

Columbia Medicine

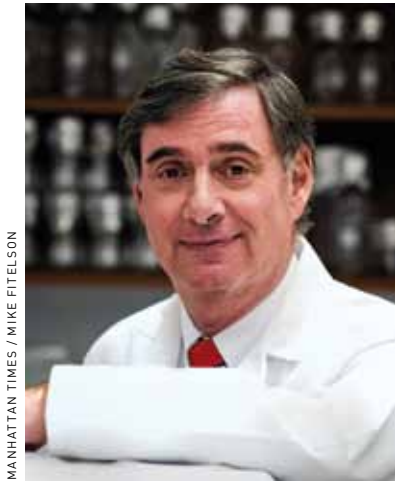
Columbia University College of Physicians & Surgeons

2015 ANNUAL REPORT

A BANNER YEAR FOR BRAIN GAIN

P&S Recruits More
Than 200 Clinicians,
Researchers,
and Educators





MANHATTAN TIMES / MIKE FITELSON

Strengthening Our Foundation for Continued Success

It is my pleasure to welcome you to a report of accomplishments that range from headline-worthy research findings to transformative faculty recruitments to important

neighborhood improvements. On these pages, we share details of research studies, patient outcomes, educational programs, and other developments that have created both real and symbolic foundations for our future.

The most obvious literal foundation that contributes to our transformation is the Medical and Graduate Education Building that is rising on Haven Avenue and changing the skyline of Upper Manhattan. The building is on schedule to open in the summer of 2016, in time for the entering Class of 2020. The building is a key part of the P&S strategic plan, "2020 Vision," which outlines the transformations that include the new state-of-the-art education building.

Other signs of physical transformation are all around us. We are expanding our capacity for primary care with new facilities being constructed on Harkness 2. A hotel under construction on 168th Street is nearing completion. A Barnes and Noble store that opened on the Haven Avenue side of the Hammer Health Sciences Center has become a new gathering spot for our community. The subway station used by our faculty, staff, students, patients, and visitors is getting a facelift that should be completed next year. Improved traffic flow on 168th Street will be appreciated by both drivers and pedestrians.

Those are improvements to our campus, but our traditional campus boundaries are no longer defined by the Washington Heights neighborhood that has been our home for nearly 90 years. Campus boundaries continue to expand through the growth of our faculty practice, ColumbiaDoctors, which opened a practice on the Morningside campus and continues to move north of the city through the North Star practice in Westchester, 22,000 new square feet of space in Tarrytown, new specialty care at NYP/Hudson Valley, and an affiliation with Lawrence Hospital. ColumbiaDoctors also plans to add an ambulatory surgery center in midtown in the near future.

The P&S strategic plan's emphasis on precision medicine also provides a blueprint for the school's future, and this year's successes in faculty recruitment—detailed in this report's cover story—are symbolic of a new foundation for that future. David Sachs and another colleague from Harvard have rejoined Megan Sykes as part of a research team that has already made great strides in

organ transplantation research. Three spine surgeons from Washington University have joined our Department of Orthopedic Surgery and will operate in a new spine hospital based at the Allen Hospital. You also will read about faculty recruitments in cancer, another priority identified by our strategic plan. The opening next year of the Jerome L. Greene Science Center in Manhattanville will allow us to recruit additional faculty to the 168th Street campus.

The recruitment of David Goldstein, director of our new Institute for Genomic Medicine, was a joint effort of NewYork-Presbyterian Hospital and Columbia University and a direct result of Columbia's new emphasis on precision medicine. On these pages, you can read more about Dr. Goldstein and about other senior and junior faculty recruited through our own efforts and as part of a special program created by Columbia's provost.

Another article in this report shows the medical school's expanding presence in countries around the world, through both student scholarly projects and our faculty's involvement in areas of need. Among our faculty who have made such contributions is emergency medicine assistant professor Craig Spencer, who continues to volunteer in Ebola-stricken areas of the world after surviving his own case.

In patient care, we explore 3-D printing, including the way it has transformed the care of some children whose heart defects are diagnosed before they are even born. It is just one example of innovative tools available to our clinicians in maintaining the highest standards of care for our patients.

The new foundations symbolized this year by faculty recruitments, campus improvements, and successes in our core missions now take their place atop our 248-year-old foundation as the nation's second oldest medical school—and the first U.S. medical school to grant an MD degree. When we mark the 250th anniversary of P&S in two years, we will celebrate the past, present, and future—a powerful combination that ensures our foundation will remain strong for future generations of students, researchers, clinicians, and patients. Thank you for your support of the work we do every day and throughout each year.

Lee Goldman, MD

2 Cover Story: Tipping the Scale

Among the more than 200 new faculty members at P&S this year are—to name a few—cancer doctors, a brain surgeon, a team of spine doctors, a human geneticist, and organ transplantation researchers.

Cover photo illustration by Stuart Bradford

8 To Be Precise

Columbia's precision medicine initiative announced in early 2014 moves to the next stage with key recruitments, scientific discoveries, and new patient care protocols.

14 Learning Medicine By Reaching Around the World

International work has long been a Columbia tradition.

20 From Printer to Patient

No longer the stuff of fantasy, 3-D printing is making its mark on patient care.

26 2015 Clinical and Research Highlights

40 P&S News

46 About P&S

- Trustees Committee on the Health Sciences
- CUMC Board of Advisors
- Cancer Advisory Council
- Cardiac Council
- Children's Board at Columbia
- Health Sciences Advisory Council
- CUMC Administration
- College of Physicians & Surgeons Administration
- Executive Committee of the Faculty Council
- Department Chairs
- University Centers and Institutes and Directors
- Affiliated Hospitals
- Facts and Statistics
- Credits



Columbia's population grew by more than 30 when David Goldstein joined P&S from Duke as founding director of the Institute for Genomic Medicine. Dr. Goldstein brought some members of his lab from Duke and recruited the rest once he arrived in New York City. Shown here are several members of the Goldstein lab, including lab technicians, graduate students, postdocs, genetic counselors, and administrative personnel.

