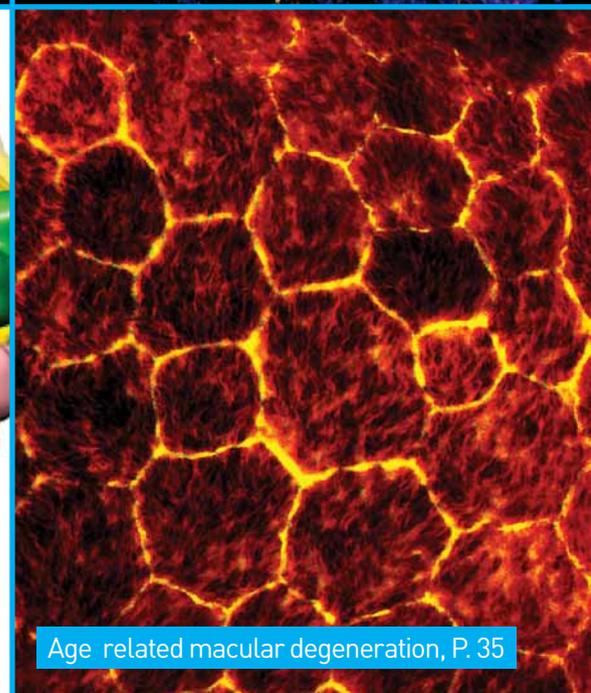
Sense of touch, P. 34



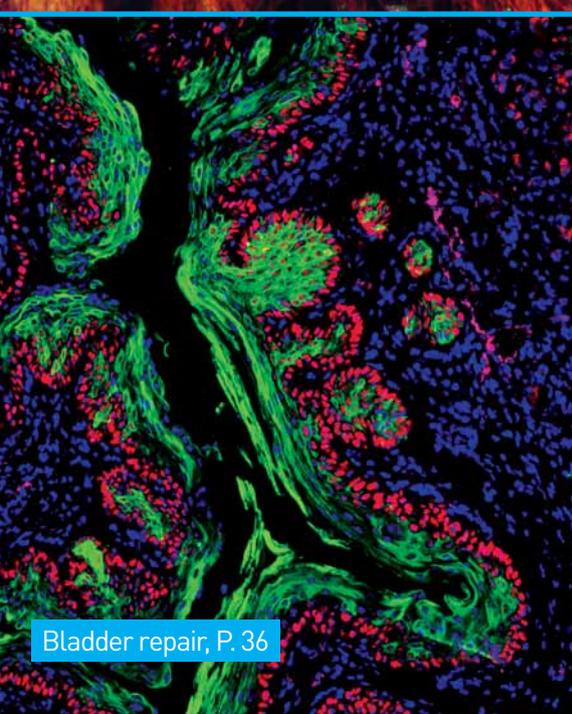
ALS, P. 26



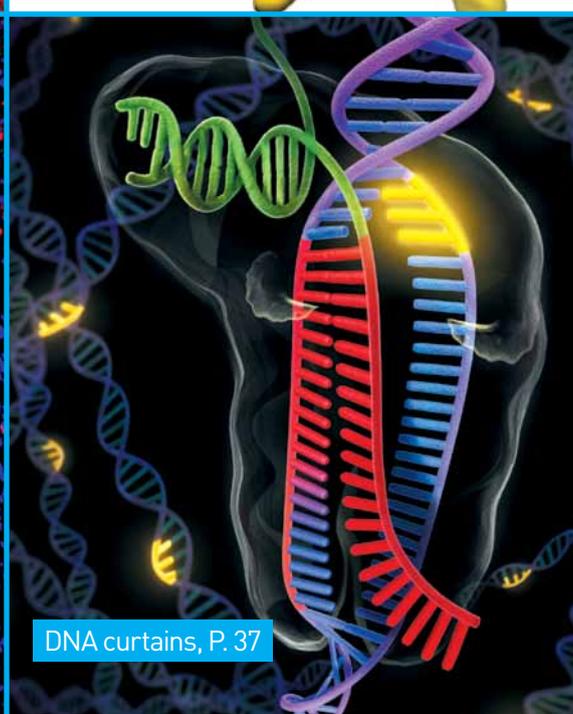
Cryo electron microscopy, P. 28



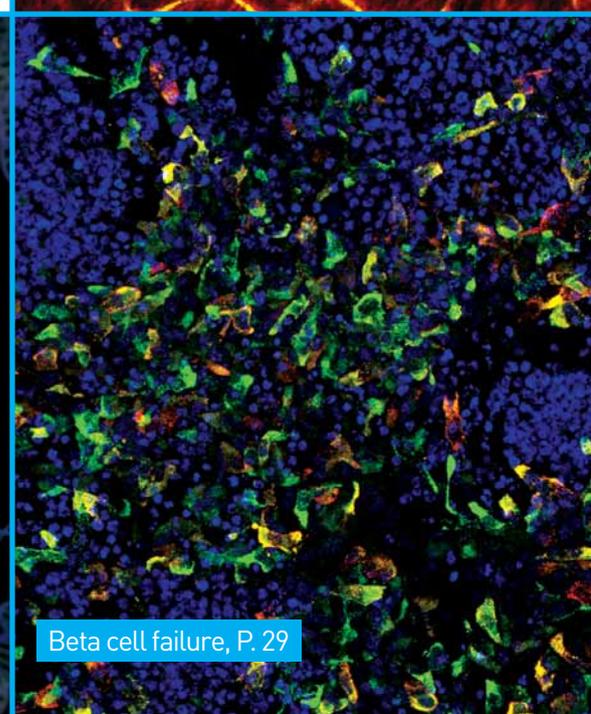
Age related macular degeneration, P. 35



Bladder repair, P. 36



DNA curtains, P. 37



Beta cell failure, P. 29

2014

Research Highlights

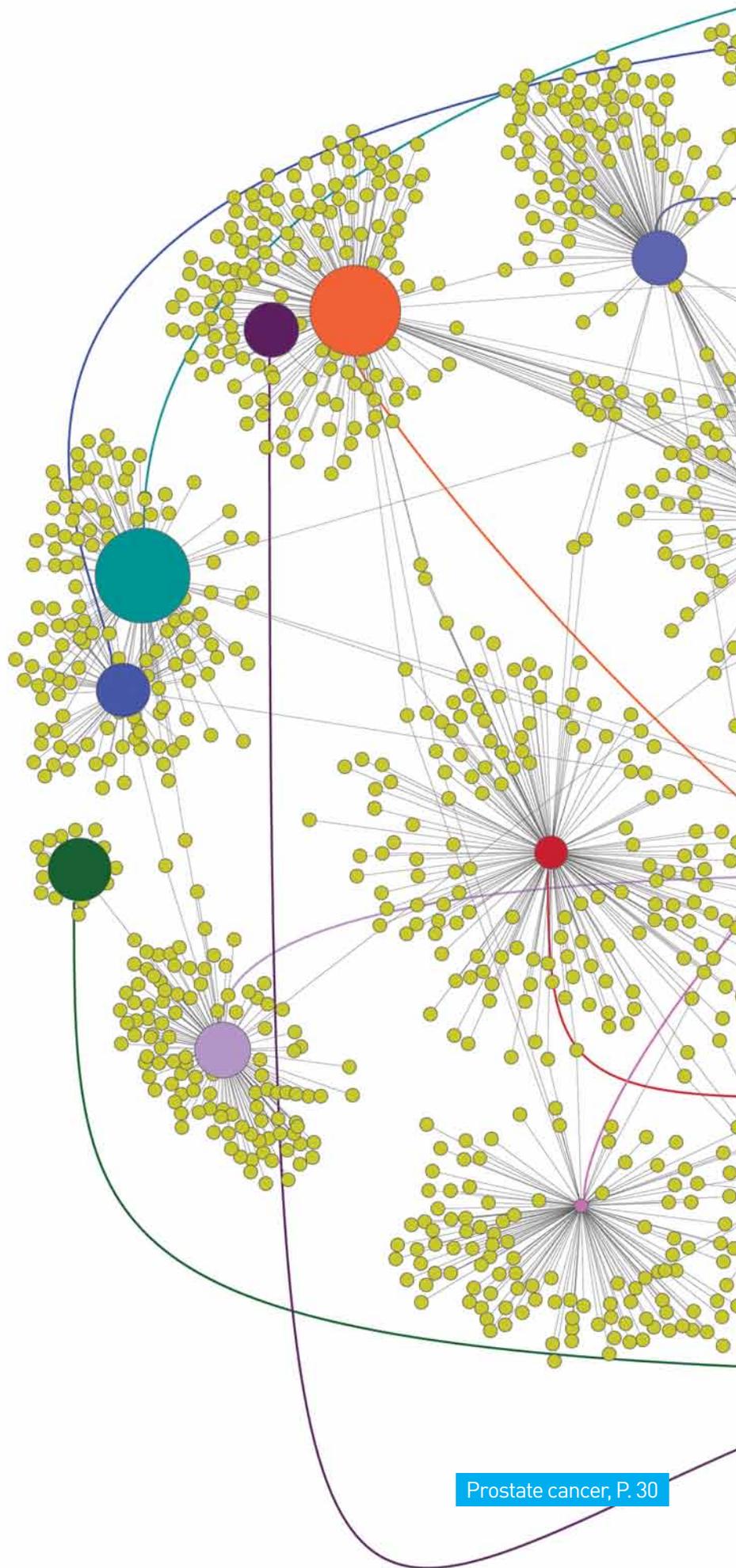
Teamwork and ingenuity are hallmarks of P&S research every year, and this year's research highlights were no exception as our investigators delved ever deeper for insights that will guide clinical care and move personalized medicine forward. The examples on these pages illustrate the range of research published during the course of 2013-14.

The research findings are a testament to the involvement of patients who furnish tissue samples and participate in clinical research; through their partnership, scientists now have new insights into glioblastoma, epilepsy, and diabetes, as well as the most aggressive form of prostate cancer.

Science is at the forefront of new techniques to reveal the progression of age-related macular degeneration and the molecular cascade of motor neuron death in amyotrophic lateral sclerosis, as well as discoveries about the bladder's unique self-healing mechanisms and new techniques to engineer replacement human hair follicles.

Increasingly, sophisticated algorithms feature in our quest to coax meaning from ever more complex data-sets. Consider, for example, findings that emerged from genomic analyses of glioblastoma and prostate cancer. Innovations in technology have revealed the once-invisible mechanisms for genetic engineering, granted new insights into the physiology of touch, and given scientists the ability to peer into the three-dimensional structures of proteins and other large organic molecules.

These are just a few examples of research done on our campus this year, but they are inspiring examples of the work that is done for the good of patients here and beyond both now and for generations to come.