PHOTOGRAPHS BY
JÖRG MEYER

BY SHARON TREGASKIS



TIPPING THE SCALE

NEW WAVE
OF FACULTY
RECRUITMENT
EXPANDS
RESEARCH,
PATIENT CARE

On the 14th floor of NewYork-Presbyterian's Herbert Irving Pavilion, dozens of hematology-oncology patients receive infusions from a bustling team of nurses and medical techs. That is not the case just a few floors below, where a new chemotherapy unit opened in June. In this new unit on the ninth floor are just nine patient bays—most with a picturesque river view. Two RNs perform every blood draw, monitor every infusion, collect every sample, and monitor each patient's vital signs.

It is more than the scale that distinguishes this new unit from the one a few floors above. Just a few strides from the nurses' station, a full-time scientist in a dedicated laboratory processes every patient sample before placing it in a cryopreservation unit across the hall for distribution to drug companies and collaborating investigators at academic medical centers around the world. Unlike the routinized drug protocols dispensed on the 14th floor, every treatment administered on the ninth floor is still under development, early in the extensive vetting process for Food and Drug Administration approval. Most of the compounds received by each patient in this unit—the Adult Research Infusion Unit—have been confirmed only in petri dishes and laboratory animals and are being tested for the first time in humans.

Already, patients participating in some 100 trials have begun receiving their medications here; over time, administrators anticipate the number of trials will grow to 300. “To do these early-phase cancer trials properly, you need a dedicated team—doctors, nurses, and research staff who know how

to conduct these complex trials, ensure that the experimental therapies are administered such that patient safety is always prioritized, manage novel side effects, and make sure patients have a full understanding of their treatment plan,” says unit director Richard D. Carvajal, MD, an expert in drug development who was recruited from Memorial Sloan Kettering Cancer Center to develop a phase 1 clinical trial program at Columbia University Medical Center. “In the clinical and treatment research space we’ve developed that is centralized on the ninth floor of NewYork-Presbyterian’s Herbert Irving Pavilion, patient care on early-phase clinical trials can now happen in a patient-oriented seamless fashion. This unit gives our patients at Columbia University Medical Center access to the most promising, most innovative therapies that are not available at most other cancer centers in the country or the world. And even though these are first-in-man trials, with the integration of routine deep molecular profiling and appropriate patient selection, these novel therapies can provide meaningful, durable benefit to our patients.”

Dr. Carvajal, who joined the center in November 2014, is among a large number of new faculty recruits advancing translational medicine at P&S, transforming the medical center campus, and changing the landscape of health care delivery throughout New York City and its suburbs. Beyond their sheer number—some 200 in 2014-15 alone—the new recruits exemplify a sea change at P&S, as the medical school, ColumbiaDoctors, and NewYork-Presbyterian collaborate to furnish the research, patient care, and infrastructure support needed to propel the scientific and clinical pursuits of new faculty. The appointments span clinical and basic science disciplines, including orthopedics, ophthalmology, genomic medicine, and translational immunology.

“Strategic recruitment is the No. 1 priority for the medical center,” says Lee Goldman, MD, P&S dean and chief executive of Columbia University Medical Center, whose strategic planning initiative has been developed in partnership with NewYork-Presbyterian Hospital administrators. “This has been a very good year, but it is just the beginning.”

When Jack Cioffi, MD, left the West Coast—Devers Eye Institute and Oregon Health & Science University—in 2012 to join P&S as the Edward S. Harkness Professor and Chair of Ophthalmology, he had a bit of trepidation about his new responsibility to recruit colleagues to Manhattan. Three years later, he says, he should not have worried. Now also president of ColumbiaDoctors, the University’s multispecialty faculty practice organization of 1,400 clinicians, he has hired more than a dozen new faculty for his own department. Other departments have enjoyed similar recruitment successes, including the Department of Orthopedic Surgery, which has recruited three senior spine surgeons from St. Louis. “Great begets great,” says Dr. Cioffi, who now oversees ColumbiaDoctors’ expansion to new clinical space in Tarrytown, N.Y. “At Columbia we believe we should lead and when we decide to do something new, we should be the best in the world.”

Take, for example, that trio of spine surgeons. Together, MDs Larry Lenke, Daniel Riew, and Ronald Lehman will establish a comprehensive spine hospital at NewYork-Presbyterian/Allen and also will treat patients at Columbia University Medical Center. William Levine, MD, chair of the Department of Orthopedic Surgery, orchestrated the recruitment of the spine doctors, who will join the strong group of orthopedic and neurosurgery spine doctors already at Columbia. “I wanted to recruit the one



Recruited from Washington University by William Levine, second from right, are Ronald Lehman, Larry Lenke, and Daniel Riew.



Megan Sykes, who was recruited from Harvard in 2010, recruited her research colleagues, Kazuhiko Yamada and David Sachs, from Harvard this year.

person in the world with the cachet to bridge multiple subspecialties like orthopedics, neurosurgery, anesthesia, podiatry, and pain management,” says Dr. Levine. “If done right, this has so many tentacles that reach into so many domains at NewYork-Presbyterian and Columbia University Medical Center.” Larry Lenke was that person. With his current practice partners, Dr. Riew and Dr. Lehman, also being recruited by several top medical centers, Dr. Levine decided to invite all three to move together to found a new hospital. “It’s my first recruitment as chair,” admits Dr. Levine, who became chair in 2014. “I’ve set a pretty high standard.”

Beyond seeing to the recruitment of key support personnel to accompany the faculty, Dr. Levine worked with NewYork-Presbyterian administrators to leverage underutilized space in the Allen Hospital to provide state-of-the-art surgical facilities to accommodate all six Columbia spine surgeons in orthopedic surgery. When the spine hospital opens, says Dr. Levine, patients will benefit from efficiencies that will speed their treatment and recuperation. The second phase of the plan includes additional operating rooms that can accommodate spine surgeons from both orthopedic surgery and neurosurgery.

The orthopedic surgeons are joining an already strong group of renowned neurosurgeons who form the Spine Center: Paul C. McCormick, MD, director; Michael G. Kaiser, MD, associate director; Donald O. Quest, MD; Peter D. Angevine, MD; Alfred T. Ogden, MD; Christopher E. Mandigo, MD; and Marc L. Otten, MD.

The Columbia Spine Health Initiative outpatient service will be based at ColumbiaDoctors Midtown. “We already have a spectacular orthopedics department, as well as neurology, neurological surgery, rehabilitation &

regenerative medicine, and the relevant ancillary departments—anesthesiology, radiology, and internal medicine,” says Dr. Cioffi. “They’ll all benefit.”

Dr. Carvajal says the prospect for collaboration was a key inducement when Gary Schwartz, MD, chief of hematology-oncology (himself a recent recruit from Memorial Sloan Kettering Cancer Center, in early 2014), approached him about founding the early-phase clinical research program. “What drew me here was the opportunity to translate the incredible science being conducted at Columbia, which represents the most cutting edge

“Recruits of the highest quality attract others of the highest quality, who in turn draw others.”

research in cancer biology and therapeutics, to the clinic and bring these promising therapies to our patients.” The list of potential collaborators was rich and deep, says Dr. Carvajal. “The basic science research in cancer genetics, epigenetics, translational immunology, informatics, imaging, and computational biology is incredibly strong at P&S.”

For basic scientists, the reverse is also true, says Megan Sykes, MD, who came to P&S in 2010 after 19 years at Harvard. “One of the great things about being here is how anxious people are on the clinical side to understand the diseases that they’re working on, to understand the immunology better, and to have that whole scientific dimension of understanding and

being on the cutting edge of new therapies,” she says. As founding director of the Columbia Center for Translational Immunology, Dr. Sykes was high on the list of prospective collaborators for several of Dr. Schwartz’s hem-onc recruits. Says Dr. Carvajal: “Figuring out the key molecular nodes and immunological processes we need to target in animal models and bringing that back to the clinic is an incredible opportunity.”

Even as she took on new collaborators this past year in response to the expansion of other departments, Dr. Sykes mounted an ambitious recruitment effort of her own, her hopes pinned on extending a fruitful research partnership of more than three decades. On July 1, Dr. Sykes’ former mentor, David Sachs, MD, and their long-time research partner, Kazuhiko Yamada, MD, resigned their Harvard faculty appointments for posts at P&S. Together, the three scientists have invested a century in pursuit of solutions to the shortage of human donor organs that currently impedes transplantation medicine. While stem cells, bioscaffolds, and 3-D printers offer the possibility of laboratory-grown replacements to make up for the shortage, another option long considered and debated is xenotransplantation the use of living tissues harvested from other species. Dr. Sykes, Dr. Yamada, and Dr. Sachs have set their sights on specially bred pigs as a source for whole organs.

Over the past four decades, Dr. Sachs has bred a herd of miniaturized pigs whose identical genetics and human scale promise the possibility of

a new source of replacement organs for human patients. “Dr. Sachs, Dr. Yamada, and I have believed from the beginning that for xenotransplantation to work, we have to induce immune tolerance in the recipient,” says Dr. Sykes. “You can’t just expect a pig organ to be accepted with immunosuppressing drugs the way we do with human organ transplants; there’s a broader and stronger immune response when the donor is a pig.” To succeed, the team must discover the keys to induced immune tolerance, insights that hold promise for bone marrow transplants, cancer immunotherapy (where the immune system could be kickstarted to fight malignancy), and type 1 diabetes. By bringing Dr. Sachs and Dr. Yamada to P&S, Columbia is also protecting the intellectual legacy embodied in Dr. Sachs’ research herd. (Though Columbia will have custody of the pigs, they will remain at an animal research facility in Massachusetts.) Already, Dr. Sykes has a team of graduate students and postdoc fellows ready to expand the group’s investigations. “Now we’re in the position to make the ideal pig to induce tolerance,” says Dr. Sykes. “It’s a huge opportunity.”

Jean C. Emond, MD, executive director of Columbia’s Transplant Initiative, also recruited outcomes researcher Onur Baser, PhD, to the Department of Surgery. Dr. Baser, editor-in-chief of the *Journal of Health Economics and Outcomes Research*, has a PhD in economics. His research interests include unwarranted variations in health care as well as comparative effectiveness research.

Much of the current wave of recruitment boils down to a model for faculty expansion piloted by Donald Landry, MD, PhD, physician-in-chief of NYP/Columbia and chair of the Department of Medicine, when Dr. Sykes was recruited in 2010. “I wanted to bring someone into the Department of Medicine who would lead in an area of science that would cut through all of the divisions of medicine, touching cardiology, pulmonary, gastroenterology, and the corresponding divisions in surgery, pediatrics, pathology,” says Dr. Landry. “The thought was to recruit in particular areas that would unite the various elements of the university and also bring us closer to the hospital.” The basic science behind transplant immunology, subsumed under the even broader umbrella of translational immunology, was an obvious prospect for bridging disciplines, and Dr. Landry began explaining his vision to his counterparts in surgery, pediatrics, pathology, and microbiology/immunology, as well as the leadership of the Herbert Irving Comprehensive Cancer Center and the Naomi Berrie Diabetes Center.

In two decades at the National Institutes of Health and at Harvard Medical School, Dr. Sykes had pioneered paired organ and bone marrow transplantation to eliminate the need for immune-suppressing drugs. Her name quickly rose to the top of Dr. Landry’s list of exemplars in the field of transplant immunology. All he had to do was partner with the hospital, university administrators, and P&S Dean Goldman to furnish the infrastructure for her success, and with this partnership the barriers vanished. “I promised her—and we delivered—20,000 square feet of space, the reopening of a specialized large animal research facility, expansion of a GMP cell therapy facility, and the build-out of an ultra-clean mouse unit in the comparative medicine facility. She also needed a clinical bone marrow transplant unit, so the hospital committed to building a \$25 million bone marrow facility,” he says. “All of these elements within the university and hospital came together, and, as predicted, recruits of the highest quality attract others of the highest quality, who in turn draw others.”



As vice dean for academic affairs at P&S, Anne L. Taylor oversees faculty appointments.



Adam M. Sonabend, a new faculty member in neurology, was recruited through a Provost's Office program that supports recruitment of faculty from underrepresented groups.

Laura Landweber, PhD, professor of ecology and evolutionary biology at Princeton (her entire lab will move to Columbia next year), and Edward Owusu-Ansah, PhD, who joined the Department of Physiology & Cellular Biophysics from Harvard University.