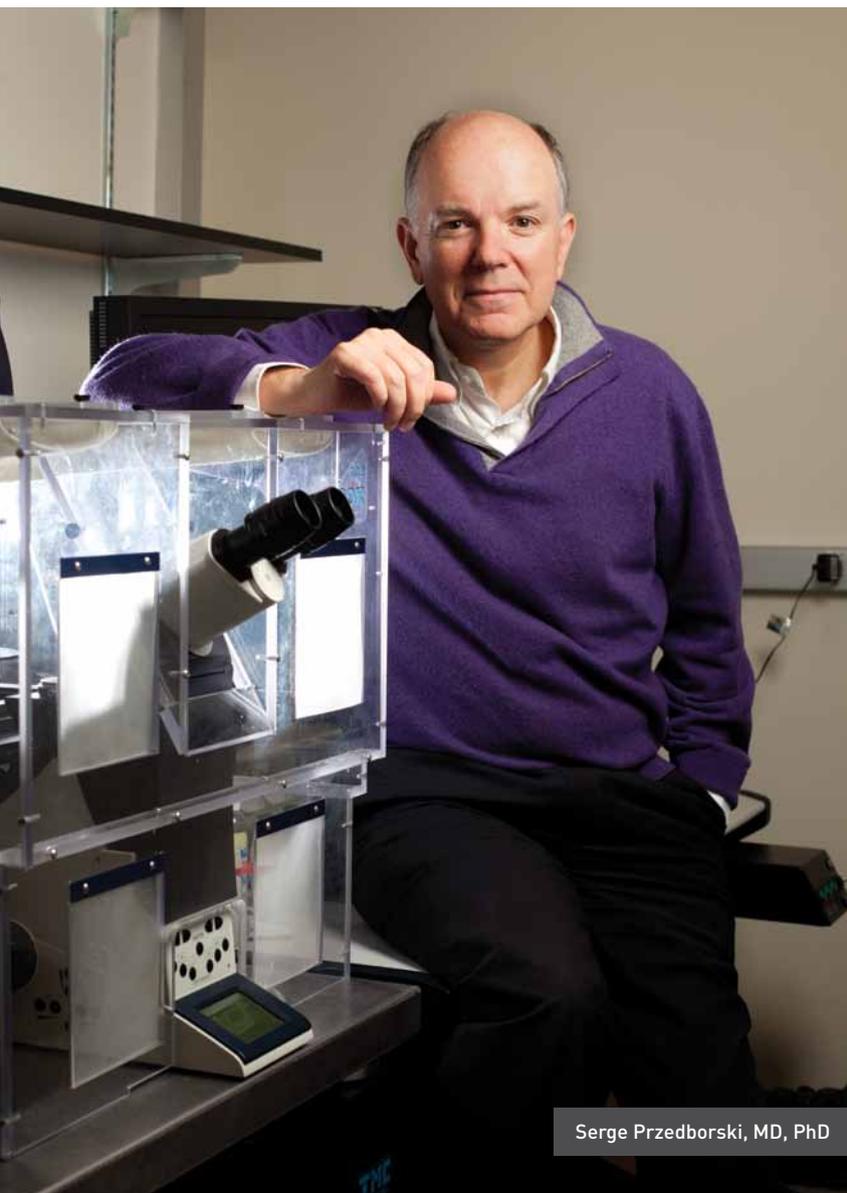


Model Scientist

In 1995, the FDA approved riluzole to treat amyotrophic lateral sclerosis (ALS), a progressive and fatal disease characterized by death of the motor neurons. Since then, more than 30 clinical trials have ended with no new treatments.

Part of the challenge is scientists' reliance on animal models of the disease, which capture only a portion of the condition's complexity in humans. Further, most models replicate forms of ALS with a known genetic cause, which account for only 10 percent of all cases.

A new model, based on human cells, has been developed by Serge Przedborski, MD, PhD, the Page and William Black Professor of Neurology (in Pathology & Cell Biology and Neuroscience) and vice chair for research in the Department of Neurology.



Serge Przedborski, MD, PhD

Dr. Przedborski and his colleagues, Diane Re, PhD, and Virginia Le Verche, PhD, associate research scientists, removed astrocytes from the brain and spinal cords of six ALS patients shortly after death and placed the cells in petri dishes next to healthy motor neurons. Because motor neurons cannot be removed from human subjects, they had been generated from human embryonic stem cells in the Project A.L.S./Jennifer Estess Laboratory for Stem Cell Research at Columbia.

Within two weeks, many of the motor neurons had shrunk and their cell membranes became damaged; about half of the motor neurons in the dish had died. Astrocytes removed from people who died from causes other than ALS had no effect on the motor neurons. Nor did other types of cells taken from ALS patients.

“Although there are many neurodegenerative disorders, for only a handful do we have access to a simplified model that is relevant to the disease and can therefore potentially be used for high-throughput drug screening. So this model is quite special,” says Dr. Przedborski. “Here we have a spontaneous disease phenotype triggered by the relevant tissue that causes human illness. That’s one important thing. The other important thing is that this model is derived entirely from human elements. This is probably the closest, most natural, model of human ALS that we can get in a dish.”

The researchers confirmed that the cause of the motor neurons’ death was a toxin released into the environment by immersing healthy motor neurons in the astrocytes’ culture media. The media, even without astrocytes, killed the motor neurons. The report follows the researchers’ previous study, which produced similar results in mice with a rare, genetic form of ALS. The current study shows that the toxins also are present in astrocytes taken directly from ALS patients.

The scientists have not yet identified the toxin, but they documented the molecular cascade it triggers and found that they could protect the motor neurons by interrupting the cascade. “Now that we know that the toxin is common to most patients, we have an impetus to track down this factor and learn how it works,” says Dr. Przedborski. “Its identification has the potential to reveal new ways to protect the motor neurons.”

This is a summary of research published in Neuron, March 5, 2014.



HELP FROM OUR FRIENDS

CLAIRE AND LEONARD TOW

Among the most influential supporters of P&S, Claire and Leonard Tow have been instrumental in advancing motor neuron disease research in amyotrophic lateral sclerosis and other disorders. Honored at the 2012 Crown Awards, Len and his late wife, Claire, have been transformative partners to Columbia with gifts to Barnard College, the School of Journalism, and Columbia University Medical Center.

A Stroke of Insight

The dramatic stroke disparities between white and black Americans are well documented: Blacks are twice as likely as whites to have a stroke, more likely to die from a stroke, and tend to have strokes at a younger age.

Many reasons have been proposed to explain these differences, including an increased rate among blacks of vascular risk factors and lack of access to health care.

To find the causes that explain most of the disparities, Jose Gutierrez, MD, assistant professor of neurology, and Olajide Williams, MD, associate professor of neurology, analyzed data from nearly 38,000 adults who participated in the National Health and Nutrition Examination Survey (NHANES) between 2000 and 2009. The survey collected data on stroke risk factors—including high blood pressure, diabetes, and smoking—as well as self-reported racial/ethnic identification, poverty, and education.

The two researchers concluded that stroke disproportionately strikes black Americans mainly because of a combination of increased prevalence of stroke risk factors among blacks and a lower degree of risk factor control.

Compared with their Caucasian counterparts, black Americans not only had a higher rate of hypertension but it was under control in fewer black Americans. And although high cholesterol was less prevalent in black Americans as compared with whites, the high cholesterol was more frequently uncontrolled in blacks. Diabetes was more prevalent in blacks, but the rates of control of diabetes were no different between the two groups.

The study also replicated the “Hispanic paradox” in the NHANES data of the nationwide population of Mexican-Americans (the dataset did not include enough data of other Hispanic groups to make accurate estimates). Though Mexican-Americans have higher rates of diabetes than whites, they have lower rates of hypertension, smoking, and high cholesterol and a lower overall incidence of stroke.

Dr. Gutierrez says, “Reducing racial and ethnic disparities in stroke requires more robust and systematic approaches to vascular risk factor control.” That will be challenging, he adds, because the study indicates that more than half of Americans with diabetes, high blood pres-



Olajide Williams, MD
Jose Gutierrez, MD

sure, or high cholesterol do not take medications, are not aware of their diagnosis, or remain uncontrolled despite medications.

Dr. Williams is trying to attack the problem with innovative programs. In 2005, he started Hip Hop Stroke, which uses hip-hop music to teach fourth, fifth, and sixth graders in African-American communities about stroke prevention. “We think that these children can serve as our conduits to older residents and spread this knowledge throughout the community,” says Dr. Williams. Recent assessments of the program suggest it is working.

Dr. Williams also co-leads the Center for Stroke Disparities Solutions, funded by the Na-

tional Institute for Neurological Diseases and Stroke, with physicians at New York University. Started in 2013, the center creates and tests programs aimed at lowering stroke risk among racial and ethnic minorities. As part of his work with the center, Dr. Williams is using short culturally tailored professionally produced films of stroke patient stories to improve stroke knowledge and prevention in adults.

“Stroke is a mysterious disease for many people,” Dr. Williams says. “It’s a huge challenge requiring very innovative, creative solutions.”

The stroke disparities research was published in the March 25, 2014, issue of Neurology.

Molecular Microscopy

The uncertainty principle in quantum physics holds that observation has the power to transform the object of our attention. Social scientists know the concept as the Hawthorne effect, after a series of industrial psychology experiments in a Flapper-era Chicago factory of the same name. Biologists see the phenomenon when they deploy an electron microscope to probe samples too small for a light microscope to reveal: Bombard a living sample with electrons, and the fragile molecules within

incinerate. Even worse, while biology spans time and space, electron microscopy generates only a two-dimensional image of an inert sample.

Joachim Frank, PhD, took a different approach. Dr. Frank, professor of biochemistry & molecular biophysics and of biological sciences at Morningside and a Howard Hughes Medical Institute investigator, is winner of the 2014 Benjamin Franklin Medal in Life Sciences. The medal—previously awarded to such luminaries as Alexander Graham Bell, Pierre and Marie Curie,

Albert Einstein, and Stephen Hawking—celebrates Dr. Frank's development of cryo-electron microscopy, his use of cryo-EM to investigate the structure of large organic molecules at high resolution, and his resultant discoveries regarding the mechanism of protein synthesis in cells.

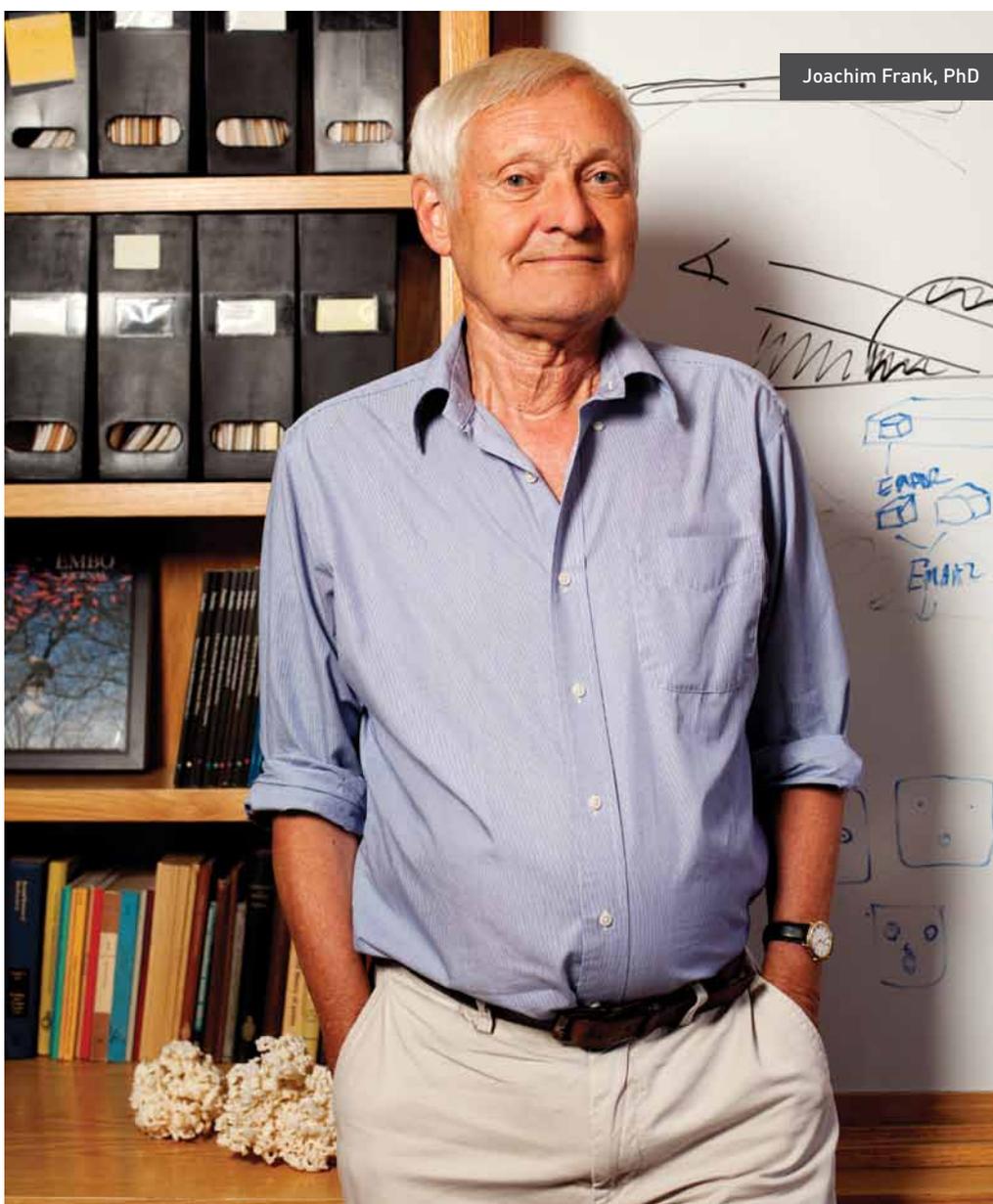
Dr. Frank's approach, conceived in the 1970s, is simple: Create a 3-D image of a biological molecule, capture images of thousands of identical molecules lying in different orientations, then combine them. Coming up with the concept was the easy part. Much more painstaking was Dr. Frank's development of the computational methods to realize his vision; 35 years later, his techniques are still used by most structural biologists who use electron microscopy.