Another recruit through the provost's program is Adam M. Sonabend, MD, former chief resident and research fellow in neurosurgery, who has joined the Department of Neurological Surgery faculty to expand the department's neuro-oncology program. Dr. Sonabend, a graduate of the National Autonomous University of Mexico Faculty of Medicine, will focus on brain tumor surgery and run a brain tumor research laboratory at the cancer center.

Dr. Goldman is the only Columbia dean, so far, who has committed to matching funds provided by the provost's diversity initiative, which targets tenure and tenure-track faculty. "He has encouraged his department chairs to scour the nation and the world to find the very best," says Dr. Mitchell.

Perhaps the most powerful example of growth at P&S over the past year has been in the Department of Medicine's hematology and oncology division, augmented recently by the latest gift from Herbert and Florence Irving to establish a \$50 million research fund, create seven new endowed professorships, and expand the Irving Scholars research program. In his first 18 months as division chief, Dr. Schwartz hired not only Dr. Carvajal but also five other faculty. Two are recruits from the National Cancer Institute: Antonio Tito Fojo, MD, PhD, an expert in neuroendocrine tumors, who will serve as chief of cancer medicine at the James J. Peters VA Medical Center in the Bronx and build a clinical trials program there, and Susan Bates, MD, whose research investigates molecular therapeutics for metastatic brain tumors. The others are Naiyer Rizvi, MD, who joined Columbia in January from Memorial Sloan Kettering Cancer Center and directs a new program in thoracic oncology and immunotherapeutics in

In his first 18 months as chief of hematology and oncology, Gary Schwartz recruited six new faculty members from other institutions to Columbia.

medical oncology; Ran Reshef, MD, a physician-scientist recruited from the University of Pennsylvania for his expertise on immunotherapy and cellular therapy; and clinician-scientist Yvonne Saenger, MD, recruited from Mount Sinai for her expertise in the use of immunotherapeutics to fight melanoma.

As the faculty roster expands, applications for residencies, fellowships, and slots in the MD-PhD program have picked up as well. Even the oncology curriculum for medical students has been overhauled. "I sometimes wake up and pinch myself," says Dr. Schwartz. "This has been an exceptional opportunity to bring together basic scientists and clinicians to make the clinical care we offer the best in the city of New York, if not the country." ♦

More recently, the recruitment of David Goldstein, PhD, founding director of the Institute for Genomic Medicine, followed a similar model. Dr. Goldman and Steven J. Corwin, MD, CEO of NewYork-Presbyterian, empaneled a committee chaired by Tom Maniatis, chair of biochemistry & molecular biophysics, that recruited Dr. Goldstein. The committee's charge: Identify exceptional scientists whose recruitment could be transformational. "Imagine," says Dr. Landry, "if we asked department chairs to look around the country, not think about their priorities, and look at people for their excellence and consider whether, if those people were in our departments, we would be delighted."

That's precisely the approach now utilized across Columbia to boost the number of women and minorities who join the faculty each year. "Columbia clearly aspires to be the greatest destination for world-class scholars," says Dennis Mitchell, DDS, MPH, the University's vice provost for faculty diversity and inclusion. "We cannot achieve that aspiration without realizing our core values of inclusion and excellence. P&S has completely embraced that vision, making diversity a fundamental goal." To facilitate an out-of-the-box focus on intellectual excellence, the Columbia provost established a competitive program, the Provost's Office Funding for Faculty Recruitments from Underrepresented Groups. Each dean submits a list of potential hires and a university-level review committee identifies the most eminent scholars to receive funding. Anne L. Taylor, MD, vice dean for academic affairs at P&S and senior vice president for faculty affairs and career development at CUMC, coordinates the medical school's participation.

Through the program, P&S has consistently led in receiving support for recruitment of faculty from underrepresented groups, including

Columbia's precision medicine initiative was announced by President Lee C. Bollinger in February 2014, but the seeds for the effort were planted years earlier with key recruits, including Tom Maniatis, who now directs the universitywide endeavor. President Bollinger and P&S Dean Lee Goldman co-chair the task force for the initiative aimed at creating new knowledge across the university, from basic research and teaching to more focused diagnostic tools and improved patient care.

That vision is now being implemented by legal scholars and human geneticists, by public health experts and data scientists, and by cancer doctors and neuroscientists. The following pages show just a few examples of how precision medicine has moved from concept to clinical relevance over the past year.

TO BE PRECISE

BY ANDREA CRAWFORD



LATE LAST YEAR, Wendy Chung, MD, PhD, received a phone call from the White House. “To be honest,” says Dr. Chung, who serves on the advisory board for the National Human Genome Research Institute, “I thought it was one of those phishing things where someone was just trying to get my Social Security number.” But in January, Dr. Chung, associate professor of pediatrics (in medicine), and Tom Maniatis, PhD, director of the Columbia University precision medicine initiative, were guests of President Obama as he presented details of his \$215 million initiative in precision medicine, which he had announced during the State of the Union address days before. Precision medicine, President Obama told those assembled, “gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen.”

To bring that great promise to fruition, Columbia University and NewYork-Presbyterian Hospital have made several investments this past year to advance work on precision medicine, following up on the launch in early 2014 of Columbia’s universitywide initiative in precision medicine. The initiative supports efforts across schools and disciplines, brings significant new investments in personnel and infrastructure, and creates a number of

administrative structures, including the establishment of the Columbia Institute for Genomic Medicine to integrate genetics and genomics into research, patient care, and education. No other major university in the world is doing what Columbia is doing, says Donald Landry, MD, PhD, chair of the Department of Medicine and physician-in-chief of NYP/Columbia. “As articulated best in a recent address by President Bollinger, perhaps once in a generation, an opportunity presents itself for the growth and development of a new academic area that allows

appointments between the institute and clinical departments, the precision medicine initiative supports knowledge and innovation across the intellectual spectrum by enhancing efforts in science, medicine, technology, privacy, and more. “It’s impacting, across the board, all of the attendant technologies and activities necessary to understand genetic information in a way that it becomes actionable medically,” says Dr. Maniatis, who chairs the Department of Biochemistry & Molecular Biophysics at P&S.

Precision medicine will require expertise from every aspect of medical delivery if the field is to create the advances in human health that it portends, he adds. That encompasses disciplines centered at Morningside Heights—basic research, engineering, law, ethics, computer science, journalism, business, and economics—and those across the medical center, from foundational basic science to clinical departments. With CUMC faculty’s commitment to innovative care, coupled with the hospital’s mission to provide the best possible service to patients, says Dr. Landry, “Precision medicine brings the university and the hospital together at the cutting edge of a new scientific and clinical venture.”

It has always been important for other sectors to work in concert with medicine, says Paul Appelbaum, MD, the Elizabeth K. Dollard Professor of Psychiatry, Medicine, and Law.

“PRECISION MEDICINE BRINGS THE UNIVERSITY AND THE HOSPITAL TOGETHER AT THE CUTTING EDGE OF A NEW SCIENTIFIC AND CLINICAL VENTURE.”

the university to achieve its highest ambitions: to understand ever more profoundly what it means to be human,” Dr. Landry says. “Precision medicine is such an area.”

With a major commitment that includes infrastructure, appointments within the Institute for Genomic Medicine, and joint



HELP FROM OUR FRIENDS



HERBERT AND FLORENCE IRVING MAKE TRANSFORMATIONAL GIFT FOR GENOMIC CANCER RESEARCH AND CARE

Herbert and Florence Irving have extended their generous and longstanding support for Columbia University with three new gifts. The Irvings have established a new endowed fund, the Herbert and Florence Irving Cancer Fund, with a gift of \$50 million to support basic and clinical research exploring the genomic nature of cancer, with the goal of understanding the fundamental biological basis of cancer and developing more effective prevention, diagnosis, and treatment.

In addition, the Irving Scholars program will be expanded to support two more scholars who specialize in oncology and related areas each year. The Irvings also are creating seven new endowed professorships at CUMC in recognition of outstanding clinicians who have worked with them over the years. Each professorship will support a top researcher who focuses on precision medicine to enhance patient care.

The professorships and the seven Columbia physicians they honor:

- Florence Irving Professorship of Neurology in honor of Linda Lewis, MD
- Herbert and Florence Irving Professorship of Cardiology in honor of LeRoy Rabbani, MD
- Herbert and Florence Irving Professorship of Ophthalmology in honor of Stanley Chang, MD
- Herbert and Florence Irving Professorship of Dermatology in honor of David Bickers, MD
- Herbert and Florence Irving Professorship of Rheumatology in honor of Ralph Blume, MD
- Herbert and Florence Irving Professorship of Plastic & Reconstructive Surgery in honor of Jeffrey Ascherman, MD
- Herbert and Florence Irving Professorship of Medicine in honor of Jeffrey Stein, MD



David Goldstein, PhD
Tom Maniatis, PhD

JÖRG MEYER

And precision medicine—with its use of highly sensitive personal data, information that is predictive as well as diagnostic and could be used for discriminatory purposes—raises the stakes. “When we make these findings in medicine, they don’t stay in medicine. They affect societal views of illness and people who have illnesses,” says Dr. Appelbaum, who directs a center funded by the National Human Genome Research Institute that looks at the ethical, legal, and social implications of genetics. When an individual’s genome is sequenced and analyzed, for example, an almost limitless amount of data could be generated. “If you ask most people, they will say they want to know everything about their genomes. But much of what could be told to them today would be of uncertain significance, leaving them without much to do and without much clarity about the implications of the findings,” he says. “We need to be sure that the information we generate offers benefits to patients that outweigh the potential harms.”

During the past year, Columbia’s precision medicine initiative task force set to work to identify all of the disciplines and departments across the university and medical center whose participation would contribute to the effort. They then began to plan the necessary enhancements in infrastructure and faculty recruitment. “Recruitment of highly talented individuals is our most important response to the opportunities that present themselves through Manhattanville,” says Dr. Landry, for as those new facilities open and many neuroscience faculty move there, vacancies arise at the medical center, allowing for recruitment of scientists with a predominant focus in precision medicine.

David Goldstein, PhD, who joined Columbia in January as founding director of the Institute for Genomic Medicine and who already had a long record of collaboration with Columbia investigators, was the first hire, and his recruitment included provisions to hire others in clinical and basic science departments. “We recognized that human genetics and modern



Andrea Califano, PhD

USING **BIG DATA** TO ZERO IN ON CANCER

JÖRG MEYER

IN JANUARY, Andrea Califano, PhD, the Clyde and Helen Wu Professor of Chemical Biology, professor of biochemistry & molecular biophysics, and founding chair of the Department of Systems Biology, and Aris Floratos, PhD, executive research director at Columbia's Center for Computational Biology and Bioinformatics, received a two-year \$624,236 subcontract from the National Cancer Institute to develop a new classification system of cancer subtypes.

Dr. Califano's approach to understanding and treating cancer is different from that of most genomic researchers. He does not target genes bearing mutations because relatively few are relevant for treating disease, he says, and most disease-causing mutations inactivate gene function, so they are not good targets for therapy.

Instead, he has focused his research on genes or proteins that have critical functions in cancer cells. He calls these genes non-oncogene dependencies. "The cancer cell needs the proteins encoded by these genes to survive, and if you shut them down, it will die," says Dr. Califano. His team has found these non-oncogene dependencies to be highly responsive to drug therapy. These "master regulator" genes of cancer can be discovered systematically by analyzing the regulatory networks of the cancer cell using novel algorithms developed in the Califano lab.

Some 75 percent of cancer patients today, says Dr. Califano, do not have mutations that inform therapeutic approaches; of those who do have an action-

able mutation, only about 20 percent receive durable clinical benefit from that information. Even in the well-known success story of breast cancer caused by amplification of the gene HER2—which led to the development of the drug Herceptin—70 percent of patients initially respond favorably to the drug, but 70 percent of those eventually relapse to a version of the disease no longer responsive to the drug.