Using those techniques himself, Dr. Frank has revealed the 3-D shape of ribosomes, complex protein-synthesizing factories in all cells. Combining his mathematical methods with techniques that freeze the ribosome in a thin layer of liquid ice (the cryo in cryo-EM), he obtained the first 3-D image of the molecule that clearly showed its two separate subunits and, later, an even more detailed image that gave scientists new insights into how the ribosome works.

He also has investigated how these molecular machines interact with other molecules during the different steps of protein production. Like multiple still shots for a movie, his studies have revealed how one subunit of the ribosome rotates back and forth in a ratcheting motion to add amino acids during protein production, a process that is the same in all kingdoms of life.

In a study published in *Nature*, Dr. Frank's team uncovered details of the ribosome from the parasite that causes African sleeping sickness, details that may lead to drugs to kill the parasite. Another *Nature* paper showed how viral RNA commandeers the ribosome of the virus's host to produce new viruses.

Dr. Frank is a member of the National Academy of Sciences and the American Academy of Arts & Sciences and a fellow of the American Association for the Advancement of Science and the Biophysical Society. He shared the Elizabeth Roberts Cole Award of the Biophysical Society for developing methods of 3-D reconstruction of biological macromolecules.



Stress Response

By re-engineering skin cells donated by patients with Wolfram syndrome, a rare genetic disease, a team of P&S scientists and clinicians collaborating with the New York Stem Cell Foundation has elucidated an important biochemical pathway for beta cell failure in diabetes. A report on the findings was authored by Linshan Shang, PhD, a New York Stem Cell Foundation researcher and associate research scientist in pediatrics at P&S, and colleagues.

Wolfram syndrome affects just 1 in 100,000 people in North America, producing insulin-dependent diabetes, vision loss, and deafness. Since all forms of diabetes are ultimately the result of an inability of pancreatic beta cells to provide sufficient insulin in response to blood-sugar concentrations, the Wolfram stem cell model created by the P&S team facilitates analysis of a specific pathway leading to beta cell failure in more prevalent forms of diabetes. It also enables the testing of strategies to restore beta cell function that may be applicable to all types of diabetes.

Starting with the donated skin cells, the scientists produced induced pluripotent stem cells, from which they produced pancreatic, insulin-producing beta cells—creating an *in vitro* model of Wolfram syndrome. They then showed how and why the beta cells failed to secrete insulin normally in Wolfram syndrome: In these cells, an abnormal endoplasmic reticulum stress (ER stress) response leads to the inability to compensate for misfolded proteins and, ultimately, beta cell failure. The beta cell produces large quantities of insulin, making it particularly susceptible to this sort of stress. They also found that a drug called 4-phenyl butyric acid relieves this ER stress and prevents the beta cells from failing. These findings suggest a potential drug target for clinical intervention for patients with Wolfram syndrome, as well as for preventing beta cell demise in more



Rudolph L. Leibel, MD
Linshan Shang, PhD

common types of diabetes. Plans are under way to test this strategy at the Naomi Berrie Diabetes Center.

“This work highlights again the utility of close examination of rare human disorders as a path to elucidating more common ones,” says team member Rudolph L. Leibel, MD, the Christopher J. Murphy Memorial Professor of Diabetes Research, professor of pediatrics and of medicine, and co-director of the Naomi Berrie Diabetes Center. “Our ability to create functional insulin-producing cells using stem-cell techniques on skin cells from patients with Wolfram syndrome has helped to further elucidate the role of ER stress in the pathogenesis of diabetes. The use of drugs that reduce such stress may prove useful in the prevention and treatment of diabetes.”

This is a summary of research published in Diabetes, March 2014.

HELP FROM OUR FRIENDS

NATASHA LEIBEL, MD, AND HARLAN LEVINE, MD

“People can’t believe how difficult and expensive it is to run a center like this without the generous support of donors,” says Natasha Leibel, MD, assistant professor of pediatrics at Columbia’s Naomi Berrie Diabetes Center. As the daughter of Rudolph Leibel, MD, co-director of the Berrie Center, Natasha grew up keenly aware of the challenges medical researchers face.

As one of the generous donors who have consistently funded Berrie Center research, Natasha is also an essential part of what keeps the science moving

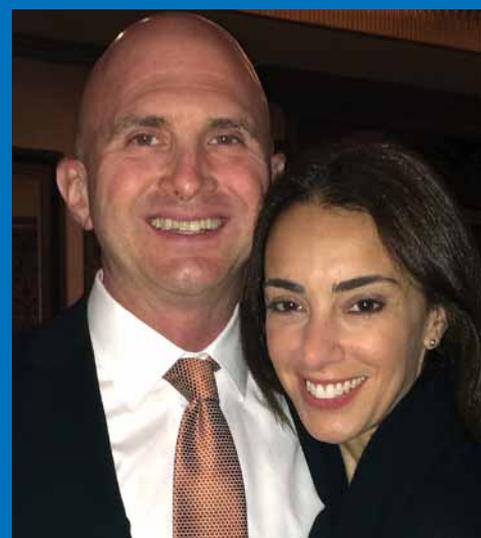
forward. Natasha and her husband, Harlan Levine, MD, have provided transformative support to advance molecular genetics research related to diabetes.

“I have an incredible personal attachment to the Berrie Center on many levels,” she says. “Every day I treat patients who are struggling with this extremely challenging illness and I am always amazed to see how the families and children rise to the occasion.”

As a pediatric clinician, Natasha Leibel specializes in children with type 1 and type 2 diabetes and contributes to ongoing

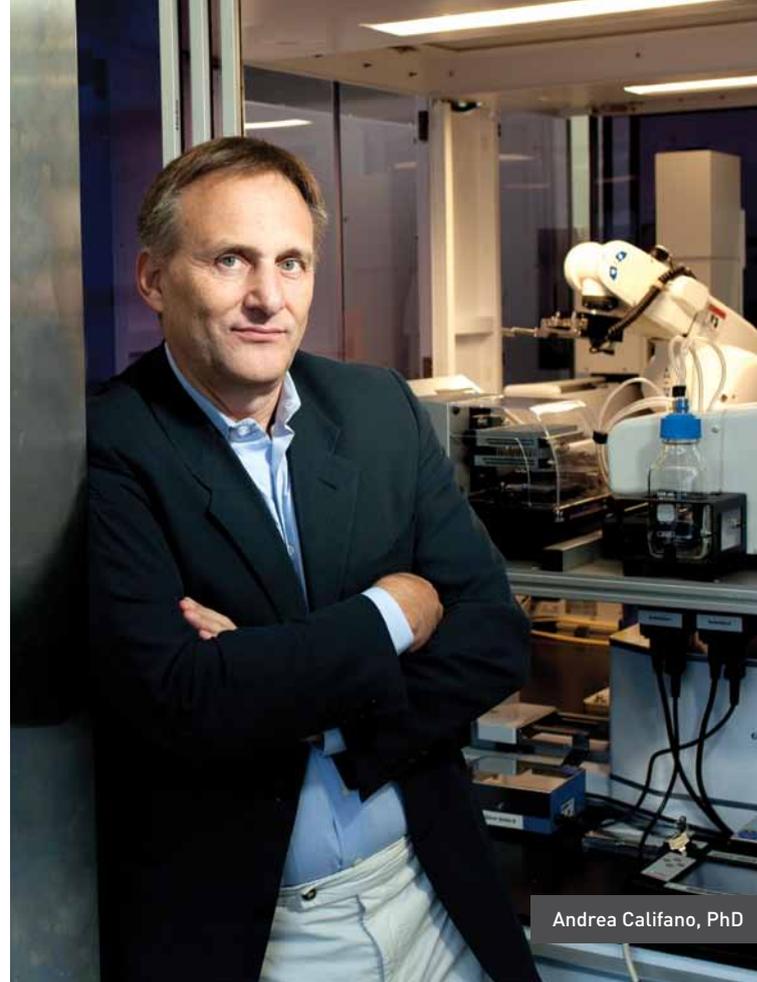
clinical studies of type 2 diabetes in teenagers. She has been at Columbia since 1998, when she began her residency at Morgan Stanley Children’s Hospital. She decided to focus on diabetes out of a desire to help combat an emerging global health crisis.

“This is a disease that almost everyone is going to face, either directly or through someone they know,” she says. “It’s that prevalent. Harlan and I agree that we can’t think of a better way to give back than to support the research that will benefit patients and one day lead us to a cure.”





Cory Abate-Shen, PhD



Andrea Califano, PhD

A Toxic Combination

For most men with prostate cancer, the best medicine is a wait-and-see approach—the disease progresses so slowly that the side effects of treatment pose too great a risk. Sometimes, however, it rages and kills quickly. For doctors, the challenge is finding clues to guide a personalized approach.

A computational comparison of the gene regulatory networks that drive prostate cancer in humans with those in a genetically engineered mouse model of the disease has revealed that the most lethal form of prostate cancer is the result of a synergy between the genes FOXM1 and CENPF. While each gene had previously been implicated in prostate cancer, neither has a significant effect by itself. Together, the two wreak havoc.

These findings could inform development of a diagnostic test and the design of novel drug therapy. “Ultimately, this finding could allow doctors to identify patients with the most aggressive prostate cancer so they can get the most effective treatments,” says co-senior author of the study, Cory Abate-Shen, PhD, the Michael and Stella Chernow Professor of Urologic Sciences and professor of pathology & cell biology. “Having biomarkers that predict which patients will respond to specific drugs will inform a more personalized approach to cancer.”

Scientists widely recognize that multiple genetic changes pave the way for cancer. “However, distinguishing the handful of genes that drive the cancer from the many whose altered expression does not contribute directly has proved to be a daunting task,” says co-senior author Andrea Califano, PhD, the Clyde and Helen Wu Professor of Chemical Biology (in Biomedical Informatics and the Institute for Cancer Genetics), professor of

biochemistry & molecular biophysics, chair of the Department of Systems Biology, and director of the JP Sulzberger Columbia Genome Center. “It becomes even more difficult when genes work synergistically, because they must be analyzed in pairs. The approximately 1,000 genes that have been linked to cancer can be combined into about 500,000 gene pairs, each of which may represent a synergistic tumor driver. That volume defies our best statistical tools and requires sophisticated systems biology approaches.”

To identify FOXM1 and CENPF, the researchers turned to a computer at CUMC, one of the world’s largest supercomputers in cancer research. To validate their findings, they manipulated the genes singly and together, in both human prostate cancer cell lines and mouse models. A further analysis in 900 patient samples revealed a striking correlation between the co-expression of FOXM1 and CENPF and the poorest disease outcome. Expression of either gene alone did not correlate with aggressive disease, and tumors in which neither gene was aberrantly expressed had the best prognosis.