A computational approach called unsupervised clustering, which looks for shared features among different cancers, shows that many cancers are similar to each other in terms of their genetic programs (transcriptome). Basal breast cancers, for example, are virtually identical to one another. But their mutational profiles have little in common. "It appeared to be a paradox, how cancer cells that appear to be so similar in their pathology and transcriptomes can be so different at the level of genetics," says Dr. Califano. In an effort to explain this apparent paradox, he theorized the existence of complex regulatory pathways with different origins but a common endpoint. He refers to these endpoints, which can be discovered by an algorithm called VIPER, as "cancer bottlenecks."

"Instead of treating each genetic variant of the same type of cancer with a different drug, we can identify and target the single bottlenecks they converge on with the same drug," he says. The Califano lab is attempting to extend this concept to neurodegenerative diseases, such as ALS, Parkinson's, and Alzheimer's, as recently published

in *Nature Neuroscience*, *Cell*, and *Cell Reports*, as well as to other diseases—some 40 in all.

Dr. Califano is now moving these ideas from the lab to patients in studies done in collaboration with other researchers, including an innovative clinical trial for patients with rare or untreatable malignancies. Researchers will identify each patient's cancer bottleneck using VIPER and then test different therapeutic strategies targeting these bottlenecks in mouse "avatars" (a mouse that has been transplanted with the patient's tumor). The best-performing strategy will then be available to the patient. The study, which is currently enrolling up to 260 patients, is funded by the National Cancer Institute and private gifts.

Similarly, a new study has begun that uses a combination of trastuzumab (Herceptin) and ruxolitinib to treat HER2-amplified breast cancers that no longer respond to trastuzumab. The unexpected combination was identified as targeting a non-oncogene dependency discovered by VIPER and by RNAi screening. Preliminary results are encouraging, Dr. Califano says, with patients showing stable disease for almost three months.

Dr. Califano and Dr. Floratos are developing a cloud-based resource to make their tools accessible to other researchers. "It means that the number of drugs we have to develop is actually much, much smaller than the number you would have to develop if you had to target each mutation individually."

applications of high throughput sequencing in this field were not strengths at Columbia,” says Dr. Maniatis. “David Goldstein was identified as being the best, and we were extremely fortunate to recruit him. This strategy must be taken in discipline after discipline that impacts precision medicine.”

The power of genomic research is based on the magnitude of data; to gather large cohorts of patients and their genomic data, scientists from around the world often collaborate. Dr. Maniatis and Dr. Goldstein have worked together as part of a consortium of some 60 institutions investigating the genetic basis of ALS. One result of their collaboration was the discovery of a gene newly implicated in ALS; Dr. Goldstein’s resulting paper, which Dr. Maniatis and Dr. Chung co-authored, was fast-tracked for February publication in *Science*. By sequencing the exome, or protein-coding portion of the genome, the consortium collected nearly 3,000 DNA samples from patients with ALS and more than 6,000 unaffected patients whose data served as a reference. In addition to finding the newly associated gene, the researchers confirmed many of the genes previously implicated in the disease and discovered that one gene, known as OPTN, which had been thought to play a minor role in ALS, may play a major role.

The gene newly believed to be associated with ALS, TBK1, had been the focus of investigation within the Maniatis lab in the context of the immune system since 2003 but was not known to be associated with ALS. In ALS, several mutations lead to the generation of aggregates in proteins, similar to what occurs in Parkinson’s and Alzheimer’s diseases. Once these aggregates form, the cell has two pathways to remove them: through the proteasome, a large protein complex that acts like the garbage disposal of the cell, grinding up aggregated proteins, and through a process called autophagy. Autophagy is an intracellular recycling system in which damaged proteins or organelles are surrounded by a membrane to form an “autophagosome” that fuses with lysosomes (bags of chemicals and enzymes that degrade proteins). The breakdown products are recycled to build new proteins and membranes. TBK1 plays a key role at the intersection of two essential pathways—inflammation and autophagy—interacting with and modifying other proteins previously shown to play a role in ALS. Says Dr. Goldstein: “Remarkably, the TBK1 protein and optineurin, which is encoded by the OPTN gene, interact physically and functionally. Both proteins are required for the normal function of inflammatory and autophagy pathways, and now we have shown that mutations in the genes encoding either protein are associated with ALS.”

Large-scale genetic studies like this illuminate pathways that can then become targets for drug delivery. “ALS is an incredibly diverse disease, influenced by mutations that can occur at any of several hundred different genes, which we’re only beginning to discover,” says Dr. Goldstein. “The more of these mutations we identify, the better we can decipher—and influence—the pathways that lead to disease.” The TBK1 gene is also thought to play a role in tumor-cell survival, as well, and

compounds targeting it have already been developed for use in cancer patients. “The more we learn about the function of the normal TBK1 gene, and the dysfunction of TBK1 genes bearing the ALS-associated sequence variants, the more likely we will be able to find a treatment for ALS,” says Dr. Maniatis. “The key here, and to precision medicine more widely, is to connect the genetics of disease with the underlying biology and use that knowledge to develop new therapies.”

Medicine is in a moment of profound transition following decades of what Dr. Landry calls “an explosion of knowledge,” as a precise, detailed, molecular understanding of disease emerges coupled with advances in computer science. “We are merely at the threshold of a new age,” he says, “and yet we have a glimpse of the future.”

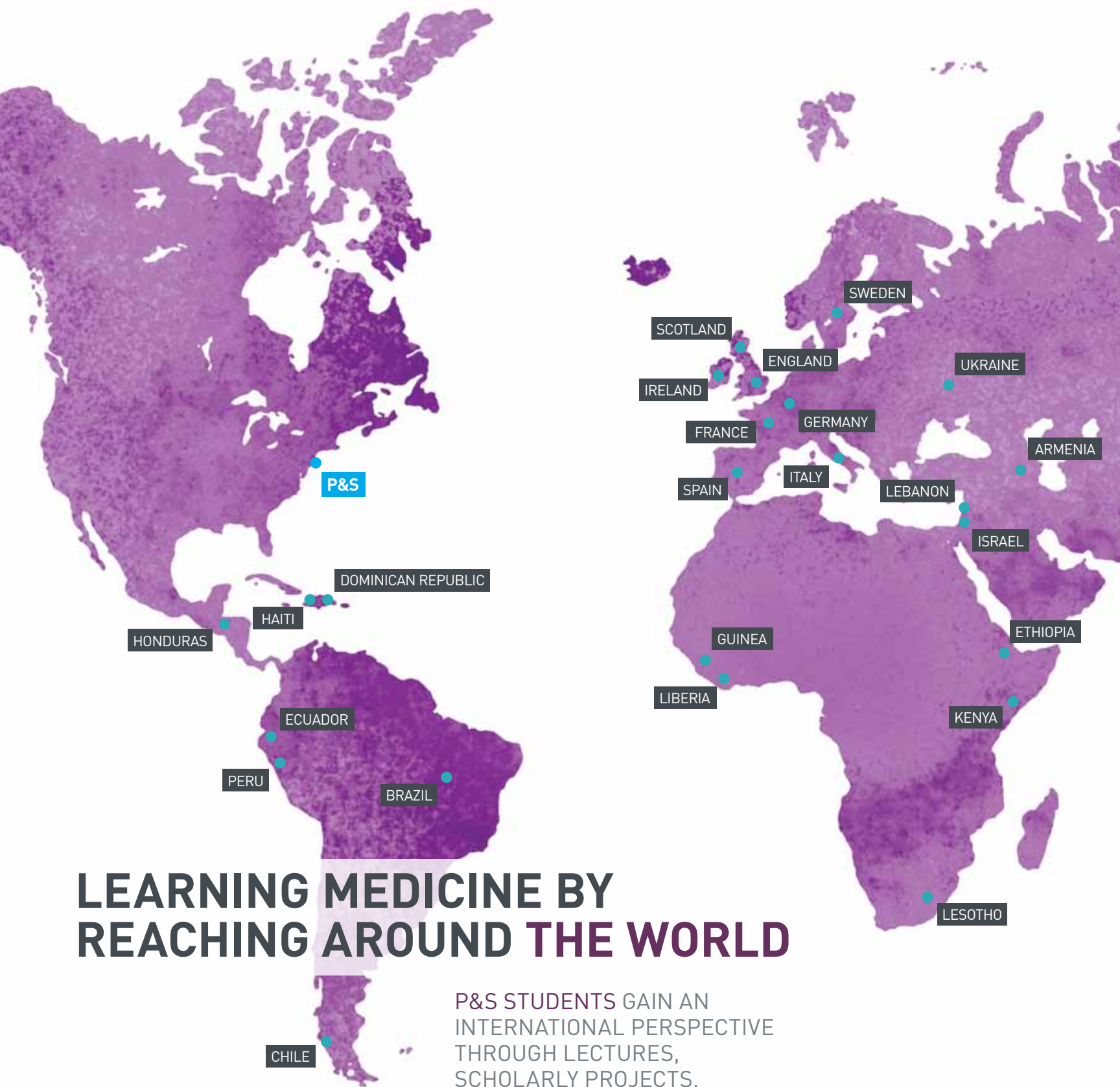
At the forefront, says Dr. Chung, is the work of identifying how genes act in regulatory networks, a fresh approach that

“PRECISION MEDICINE AFFECTS EVERY ASPECT OF HEALTH CARE FROM THE TIME OF CONCEPTION TO THE TIME OF DEATH.”

holds promise for both treatment and prevention. “What’s truly beautiful and elegant is that when you start to define a large number of the genes, you can step back and see the organization,” says Dr. Chung. In the case of autism, for example, scientists now estimate that some 500 genes are involved. “It’s not 500 random genes that you picked throughout the genome. It’s actually genes that have to do with very specific cellular processes.” In autism, those include genes that function in synaptic transmission and when defective can affect neurological conditions; in other cases, as with epilepsy, those include genes that encode ion channels, proteins that regulate the passage of ions through cellular membranes, which form the basis of electrical conduction in neurons.

As a physician treating patients with different types of diseases, Dr. Chung says it is easy to see the connections between heart disease and brain disease, for example. Underlying these connections are the genetic regulatory networks that determine when, where, and how proteins are produced.

The mapping of these networks is an important step forward for understanding disease mechanisms. Precision medicine offers the possibility for physicians to not only treat diseases, but also focus on wellness and prevention by making genome-informed predictions about the conditions that individuals or families are at risk for, then designing tailored wellness programs that, for example, feature enhanced screening for those conditions. “Precision medicine affects every aspect of health care from the time of conception to the time of death,” says Dr. Chung, “and it truly permeates everything that we do.” ♦



LEARNING MEDICINE BY REACHING AROUND THE WORLD

P&S STUDENTS GAIN AN
INTERNATIONAL PERSPECTIVE
THROUGH LECTURES,
SCHOLARLY PROJECTS,
FOREIGN EXCHANGES

By Andrea Crawford



Although he rejects the label, Craig Spencer, MD, MPH, is often called a hero. “He’s a hero to our students,” says Stephen Nicholas, MD, associate dean for admissions at P&S and a leader in global health. “He’s a hero to me.”

Dr. Spencer, of course, is the Columbia emergency physician who volunteered for Doctors Without Borders to treat people with Ebola in Guinea last year and after returning home became the first person diagnosed with the disease in New York City. Following news of his diagnosis, the assistant professor of medicine was both vilified and lionized, called a fraud and a hero. “The truth is,” Dr. Spencer wrote in the *New England Journal of Medicine* in March, “I am none of those things. I’m just someone who answered a call for help and was lucky enough to survive.”

But answering that call for help despite the risks he would face—like so many others before and since—in fact resonates powerfully among Dr. Spencer’s peers in health care. “These experiences touch very deeply the core values that bring you into caring for others,” says Dr. Nicholas, a pediatrician. “These are not old-fashioned values; they’re timeless and the reminder of where your interest comes from in the first place.” That may be especially so for physicians in training, students like many today at Columbia who demonstrate a growing interest in global health education and training opportunities.