“This is just a first step toward a deeper understanding of the genetics of cancer,” says Michael M. Shen, PhD, professor of medical sciences, of genetics & development, and of urological sciences, who contributed to the study. “The tools and approaches developed in this study may have broad utility in studying prostate cancer; cross-species computational analyses also could be used to identify the causes of other cancers and other complex diseases.”

This is a summary of research published in Cancer Cell, May 12, 2014.

Growing New Hair

Bald is beautiful, but for some people with hair loss, taming a tangle of tresses is an appealing alternative. A team led by Angela M. Christiano, PhD, announced progress this year toward a new approach to granting that wish: a technique using stem cells to generate new human hair growth.

The approach could significantly expand the use of hair transplantation. “About 90 percent of women with hair loss are not strong candidates for transplantation because of insufficient donor hair,” says Dr. Christiano, the Richard and Mildred Rhodebeck Professor of Dermatology and professor of genetics & development. “This method offers the possibility of inducing large numbers of hair follicles or rejuvenating existing hair follicles, starting with cells grown from just a few hundred donor hairs. It could make hair transplantation available to individuals with a limited number of follicles, including those with female-pattern hair loss, scarring alopecia, and hair loss due to burns.”

Until now, scientists attempting to expand dermal papilla cells, the precursor to hair follicles, had been stumped. “Once the dermal papilla cells are put into conventional, two-dimensional tissue culture, they revert to skin fibroblasts and lose their ability to produce hair follicles,” says co-study leader Colin Jahoda, PhD, co-director of the North East England

Stem Cell Institute. “We were faced with a Catch-22: how to expand a sufficiently large number of cells for hair regeneration while retaining their inductive properties.”

Mice offered a clue. Rodent papillae can be easily harvested, expanded, and successfully transplanted back into rodent skin, a method pioneered by Dr. Jahoda several years ago. The researchers hypothesized that perhaps the difference between success in rodent models and failure in human cell experiments was a result of the tendency for rodent dermal papillae to spontaneously aggregate, or form clumps, in tissue culture. “We hypothesized that if we designed our human papillae culturing technique to promote aggregation—as naturally happens with rodent cells—we could create the conditions needed to induce hair growth in human skin,” says Dr. Jahoda.

To test their hypothesis, the scientists harvested dermal papillae from seven human donors and cloned the cells in tissue culture; no additional growth factors were added to the cultures. After a few days, the cultured papillae were transplanted between the dermis and epidermis of human skin that had been grafted onto the backs of mice. In five of the seven tests, the transplants resulted in new hair growth that lasted at least six weeks. DNA analysis confirmed that the new hair follicles were human and genetically matched the donors.

“This approach has the potential to transform the medical treatment of hair loss,” says Dr. Christiano. “We have the potential to actually grow new follicles using a patient’s own cells. This could greatly expand the utility of hair-restoration surgery to women and younger patients—now it is largely restricted to the treatment of male-pattern baldness in patients with stable disease.”

This is a summary of research published in PNAS, December 3, 2013.



HELP FROM OUR FRIENDS

LOCKS OF LOVE

Locks of Love has generously supported the Department of Dermatology’s research of alopecia areata, an autoimmune disease resulting in hair loss that ranges from partial to total loss of body hair. A nonprofit organization, Locks of Love provides custom cranial prostheses to American and Canadian children suffering from long-term medical hair loss from any diagnosis.

Many of the children helped by Locks of Love have lost their hair because of alopecia areata, the most prevalent autoimmune disease in the United States. The visionary philanthropy provided by Locks of Love has propelled Columbia research and enabled the team of scientists, led by geneticist Angela M. Christiano, PhD, who has alopecia areata herself, with immunologist Raphael Clynes, MD, PhD, and dermatologist Julian Mackay-Wiggan, MD, to move closer to the goal of testing new targeted therapies in patients with alopecia areata.

With support from Locks of Love, researchers have made significant progress toward offering new hope to the millions of patients who are affected by alopecia areata.



Angela M. Christiano, PhD

Exploring Epilepsy

More than 2 million people in the United States have epilepsy, a group of neurological conditions characterized by abnormal firing of nerve cells in the brain. While scientists have identified a few genes associated with rare, inherited forms of the disorder, genes associated with the majority of epilepsies have been more elusive.

In a report published by the journal *Nature*, scientists have detailed the discovery of 25 novel epilepsy-causing mutations, including two new genes associated with infantile epileptic encephalopathies, a particularly severe form of the disease. The work was a collaboration of the Epilepsy Phenome/Genome Project (EPGP)—a \$25 million program supported by the National Institute of Neurological Disorders and Stroke involving a 61-member international research team—and Epi4K, the first NINDS-funded Center Without Walls for Collaborative Research on the Epilepsies. To compile the *Nature* report, scientists at dozens of participating research institutions shared medical histories and DNA sequences of 4,000 people with epilepsy.

Ruth Ottman, PhD, professor of epidemiology (in neurology and the Gertrude H. Sergievsky Center), was a coauthor on the study and principal investigator of two NIH grants that supported the work. She is a member of both the Epi4K and EPGP teams.

Melodie Winawer, MD, associate professor of neurology in Columbia's Gertrude H. Sergievsky Center and director of clinical neuroscience education at P&S, is also a co-author of the study.

By sequencing only 1 percent of participants' DNA—the short, functionally important sequences known as exons—the investigators were able to home in on relevant genetic patterns without incurring the expense of whole genome sequencing. The technique, known as exome sequencing, was used to analyze the DNA of affected individuals and their biological parents to search for *de novo* mutations.

Epilepsy investigators now suspect that many conditions once considered comorbidities—including depression, anxiety, suicidality, and migraine—may actually be vital clues to the identification of underlying



Melodie Winawer, MD
Ruth Ottman, PhD

ing genetic features, making projects like EPGP and Epi4K that integrate analyses of genotype with phenotype all the more important. “When we define epileptic phenotypes, we may have to not only define different types of epilepsy,” says Dr. Winawer, “but in some cases actually tie together other comorbidities. It’s an expanded notion of what constitutes a phenotype—a network of interconnected symptoms or disorders.”

In 2013, Dr. Winawer deployed the EPGP dataset to investigate the relationship between epilepsy and migraine with aura, finding a genetic link. “A lot of the progress in epilepsy genetics has come with the help of careful phenotype definition,” she says. “The identification of specific clinical features has enabled us to classify patients into groups likely to share susceptibility genes.”

In May, *Nature Reviews Neurology* published a special Focus on Epilepsy, including a report by Dr. Ottman with colleagues on the benefits and risks of genetic testing. “Genetic testing in the epilepsies has the potential to revolutionize the care of affected patients,” the authors write, “but to ensure services are delivered in the most effective, sensitive, and equitable manner possible, we need to devote attention to the challenges involved and establish mechanisms to address them.”

HELP FROM OUR FRIENDS



DAVID AND CONNIE LITTMAN

As members of the advisory council for the Department of Neurology at P&S, David and Connie Littman understand the challenges facing junior faculty in launching their research careers. Between the demands of clinical practice and what has become an unfortunate financial reality of academic medicine, junior faculty often find it difficult to devote time for the independent research and education so vital for their growth.

To address this need, the Littmans made a generous pledge to establish a junior faculty startup fund, enabling young faculty within the department's epilepsy division to receive financial support for up to three years. This allows them time to gain preliminary data and further research experience so they can more effectively compete for support from NIH and other major research foundations.

The first recipient of their generosity is Lisa Bateman, MD, associate professor of neurology in Columbia's Comprehensive Epilepsy Center. In addition to caring for patients with epilepsy, Dr. Bateman is recognized for her expertise in, and advocacy for, patient safety in epilepsy monitoring units. Her research focuses on peri-ictal physiology and its relationship to morbidity and mortality in epilepsy patients, particularly sudden unexpected death in epilepsy.

Waiting to Exhale

When you inhale, your alveoli—150 million sacs within each lung—expand to fill with air. When you exhale, those small elastic balloons, each just a single cell thick, push carbon dioxide back out into the world. Every day, alveoli expand and contract some 23,000 times.

Among people with idiopathic pulmonary fibrosis (IPF), rigid scar tissue slowly and steadily takes over where flexibility once pre-

vailed. The damage begins at the edges of the lung, near the diaphragm. Slowly, the scarring spreads inward and upward. Breathing gets harder and gas exchange less efficient. Eventually, the condition is fatal.

Treatment for IPF has been limited to pulmonary rehabilitation, supplemental oxygen, and lung transplantation. Now, clinical trials have found that two new drugs to interrupt IPF—

nintedanib and pirfenidone—were each able to slow the loss of lung function in some patients.

“This is an amazing day for idiopathic pulmonary fibrosis,” says pulmonologist David Lederer, MD, associate professor of medicine and epidemiology (in pediatrics), who was on the steering committee of the pirfenidone trial. “Before this week we had no drugs that can treat IPF, and now we have two.”

Dr. Lederer cautioned that neither drug is a cure for IPF, both have side effects, and they have not been approved by the FDA, which will review the data later this year. Nintedanib, an experimental compound that is not approved for any medical condition, blocks the effect of tyrosine kinases, proteins that tell the lung to make scar tissue. Pirfenidone is approved and available to treat IPF in Europe, Canada, and Japan, but its mechanism of action is unknown.

“These drugs are promising, but we still need to find out what causes the disease and develop treatments that can halt the scarring and maybe even reverse the damage,” says Dr. Lederer, whose research suggests that sleep apnea may cause IPF. He hopes to start a trial to test whether continuous positive airway pressure can slow the rate of lung scarring and loss of lung function in patients.

Dr. Lederer also writes a blog for patients and their families who are dealing with pulmonary fibrosis (PF). “There is a world of confusion out there about PF,” he writes. “What is it? What’s the difference between IPF, PF, and interstitial lung disease? What causes PF? Will my kids get it? Which treatments work?”

Even worse than the confusion about treatment, he says, is the tortured process that often precedes a PF diagnosis, with patients first told that their cough or difficulty breathing is due to asthma, chronic obstructive pulmonary disease, emphysema, heart disease, sleep apnea, or obesity and poor lung capacity. “It’s no surprise that just about every single one of my patients with PF is frustrated and confused when he or she walks in the door,” says Dr. Lederer. “That’s why I created my blog—to clear up the confusion.”

This is a summary of research published in New England Journal of Medicine, May 29, 2014.



David Lederer, MD

Touch of Genius

Since 1940, pint-sized readers have stoked their sensory vocabulary with Dorothy Kunhardt's interactive "Pat the Bunny," running their fingers over the fluffy "fur" of a rabbit and the sandpaper facsimile of "daddy's scratchy face." Touch is a prized sensory capacity, honed early in childhood, but the cellular and molecular mechanisms behind the sensation have evaded neuroscientists.

"One aspect of our sense of touch that has perplexed scientists for more than 40 years is

how we distinguish fine shapes and textures," says Ellen A. Lumpkin, PhD, associate professor of somatosensory biology, whose research is devoted to exploring the question. "We need the ability to sense touch with high-tactile acuity, because that guides fine motor skills for virtually everything we do with our hands."

Using optogenetics—a new method that deploys laser light as a signaling system to turn neurons on and off on demand—Dr. Lumpkin and her team revealed that skin cells known as

Merkel cells initiate the sense of touch and that they work closely with the skin's neurons to create what we perceive as fine details and textures.

"These experiments are the first direct proof that Merkel cells can encode touch into neural signals that transmit information to the brain about the objects in the world around us," says Dr. Lumpkin, who also investigates the perceptions of temperature and itch. Her team's findings not only describe a key advance in the understanding of touch sensation, but also may stimulate research into loss of sensitive-touch perception.

Several conditions—including diabetes and some cancer chemotherapy treatments—and normal aging are known to reduce sensitive touch. Merkel cells begin to disappear in a person's early 20s, at the same time that tactile acuity starts to decline. "No one has tested whether the loss of Merkel cells causes loss of function with aging—it could be a coincidence—but it's a question we're interested in pursuing," says Dr. Lumpkin.

These findings eventually could inform the design of new "smart" prosthetics that restore touch sensation to limb amputees, as well as introduce new targets for treating skin diseases such as chronic itch.

Dr. Lumpkin and her team conducted a second study in collaboration with the Scripps Research Institute. The companion study identifies a touch-activated molecule in skin cells, a gene called *Piezo2*; the discovery has the potential to advance the field of touch perception.

"The new findings should open up the field of skin biology and reveal how sensations are initiated," says Dr. Lumpkin. Other types of skin cells also may play a role in sensations of touch, as well as less pleasurable skin sensations, such as itch. The same optogenetics techniques that Dr. Lumpkin's team applied to Merkel cells can now be applied to other skin cells to answer these questions. "It's an exciting time in our field," she says. "There are still big questions to answer, and the tools of modern neuroscience give us a way to tackle them."

This is a summary of research published in Nature, May 29, 2014.



Ellen A. Lumpkin, PhD

Stem Cells and Personalized Medicine

In the lab, rodents have a lot to recommend them: They are small and relatively easy to keep in close quarters, and for many diseases, they are an excellent model of human biology. But not when it comes to macular degeneration.

Most strikingly, rodents lack a macula, the small, highly sensitive part of the human retina that allows for detailed perception (e.g., facial recognition, reading, and driving). No big deal for nocturnal creatures equipped with optimized hearing and strong noses, but bad news for scientists investigating age-related macular degeneration, the leading cause of vision loss among people over age 50.

A new patient-specific model for age-related macular degeneration (AMD) has been developed by Janet Sparrow, PhD, the Anthony Donn Professor of Ophthalmic Sciences (in ophthalmology) and professor of pathology & cell biology, and Stephen Tsang, MD, PhD, the Laszlo Z. Bito Associate Professor of Ophthalmology and associate professor of pathology & cell biology. Using cells donated by people with AMD, Drs. Sparrow and Tsang created a petri-dish technique that allows scientists to study the full progression of the disease.

Dr. Tsang and postdoctoral fellow Jin Yang, MD, PhD, used skin cells donated by patients who carry genes that increase the risk of

developing AMD. They converted those skin cells first to stem cells and then to retinal cells. They then used a method developed by Dr. Sparrow to accelerate the aging process. “We added debris products of vitamin A—which accumulate in the eye over decades of normal aging—and then exposed these cells to the equivalent of sunlight,” Dr. Tsang says. “After 10 days, by most criteria, the cells behaved like 60-year-old cells.”

By comparing aged retina cells from AMD patients with those from healthy controls, the researchers were able to determine why the patients had developed the disease. “The eye is constantly exposed to light, which causes lots of damaging oxygen radicals to build up in the eye,” Dr. Tsang says. “We found that in AMD patients, the eye cannot protect itself from oxygen radicals because an antioxidant-defense enzyme inside the eye—called SOD2—does not work well.” This means that compounds that increase SOD2 activity may be effective at preventing cell death

and vision loss in people who carry genetic risk factors linked to AMD.

The P&S team’s effort to create patient-specific cells and “AMD in a dish” may be critical to finding such compounds. “Instead of testing each drug candidate on thousands of patients, it will be easier and faster to screen for drugs on a couple of thousand cell lines to see which ones have the greatest potential,” says Dr. Tsang.

Ultimately, the cell model also may be used to personalize treatment of the disease. “For people who don’t have the disease but have a high genetic risk,” Dr. Tsang says, “we can take their skin cells, make them into retinal cells, age them, and then find the drug that is the most likely to prevent macular degeneration and vision loss in that individual as an application of personalized medicine.”

This is a summary of research published in Human Molecular Genetics, July 1, 2014.



HELP FROM OUR FRIENDS



BARBARA AND DONALD JONAS

Barbara and Donald Jonas have shared wide-ranging generosity with Columbia, including current support of research into late-onset retinal dystrophy, a rare hereditary condition that destroys the cells responsible for peripheral vision and depth perception.

Their generosity includes support for the stem cell research of Stephen H. Tsang, MD, PhD. The Jonases have a long history of philanthropic support for health care at Columbia, particularly in nursing and mental health.



Stephen Tsang, MD, PhD
Janet Sparrow, PhD

Mendelsohn's Mice

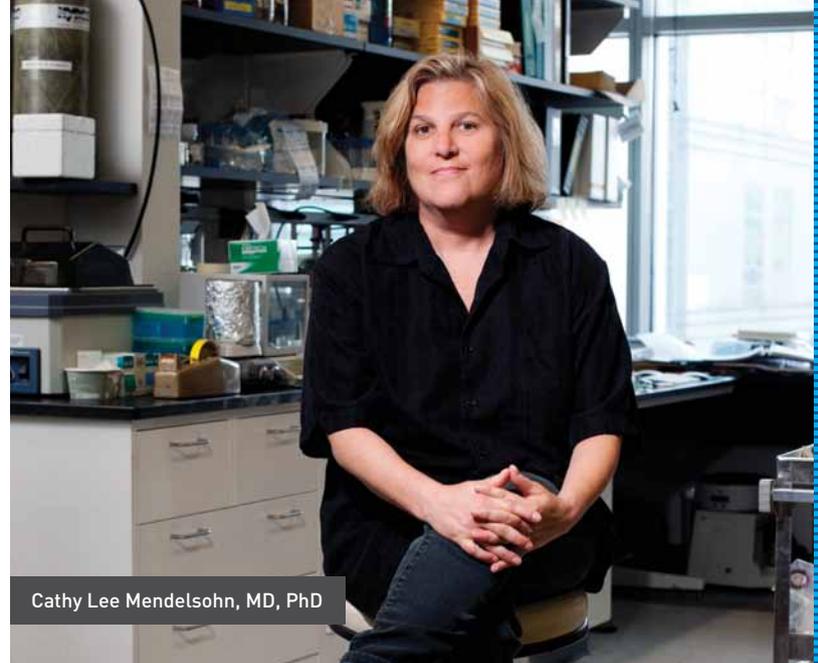
The bladder's inner lining is like no other biological barrier in nature. The urothelium, the multilayered tissue, prevents leakage under pressure, fends off pathogens with a unique protein barrier, and protects underlying neurons, muscle, and blood vessels from toxins in the urine. For patients whose urothelium has been damaged—by cancer, recurrent infection, or other insults—existing treatments promise to restore only a weak approximation of the healthy tissue's function.

Cathy Lee Mendelsohn, MD, PhD, professor of urology, pathology & cell biology, and genetics & development (in the Institute of Human Nutrition), has dedicated her career to investigating the signals that drive the development of the urogenital tract, looking for clues both to the origins of congenital defects in utero and to the many types of cancer that invade the bladder.

Now Dr. Mendelsohn has analyzed the body's own bladder repair process. Her findings upend conventional wisdom, chart a new approach to treatments for chronic bladder pain, and suggest tactics for bioengineering breakthroughs to create replacement tissue for patients with damaged bladders. Like her earlier studies, which documented the precise mechanical and chemical processes by which components of the urogenital tract migrate during fetal development to their final locations, the recent work published in *Developmental Cell* used new mouse models to subject long-standing hypotheses to experimental scrutiny.

"Bladder pain syndrome (aka interstitial cystitis) is a disease associated with chronic UTI or injury that affects primarily women," says Dr. Mendelsohn. "The urothelium is not very proliferative, however progenitors are present in adults that can rapidly replace the urothelium in response to acute damage from UTI or exposure to toxins. Chronic damage, however, compromises the urothelial barrier and can severely damage the bladder, exposing underlying tissue including nerve endings that would normally be protected. At present, there is no known way to regenerate the urothelium under these circumstances or to replace a damaged bladder."

These clinical observations led to the idea that progenitor cells in the adult urothelium can be damaged or eliminated by continuous injury—



Cathy Lee Mendelsohn, MD, PhD

and that protecting them may help patients with chronic conditions—but the identity of the progenitor cells was unclear.

Unlike skin cells, which regenerate through basic division to heal injuries, cells of the uppermost urothelial layer rarely divide. Rather, old cells slough off and progenitor stem cells deeper in the organ produce new cells to take their place. Scientists had long thought that basal cells were the progenitors of that outer layer.

Dr. Mendelsohn, a member of Columbia's Stem Cell Initiative, used fluorescent tags to trace the progeny of cells in different layers of the urothelium in mice. The tags revealed two distinct progenitor populations—one that exists for a short time during embryonic development and a second one, in adults, that regenerates the barrier's outer layer after damage.

Basal cells, the team found, yielded only more basal cells. The scientists traced formation of the outer urothelium in a developing embryo to a new cell type, the P-cell, which disappears before birth. In adults, Dr. Mendelsohn found that cells in the urothelium's middle layer can self-renew and regenerate the urothelium's outer layer. Both types of progenitor cells depend on retinoic acid, a derivative of vitamin A, for their functions.

*This is a summary of research published in *Developmental Cell*, September 16, 2013.*

HELP FROM OUR FRIENDS

CAROLE WHITE



Irwin White

Since its inception, the Department of Urology has focused on the singular purpose of advancing the field of urology to provide the most comprehensive, high-quality, and compassionate care to patients. Essential to this mission is the fellowship program, which provides training for future academic leaders, physician-scientists, and clinical educators in urologic disease.

In 1995, Carole White and her sons, Jonathan and Gregory, established the White Fellowship Fund in Prostate Cancer, in memory of their husband and father, Irwin White. The fund's purpose is to support young fellows working in the laboratory to accelerate research efforts for the diagnosis, treatment, and prevention of prostate cancer. Thanks to the visionary

partnership of the White family and other donors, the Department of Urology has been able to maintain its standing as No. 1 in New York (based on hospital urology specialty rankings compiled by U.S. News & World Report). This helps Columbia attract the best candidates in the field while providing crucial support to young investigators in the early stages of their careers.

Behind the Curtain

Automotive engineers have crash test dummies, and biochemists have DNA curtains, courtesy of Eric Greene, PhD, associate professor of biochemistry & molecular biophysics. Dr. Greene's novel invention works on the nanoscale, using strands of DNA tethered to a glass slide, like a curtain of glass beads. Like engineers documenting the impact of a collision on a dummy, scientists using Dr. Greene's technique throw proteins at the curtain then document what happens next.

"We call it visual biology, or visual biochemistry, because we can see at the molecular level

what's happening," says Dr. Greene. "We're watching them in real time, instead of relying on more traditional techniques that may only indirectly suggest what's going on."

Dr. Greene has worked with graduate student Sy Redding and a team in California on the mechanisms behind CRISPR, a popular genetic-engineering tool. Like many laboratory techniques used to cut and paste DNA, the CRISPR system was appropriated from bacteria.

A bacterium steals small snippets of viral DNA and retains the fragments in a sort of

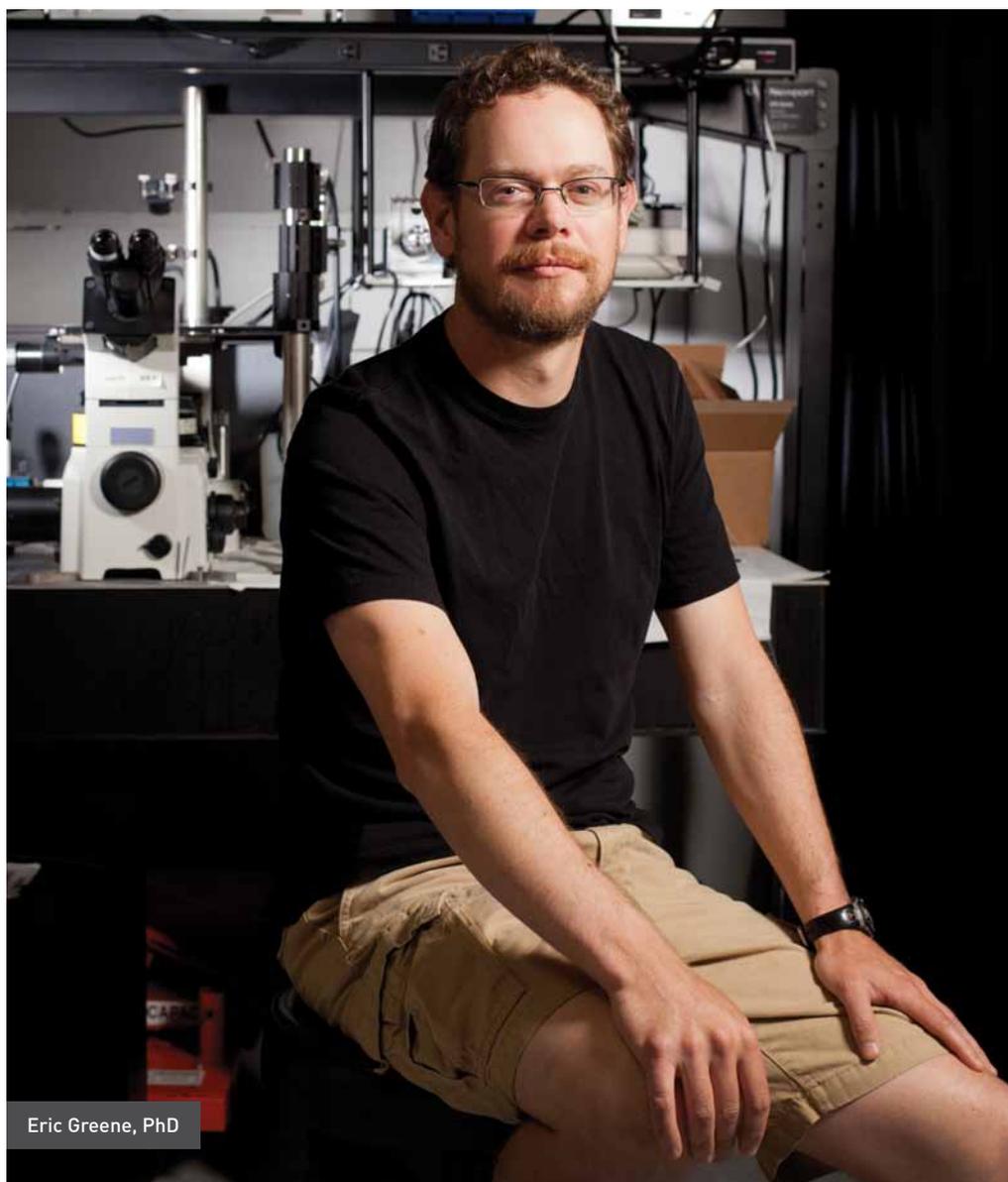
library of viruses to which it has been exposed in the past. If a virus returns, the bacterium makes RNA copies of the DNA sequences. In CRISPR, a protein called Cas9 then grabs the bits of RNA and uses them like fingerprints to identify the viral invaders. The Cas9-RNA complexes patrol the genome to sniff out invading viruses and destroy the viral DNA.

Taking advantage of the high specificity and programmability of Cas9, scientists have co-opted CRISPR systems as a powerful new tool to delete any gene they wish in any type of cell, as well as to turn genes on and off. But because scientists didn't know precisely how CRISPR worked, they wondered whether it might have unwanted side effects elsewhere in the genome.

Scientists suspected that the Cas9 complex worked by grabbing onto the DNA, then sliding along the strand, looking for its target. "But what we saw was pure, random, three-dimensional diffusion," says Dr. Greene. "Despite those random collisions, Cas9 is looking for something very specific." Its target: a three-nucleotide sequence known as PAM, the first step of a two-part search. "It's asking whether the adjacent DNA matches the virus that it's trying to destroy. This two-part mechanism sets Cas9 apart from any other target search we've looked at."

It is also much faster than the mechanism scientists had thought was in play. "Consider how you find your favorite pair of red socks in the morning," suggests Mr. Redding, the chemistry graduate student. "You don't randomly open all of your dresser drawers until you happen to find your red socks. You just open your sock drawer and pick out your favorite pair of red socks. Cas9 does essentially the same thing: First it looks for the PAM (the "sock drawer"), then it asks whether the sequence next to the PAM is correct (the "red socks"). This way, Cas9 avoids wasting time searching through the entire genome by restricting its search to sites that have PAM sequences."

This is a summary of research published in Nature, March 6, 2014. An educational video about the research is available on YouTube: <http://bit.ly/1qfL66i>.



Eric Greene, PhD



Anna Lasorella, MD



Antonio Iavarone, MD

Focus on Fusion

A year after the journal *Science* published the identity of a gene fusion responsible for 3 percent of glioblastoma multiforme, the most common—and most aggressive—form of brain cancer in adults, *Nature Genetics* published a report by the same P&S scientists identifying an additional 18 genes; together they represent 15 percent of glioblastoma cases.

“Cancers rely on driver genes to remain cancers, and driver genes are the best targets for therapy,” says Antonio Iavarone, MD, professor of neurology and of pathology & cell biology and a principal author of the paper. “Once you know the driver in a particular tumor and you hit it, the cancer collapses. Our study has identified the vast majority of drivers in glioblastoma—and therefore a list of the most important targets for glioblastoma drug development and the basis for personalized treatment of brain cancer.”

Individually tailored treatment for some patients is not far off, says Anna Lasorella, MD,

associate professor of pediatrics and of pathology & cell biology and also a principal author. “This study—together with our study from last year—shows that about 15 percent of glioblastomas are driven by genes that could be targeted with currently available FDA-approved drugs,” she says. “There is no reason why these patients couldn’t receive these drugs now in clinical trials.”

Beyond showing potential for people with glioblastoma multiforme, the team’s work promises powerful new analytic tools to analyze the deluge of data drawn from the cancer genome. Raul Rabadan, PhD, assistant professor of biomedical informatics and of systems biology, collaborated with Drs. Iavarone and Lasorella to create TX-Fuse, an algorithm that hunts for unique fusion genes within the RNA of a tumor sample. “The development of sequencing and computational techniques is becoming more and more important to teams trying to understand the complexity of data,” says Dr. Rabadan, a theoretical physicist. “I see my work as a trans-

lator—taking a problem in biology and making it intelligible to a computer, something that can be coded and solved. Anna and Antonio move the information from a line in the computer code to something that can make a drug, can make a difference.”

Using high-throughput sequencing, the team analyzed nearly 140 brain tumors, sequencing the DNA and RNA of every gene and identifying all of the mutations in each tumor. They then applied TX-Fuse to distinguish driver mutations from other genetic anomalies. The analysis found 18 new driver genes never before implicated in glioblastoma and correctly identified the 15 previously known driver genes.

“If you block the function of the gene fusion, you can have a strong anti-tumor effect,” says Dr. Iavarone. “That’s why we’re very excited about the therapeutic opportunities.”

This is a summary of research published in Nature Genetics, August 5, 2013.



HELP FROM OUR FRIENDS

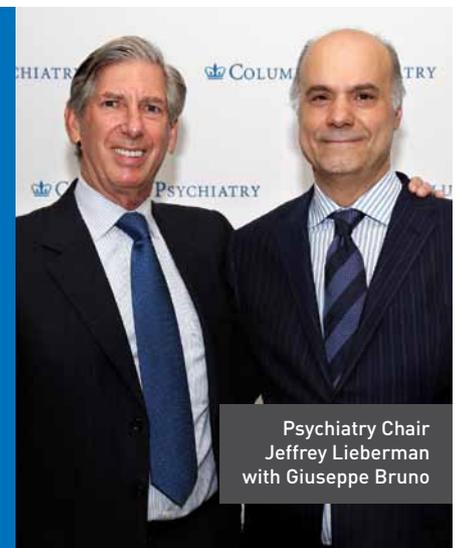
GIUSEPPE BRUNO

The remarkable progress of the Institute for Cancer Genetics is due in part to the visionary partnership of Giuseppe Bruno. A philanthropist, chef, and restaurateur, Mr. Bruno owns *Sistina*, *San Pietro*, and *Caravaggio*, three of the most celebrated Italian restaurants in New York

City. Mr. Bruno has organized dazzling events to raise funds for pediatric brain cancer research, posttraumatic stress disorder research, and pediatric psychiatry programs.

His volunteer efforts and generous gifts have been instrumental in allowing Columbia

to provide help for some of the most fragile and underserved individuals who have served our nation. This year, Mr. Bruno was honored at the Gray Matters at Columbia spring benefit luncheon for his unyielding support of investigations into psychiatric disorders.



Psychiatry Chair Jeffrey Lieberman with Giuseppe Bruno

Malaria Meets Its Match

When it comes to evolutionary advantage, *Plasmodium* has had a lead on its human hosts for as long as stagnant water has been around. A unicellular eukaryotic parasite whose life cycle features a stint in the gut of female *Anopheles* mosquitoes, the organism that causes malaria divides and mutates so fast that it is already resistant to all three major classes of treatment.

An international team including Marcus C.S. Lee, PhD, associate research scientist in microbiology & immunology, announced a discovery that may even the score: a metabolic enzyme required by the species *Plasmodium falciparum* for survival at each stage of infection in humans. The findings raise the possibility of developing a drug to combat one of the world's deadliest diseases.

"Most anti-malarials are effective at killing the parasites only as they circulate in the bloodstream," says Dr. Lee. "However, some species of this parasite can hide in the liver for years before re-emerging and triggering a relapse of the disease. By identifying this enzyme, we may be able to develop a way to kill the parasites in their dormant stage."

The team, which included investigators from UC San Diego and the Novartis Institute of Tropical Diseases, screened more than 1 million drug compounds against *Plasmodium falciparum* cultured blood stage parasites to find a new way of killing the parasite. The process revealed a class of compounds known as imidazopyrazines, which kill several species of *Plasmodium* at each stage of the parasites' life cycle in the vertebrate host yet have no effect on human cells. Once researchers identified the imidazopyrazines, they evolved parasite cell lines resistant against them and analyzed the mutated parasites' genomes for the changes that conferred resistance. Those mutations pointed to the gene that encodes phosphatidylinositol 4-kinase (PI4K), the novel drug target.

The Columbia team, led by David Fidock, PhD, professor of microbiology & immunology and medical sciences (in medicine), used novel genetic tools to confirm that PI4K was being directly targeted by the imidazopyrazines. Using cellular imaging, the team determined that imidazopyrazines interfere with the function of PI4K in the Golgi, the organelle within



David Fidock, PhD

the parasite that packages proteins for delivery to other cellular destinations.

Dr. Fidock has also modeled current strategies to make malaria control measures more effective. PLOS Computational Biology published a mathematical model developed by Dr. Fidock and colleagues that suggests malaria could be eliminated in many parts of the world by promptly giving artemisinin-based combination therapies (ACTs) to the 80 percent to 85 percent of people who are not otherwise offered this current first-line anti-malarial drug therapy. Adding the transmission-blocking drug primaquine—a strategy currently being considered internationally—does not significantly increase the benefits, according to the model, which incorporates such factors as how the drugs are absorbed in the body, immune responses, patient variability in response to the drugs, and how the drugs affect different parasitic stages in the infected person and in the mosquito.

"Despite its current endorsement, primaquine is not a game changer," says Dr. Fidock. "Our modeling indicates that a far more effective strategy would be to treat more than 93 percent of infected individuals with ACTs within five days of the onset of fever, which we predict would reduce malaria to near-elimination levels in most parts of Southeast Asia, the Western Pacific, and South America. The extreme levels of disease transmission observed in much of sub-Saharan Africa, however, mandate the development of far more effective interventions before malaria in Africa can be brought to near-elimination levels. New means such as the development of pan-active PI4K inhibitors as drugs that can radically cure infected humans of all stages of parasite development would represent one such path to achieving this goal."

This is a summary of research published in Nature, December 12, 2013, and PLOS Computational Biology, January 23, 2014.

ColumbiaDoctors Continues to Expand

ColumbiaDoctors, the faculty practice organization of P&S, has continued to grow since opening a midtown location at 51 W. 51 St. near Rockefeller Center, in January 2013. Total patient visits to the practice are up 20 percent, and new patient visits are up 16 percent.

In February, ColumbiaDoctors acquired the North Star Medical Group in the Lower Hudson Valley, making ColumbiaDoctors one of the largest medical practices in Westchester. The acquisition added 15 physicians in nine offices specializing in family medicine, internal medicine, gastroenterology, and pulmonary medicine. The ColumbiaDoc-

Hospital. The hospital expanded its reach in Westchester with a new partnership with Lawrence Hospital to enhance care, improve access, and lower health care costs for residents of Bronxville and surrounding communities in Westchester County. Lawrence Hospital has been renamed NewYork-Presbyterian/Lawrence Hospital.

The ColumbiaDoctors expansion into Westchester and the Hudson Valley represents the latest phase in the growth of the FPO over the past seven years. ColumbiaDoctors Midtown now sees more than 1,000 patients a day and offers extended and Saturday hours. The facility has diagnostic imaging

tion, held by the International Interior Design Association. The ambulatory care category recognizes “outstanding originality and excellence in the design and furnishings of health care interior spaces.”

The facility, designed by Perkins+Will, features large windows at the ends of the halls, which flood the building with natural light. Eco-friendly design features, including vinyl-free flooring and low-mercury lighting, make the practice energy-efficient and consistent with the rest of the building, which was awarded LEED Gold certification. The floor plan was laid out with patients’ needs in mind, placing related disciplines—e.g., pediatrics and obstetrics & gynecology—adjacent to one another. This not only is convenient for patients, but also facilitates collaboration among doctors.

At the CUMC campus, ColumbiaDoctors facilities are under renovation. The first phase of a new internal medicine suite in the Harkness Pavilion opened in March. Additional renovations are under way in the Herbert Irving Pavilion at 161 Fort Washington Ave.

ColumbiaDoctors also has new leadership. After three years as president, Louis Bigliani, MD, outgoing chair of orthopedic surgery, has been succeeded by George A. (Jack) Cioffi, MD, chair of the Department of Ophthalmology. Dr. Cioffi, an internationally recognized glaucoma scientist and clinician, is the Edward S. Harkness Professor of Ophthalmology and the Jean and Richard Deems Professor of Ophthalmology. He joined Columbia in 2012.

John Chabot, MD, vice president of ColumbiaDoctors since 2011, was re-elected vice president. Dr. Chabot, the David V. Habif Professor of Surgery at CUMC, is chief of the Division of GI/Endocrine Surgery, executive director of the Pancreas Center, and associate director of clinical affairs at the Herbert Irving Comprehensive Cancer Center.



JORG MEYER

tors network now has more than a dozen locations throughout the New York metro area.

Comprising 1,200 practitioners from P&S, the College of Dental Medicine, and the School of Nursing, ColumbiaDoctors provides coordinated care across Columbia’s specialties. The organization’s suburban practices are linked to Columbia’s main clinical affiliate, NewYork-Presbyterian

services—X-ray, PET/CT and MRI, mammography, and fluoroscopy—plus more than 125 exam rooms and 30 rooms equipped for endoscopy procedures, skin treatments, and cardiac stress tests. Extensive facilities for physical therapy, occupational therapy, and sports therapy also are on site.

ColumbiaDoctors Midtown won an award in the 2013 Healthcare Interior Design Competi-

New Faculty, New Roles for Other Faculty

The 122 new faculty members who joined P&S this past year include a department chair and senior and junior faculty in all disciplines of the medical school.

Lawrence Lustig, MD, one of the nation's leading experts in hearing loss, was named chair of the Department of Otolaryngology/Head and Neck Surgery. He joined P&S from the University of California, San Francisco, where he was chief of the Division of Otolaryngology & Neurotology at both UCSF and San Francisco General Hospital, director of the Douglas Grant Cochlear Implant Center, clinical chief of the otolaryngology service on the Parnassus campus, and co-director of the Center for Balance and Falls. At P&S he is the Howard W. Smith Professor of Otolaryngology.

Dr. Lustig succeeds Lanny Close, MD, professor of otolaryngology/head and neck surgery, who stepped down in May 2013 after nearly 20 years as chair.

The Department of Orthopedic Surgery also has new leadership. Louis U. Bigliani, MD, retired as chair after leading the department for 16 years. Department vice chair for education, William N. Levine, MD, was named to chair orthopedic surgery; he joined Columbia in 1998.

Dr. Levine also has directed the department's residency and fellowship programs, served as chief of the shoulder service, and been co-director of the Center for Shoulder, Elbow & Sports Medicine. He is professor of orthopedic surgery at CUMC.

Also notable among new faculty roles is a new title for Lynn L. Simpson, MD, chief of the Division of Maternal Fetal Medicine, professor of



Lawrence Lustig, MD



William N. Levine, MD

obstetrics & gynecology, and an international expert in maternal medicine, prenatal pediatrics, and high-risk deliveries.

Dr. Simpson is the inaugural incumbent of the Hillary Rodham Clinton Professorship in the Department of Obstetrics & Gynecology, one of several new professorships endowed at P&S. An anonymous donor endowed the Clinton professorship, which is the fourth endowed chair added to the department in the past three years and the 16th new endowed chair in P&S since 2012.

Clinicians Receive Jerry Gliklich Awards for Exemplary Clinical Care



Spencer Amory, MD, and David Markowitz, MD

Spencer E. Amory, MD, the José M. Ferrer Professor of Surgery and chief of the general surgery division in the Department of Surgery, and **David D. Markowitz, MD**, associate professor of medicine, received 2014 Jerry Gliklich Awards for Exemplary Clinical Care from the Society of Practitioners at Columbia University Medical Center.

Dr. Amory received his MD degree from Johns Hopkins and trained at Columbia University Medical Center. He has developed techniques in laparoscopic cholecystectomy that enabled his team to have the lowest open cholecystectomy rates in the state.

Dr. Markowitz, a graduate of P&S, has been on the Columbia faculty since 1992. He completed his residency in medicine and a fellowship in gastroenterology at Columbia. His research focuses on esophageal motility and gastroesophageal reflux disease. He has a clinical interest in the nutritional aspects of ALS.

The Jerry Gliklich Award for Exemplary Clinical Care, formerly called the Practitioner of the Year award, is given to physicians who demonstrate exceptional care to patients, engender respect and collegiality with peers, and have noteworthy clinical outcomes.

The award has been granted since 1982 and was renamed the Jerry Gliklich award this year to honor Dr. Gliklich, who has been a clinician at Columbia since 1981. At P&S, Dr. Gliklich is a cardiologist and the David A. Gardner Professor of Medicine.

Interdisciplinary Aging Center Named for P&S Graduate

Columbia University has established a university-wide, interdisciplinary aging center, the Robert N. Butler Columbia Aging Center, named for the founding director of the National Institute on Aging. Dr. Butler, who

died in 2010, was a physician, gerontologist, psychiatrist, Pulitzer Prize-winning author, and 1953 graduate of P&S.

Inaugural director of the Butler Center is Ursula M. Staudinger, PhD, who previously served as founding dean of the Jacobs Center on Lifelong Learning and Institutional Development at Jacobs University in Bremen, Germany.

Based at the Mailman School of Public Health, the Butler Columbia Aging Center reflects the University's recognition that the study of aging is inherently multidisciplinary. The center organizes and builds on existing aging-related programs and activities, translating scientific knowledge into policy and practice. It focuses on the systemic nature of aging—the continuous interaction among biological, behavioral, and sociocultural factors that constitutes human development. It will forge partnerships with the academic, corporate, nonprofit, and public sectors to develop policies on aging, engage communities, and influence societal change.

The Butler Columbia Aging Center consists of an Aging Lab and the International Longevity Center, founded by Dr. Butler in 1990. The Aging Lab is dedicated to research on aging, as well as on ways that individuals and society can benefit from the latest scientific knowledge. That research enables the International Longevity Center to develop public policies and education and community-outreach programs. The longevity center is part of a global consortium of 13 such centers, including sites in Cape Town, Paris, and Tokyo.



Robert N. Butler '53

White Coat Ceremony Turns 20

The White Coat Ceremony, a rite of passage that marks the beginning of a student's formal medical studies, started at P&S in 1993. In the two decades since, white coat ceremonies have become a tradition at 130 schools of medicine or osteopathy in the United States and many other countries.

At Columbia's 20th anniversary of the ceremony on Aug. 12, 2013, 170 new medical students—the Class of 2017—took an oath, based on the Hippocratic Oath, to practice medicine honestly, with compassion and empathy. Before 1993, medical students generally recited the oath only at graduation; now, medical students make the pledge at both the beginning and end of medical school. In addition to reciting the oath, students are “cloaked” before family and friends in the iconic short white coat that signifies their status as medical students.

The 2013 ceremony took on added significance because the students who finish medical

school in the traditional four years will graduate in 2017—the 250th anniversary of P&S.

The Class of 2017 includes six graduates of Columbia's pipeline projects—summer programs for college students from underrepresented or economically disadvantaged backgrounds. The Summer Medical and Dental Education Program, Summer Public Health Scholars Program, and Strategic Testing Application Techniques Program are designed to help increase the number of medical students from underrepresented, disadvantaged, or low-income communities.

Four students in the inaugural class of Columbia's new PhD-to-MD degree program also were among those taking the oath and donning white coats. The PhD-trained biological scientists embarked on a 36-month program designed by the Department of Medicine and the Office of Education at P&S.

Arnold P. Gold, MD, professor of clinical neurology and of clinical pediatrics at P&S, initiated the White Coat Ceremony to “welcome entering medical students and help them to establish a psychological contract for the practice of medicine.” His eponymous foundation continues to support the ceremony.

The six graduates of pipeline programs who entered with the Class of 2017 are, from left: Leanne Duhaney, Michael Hernandez, Elvis Camacho, Nicholas Rozon, Ignacio Contreras, and Plicelianny Perez.



Faculty Honors

P&S faculty received many honors during FY14. Among the top honors were two prizes awarded to **Thomas M. Jessell, PhD**, and the election of three faculty members to prestigious organizations.

Dr. Jessell, the Claire Tow Professor of Motor Neuron Disorders (in Neuroscience and Biochemistry & Molecular Biophysics), received the 2014 Vilcek Prize in Biomedical Science and the 2014 Neuroscience Prize from the Gruber Foundation.

The Vilcek Prize, which honors the contributions of immigrants to American arts and sciences, recognized Dr. Jessell's pioneering work in discovering the principles of the molecular mechanisms that direct neuronal diversity and circuit assembly in the vertebrate central nervous system. The Vilcek Foundation noted that his work has shed light on developmental abnormalities in the central nervous system, paving the way for new possibilities using neural stem cells to treat degenerative diseases affecting motor neurons and spinal cord injuries.

The Gruber Prize honored Dr. Jessell's seminal work on the development and wiring of spinal cord neurons involved in the control of movement. The foundation noted Dr. Jessell's identification of many of the key cellular and molecular components that control the development and function of the spinal cord.

Dr. Jessell is co-director of the Mortimer B. Zuckerman Mind Brain Behavior Institute, co-director of the Kavli Institute for Brain Science, and a Howard Hughes Medical Institute investigator.

University Professor and Nobel laureate **Richard Axel, MD**, was elected to the Royal Society this year as a foreign member. The Royal Society is the United Kingdom's national academy of science, founded in the 1660s. The society elects up to 52 new fellows and up to 10 new foreign members each year. Dr. Axel is noted for his research into how the sense of smell works (for which he shared the Nobel Prize in 2004) and for his work that helped develop gene transfer techniques that permit the introduction of virtually any

gene into any animal cell. The techniques spread through academic laboratories and made possible a wide range of new drugs, including tissue plasminogen activator, which dissolves blood clots in some cases of stroke.

Mary D'Alton, MD, the Willard C. Rappleye Professor of Obstetrics & Gynecology and chair of the Department of Obstetrics & Gynecology, was elected to the Institute of Medicine in Fall 2013. Election to the IOM is considered one of the highest honors in the fields of health and medicine.

Dr. D'Alton specializes in high-risk maternal fetal medicine, performing prenatal diagnostic procedures and managing maternal health complications. She has implemented a multidisciplinary approach to treat highest-risk pregnancies and to diagnose and treat fetal complications. She was instrumental in setting up Columbia's Carmen and John Thain Center for Prenatal Pediatrics, a regional coordinated-care center for the treatment of fetal complications.

Laurence Abbott, PhD, the William Bloor Professor of Neuroscience and professor of physiology & cellular biophysics (in biological sciences), was elected to the National Academy of Sciences this year. Election to the NAS recognizes distinguished and continuing achievements in original scientific research.

Dr. Abbott trained as a physicist and worked in theoretical particle physics before a transition to neuroscience research. He is co-director of Columbia's Center for Theoretical Neuroscience. Using computational modeling and mathematical analysis, Dr. Abbott explores how single neurons respond to synaptic inputs, how neurons interact in neural circuits, and how large networks of neurons represent, store, and process information in processes including olfaction, motor-pattern generation, and memory and decision-making.

A full listing of faculty honors received during FY14 can be viewed in the 2014 State of the School presented by P&S Dean Lee Goldman in June. A link to the presentation is available on the dean's website, <http://ps.columbia.edu/about-ps/deans-page>.

Bookstore Moves to Haven Avenue

Barnes & Noble relocated the medical campus bookstore this fall from 3954 Broadway to a larger space at Haven Avenue and 169 Street, in the lower level of the Hammer Health Sciences Center. In Hammer, the new bookstore occupies 4,584 square feet.

The new bookstore carries academic course material and supplies plus a small selection of general-interest books and periodicals. A café—with both indoor and outdoor seating—serves coffee, pastries, bagels, pizza, sandwiches, and salads. The bookstore is expected to be an asset to the local community as well as the medical campus.



Society for Women Faculty: A Tribute to Virginia Kneeland Frantz

People who met Virginia Kneeland Frantz—physician, surgical pathology pioneer, teacher, loyal P&S alumnus, student admissions interviewer—were not likely to forget the woman known as “VKF.” A new organization at P&S now permanently associates Dr. Frantz’s name with the school that was her professional home for more than 40 years.

The Virginia Kneeland Frantz Society for Women Faculty was formed this year to serve, support, and celebrate the careers of women in science and medicine at P&S. Faculty of all genders and ranks, as well as students and trainees, are eligible for membership in the society.



Virginia Kneeland Frantz '22

The society presented the inaugural Virginia Kneeland Frantz Society for Women Faculty Lecture in April. In the lecture, Debora L. Spar, PhD, president of Barnard College, spoke of the consistently low number of women who make it to the top of any profession. She suggested ways society might “move the needle” on the advancement of women.

Dr. Frantz, a 1922 graduate of P&S, was the first woman to pursue an internship in surgery at what is now New York-Presbyterian Hospital and the first woman to become

president of the American Thyroid Association. Internationally recognized in surgical pathology, she remained at Columbia despite an offer to become president of Bryn Mawr College, her undergraduate alma mater.

She made several scientific and clinical contributions during her career. She founded a multidisciplinary thyroid clinic at Columbia and made a series of discoveries related to the diagnosis and treatment of thyroid, breast, and pancreatic tumors. She published an account of pancreatic tumors for the *Armed Forces Atlas of Tumor Pathology* that became the standard text on the subject. She was also one of the first to prove the usefulness of radioactive



Debora L. Spar, PhD



Anne Taylor, MD

iodine in the diagnosis and treatment of metastatic thyroid cancer. Dr. Frantz and famed surgeon Allen O. Whipple were the first to describe the insulin secretion of pancreatic tumors. During World War II, she studied the control of bleeding during surgery with Dr. Raffaele Lattes, leading to the discovery of oxidized cellulose as an aid to wound healing that could be absorbed by the body. For this work, she received the Army-Navy Certificate of Appreciation for Civilian Service.

The Virginia Kneeland Frantz Society, which evolved from the Committee for Women Faculty, serves women at P&S by offering education and professional development; supports women through mentorship, advocacy for equity, sponsorship, work/life resources, and networking; and celebrates women’s career achievements and advancement while also honoring individuals who mentor and support women.

“The Virginia Kneeland Frantz Society will empower women faculty to advance in their careers, develop personally, and be full participants in institutional growth and vitality. In turn, the institution will have the full benefit of its formidable intellectual capital,” says Anne L. Taylor, MD, vice dean for academic affairs at P&S and the John Lindenbaum Professor of Medicine at CUMC.



EILEEN BARROSO

Community Brain Expo

The annual **Community Brain Expo**, cosponsored by the Mortimer B. Zuckerman Mind Brain Behavior Institute at Columbia University, was held in March for school students, parents, and teachers interested in learning about the brain through demonstrations, experiments, and activities for all ages.

“Kids and adults alike are fascinated by the three-pound organ that rules the body, so we were eager to engage people about their brain,” says Kelley Remole, PhD, director of neuroscience outreach for the Zuckerman Institute.

The brain expo was part of Brain Awareness Week in New York City.

“Young Docs” Inspire Future Doctors

Donning white coats and carrying stethoscopes, nine P&S students spent a March afternoon in a first-grade classroom in Inwood, teaching kids about the human body and what it is like to be a doctor. The P&S students, part of the Black and Latino Student Organization’s “Young Docs” program, visit local schools once a month in collaboration with the Office of Government and Community Affairs.

Young Docs has visited local classrooms and hosted workshops in the Washington Heights, Inwood, and Harlem communities since 2010, when it was founded by Jack Angiolillo’15. As minorities continue to be underrepresented in medicine, the mission of BALS0’s Young Docs program is to expose school-age children to the medical field and encourage them to become lifelong learners and leaders within their communities.

“My first introduction to Young Docs was as a first-year medical student in a classroom full of eager third graders,” says Alani Gregory’15. “As I looked around, I saw the students smiling in amazement at the sound of their own heartbeats as they played with stethoscopes and gig-



P&S student Pliceliany Perez visits with students at P.S. 314 in Northern Manhattan as part of BALS0’s Young Docs program.

gling as they came face-to-face with our life-sized skeleton. By the end of the session, many students were telling us that they wanted to become doctors. Whether or not these children end up working in health care, we hope our visits help them dream big and think about ways they can give back to their communities.”

Exploring Diversity Through Theater



Auditions for “Me Too Monologues”

Most people have had experiences that made them think deeply about some aspect of their identity, such as race, religion, gender, sexuality, culture, or nationality. Such experiences may be deeply personal, but they are also universal.

To give them a public platform, the Office of Diversity and Multicultural Affairs at P&S presented “Me Too Monologues,” a theater performance that explored true stories about these issues.

Directed by Steven Li’17, student-actors performed monologues about identity written and submitted anonymously by students, faculty, and staff throughout the medical center.

New Centers in Medicine, Psychiatry

The Department of Medicine launched a center called the Center for Human Development under the leadership of Wellington Cardoso, MD, PhD, professor of medicine, a recent recruit from Boston University. At Boston University, Dr. Cardoso was professor of medicine and pathology and director of the Lung Development and Progenitor Cell Biology Program.

The center will bring together investigators with state-of-the-art knowledge in developmental and stem/progenitor cell biology to study the developmental origins of human disease, providing potential venues for new disease intervention.

Dr. Cardoso plans to recruit new faculty members and reestablish the Lung Development and Progenitor Cell Biology Program with Columbia investigators.

In the Department of Psychiatry, the Center for Research on the Ethical, Legal and Social Implications of Psychiatric, Neurologic and Behavioral Genetics was created under the leadership of Paul Appelbaum, MD, to bring together clinicians and researchers from

across the medical center, along with colleagues from the Hastings Center, a research institute that addresses fundamental ethical questions in health, medicine, and the environment.

As understanding of the genetic contributions to psychiatric, neurologic, and behavioral (PNB) traits and disorders advances, the knowledge is being quickly translated into clinical practice. The nature of PNB genetic information, however, raises complex questions about the impact the data will—and should—have in both clinical and nonclinical settings.

“Our center offers the opportunity to advance knowledge of the ethical, legal, and social implications of one of the most rapidly growing areas of genetics. Drawing on our empirical studies and input from key stakeholders, we will develop strategies to guide the use of PNB genetic data in clinical and research settings, as well as in courts, legislatures, and regulatory agencies,” says Dr. Appelbaum, who is also director of the Division of Law, Ethics and Psychiatry and the Elizabeth K. Dollard Professor in the Department of Psychiatry.

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FACTS & STATISTICS, FY14

MEDICAL SCHOOL ENROLLMENT, FALL 2013

Total medical school enrollment	655
Enrollment of underrepresented minorities	141
Enrollment of minorities	257
Enrollment of international/nonresident students	18
Enrollment of in-state residents	215
Enrollment of men	317
Enrollment of women	338

ENROLLMENT BY YEAR

	MALE	FEMALE
First-Year Class	83	87
Second-Year Class	83	84
Third-Year Class	75	90
Fourth-Year Class	76	77
Total Enrollment	317	338

ETHNIC BREAKDOWN

Nonresident aliens	18
Hispanic/Latino	70
Black or African-American, non-Hispanic/Latino	51
White, non-Hispanic/Latino	335
American Indian or Alaskan Native, non-Hispanic/Latino	1
Asian, non-Hispanic/Latino	116
Two or more races, non-Hispanic/Latino	19
Race and/or ethnicity unknown	45

OTHER STUDENTS

MD/PhD students	115
PhD students	287
Other students (PT, OT, Nutrition, Informatics)	426

Data current as of July 1, 2014, except where noted.

DEGREES GRANTED, JULY 2013 TO JUNE 2014

MD	164
PhD	71
Doctor of physical therapy	50
MS in nutrition	74
MS in occupational therapy	56
Certificate in psychoanalysis	4

APPLICATIONS (CLASS ENTERING 2013)

Number of applicants	7,864
Number of applications considered	7,448
Number of applicants interviewed	1,075
Number of acceptance letters issued	325
Number of new entrants	170
Bassett Program applications	691
Number of new Bassett Program entrants	10

FACULTY, 2013-14 ACADEMIC YEAR

	FULL TIME	PART TIME
Number of clinical faculty	1,692	2,507
Number of basic sciences faculty	231	71

FACULTY HONORS

Nobel Prize in Medicine	2
National Academy of Sciences	17
Institute of Medicine	42
American Academy of Arts and Sciences	25
Howard Hughes Medical Institute	12

FINANCIALS, FY14 (except where noted)

Budget	\$1.5 billion
Philanthropic support	\$165 million
Endowment	\$1.8 billion
Endowed chairs/professorships	232
NIH research support (FY 2013)	\$366 million



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FROM LEFT:

Alejandro Ramirez	Blake Butler
Ifeanyi Onyeji	Gloria Sheng
Alejandra Perez	Alexandra Bercow
Denise Johnson	Adam Hsu
Ryan England	Krystle Collins
Ashwini Dhokte	Robert Zilinyi