This year P&S has been building upon Columbia University’s deep history in international work across the medical school and other divisions to enhance the training in global health available to its students and to respond to their heightened interest. “We’ve expanded the locations, opportunities, and funding available for students,” says Lisa Mellman, MD, senior associate dean for student affairs at P&S. Last fall, P&S launched the Dr. Edgar Housepian Global Health Lecture Series, in partnership with the Wu Center for Global Health Initiatives and the Grodman Dual Degree Program. The Wu Center, established with an endowment from Columbia University trustee emeritus Clyde Y.C. Wu’56, and his wife, Helen Tseng Wu, will oversee joint pilot research projects and exchanges of faculty and fellows between CUMC and the Zhejiang University School of Medicine in Hangzhou, China, building on a link between Columbia and China that dates to the 1920s.

These programs join a long roster of opportunities for students to gain global experiences at multiple points in the curriculum. While many of the offerings are new, they augment others in existence for decades. Recently, P&S has placed particular focus on Africa, specifically on work in Lesotho, where Columbia is helping to develop a medical school. P&S faculty and students have worked for 15 years in the Dominican Republic, where P&S has recently partnered with the Universidad Nacional Pedro Henriquez Urena (UNPHU), creating

stronger ties with a country to which 70 percent of the residents of the medical center's Washington Heights neighborhood trace their cultural heritage.

In November, P&S administrators renewed the school's affiliation with the Medical School for International Health at Ben Gurion University for another five years, perpetuating the availability of training opportunities at sites in Israel, India, Sri Lanka, Ethiopia, Kenya, Nepal, and Peru. English-speaking placements in Australia, England, and Ireland also are popular with students, says Dr. Mellman.

Students also can participate in the Next Generation Program at ICAP. Situated at the Mailman School of Public Health, ICAP at Columbia University has become a global health leader since it was established in 2004 to improve the health of families and communities currently in more than 25 countries around the world. Through ICAP, students selected for the Next Generation Program engage in real-world experience working hand-in-hand with ICAP staff in-country and with staff from organizations with which it partners. "Students spend two to six months engaged in the design, implementation, and evaluation of ICAP-supported

programs while working side-by-side with global health experts in sub-Saharan Africa and Asia," says Wafaa El-Sadr, MD, University Professor and founder and director of ICAP. "Not only do they gain so much from these experiences, but they certainly contribute through their enthusiasm, curiosity, and commitment."

The possibility for students to take advantage of global learning opportunities increased sharply a few years ago when P&S instituted a curricular overhaul. As part of the new curriculum, students pursue scholarly projects during a four- to 10-month period of dedicated research in one of six tracks, of which global health, under the direction of Dr. Nicholas, is one. In 2014, global health was the second most popular scholarly project track. The new curriculum is augmented by the option for first-year students to spend up to eight weeks doing summer international research or study. And following the major clinical year, students may pursue international senior electives, for which P&S has 29 exchange agreements in place encompassing every continent except Antarctica. Students also may pursue electives offered in conjunction with ICAP at sites in sub-Saharan Africa and



SUPPORTING GLOBAL INNOVATION

PHOTOS BY STEPHEN NICHOLAS, MD



Paul J. Planet, MD'04, PhD'03, has set out to try to solve one of the biggest threats for public health in the 21st century: the spread of antibiotic resistance.

Dr. Planet, assistant professor of pediatrics, has won a grant from the Columbia President's Global Innovation Fund for his project, "Global Antibiotic Resistance Surveillance and Epidemiology Using Whole Genomes." Through the support of Columbia Global Centers in Santiago, Chile, and Rio de Janeiro, Brazil, Dr. Planet proposes to strengthen and expand collaboration through a network of investigators focused on whole genome sequencing approaches to monitor the spread of antibiotic resistance. Whole genome sequencing of bacteria offers a new opportunity to trace outbreaks and transmission more closely, by distinguishing between resistant strains.

Dr. Planet's project is one of 16 projects awarded funding for 2015. Now in its third year, the President's

Global Innovation Fund supports faculty whose projects increase opportunities for research, teaching, and service around the world. Grantees in 2014 included Stephen Nicholas, professor of pediatrics, to develop an interdisciplinary model to provide oral health care for orphans with AIDS in Nairobi, Kenya; Wafaa El-Sadr, University Professor, to explore the scope, scale, and impact of China-Africa health assistance programs; Kathleen Pike, professor of psychology and education (in psychiatry), to convene a global mental health research consortium and train scholars to narrow the treatment gap and stimulate the expansion of research and training in global mental health; Steven Shea, the Hamilton Southworth Professor of Medicine and professor of epidemiology (in biomedical informatics), to analyze socioeconomic disparities in noncommunicable disease outcomes, risk factors, and access to health care among adults in Chile.

Central Asia; the Earth Institute's Millennium Villages Project, with sites in sub-Saharan Africa; and the IFAP global health program in the Dominican Republic, founded by Dr. Nicholas in 1999.

Students see the world, and the world's opportunities and challenges, in global terms and they come to medical school with the interest and expectation of participating in global experiences. "It's a particularly well-traveled generation, even for those without means," says Dr. Mellman. "Historically, international opportunities were limited to students whose families could afford to send them to other countries," says Dr. Nicholas. "At P&S we have tried our best to provide financial support for travel and living expenses so the opportunity is available to any student who wants the experience."

Working abroad is what brought Rachel Criswell'17 to medical school in the first place. Former copresident of the longstanding student-run interest group, which recently changed its name to the Global Health Organization, Ms. Criswell earned an undergraduate degree in Slavic languages and was awarded a Fulbright Scholarship to research women's reproductive health in Ukraine. Afterwards, she went to work for an NGO supporting rural primary health care clinics in Liberia—where she realized she wanted to do clinical work. People of her generation have often traveled on short-term medical mission or medical research trips, Ms. Criswell notes, and "when they're there, they like it and see the need for deeper involvement and a deeper understanding."

One of her classmates, David Bridgman-Packer'17, also worked abroad as an undergraduate, volunteering as an EMT in Haiti after the 2010 earthquake. There he was exposed, he says, "to the really difficult problems that exist in the NGO community in trying to respond to disasters in an appropriate and productive way when there's limited information, resources, and means." He was subsequently drawn to medicine as a way to extend his interest in science and apply it in a political and social context.

It was Mr. Bridgman-Packer, along with Nathan Brand'17, who approached Dr. Nicholas last year to express interest in starting a medical student journal club devoted to global medicine. "What's great about Columbia is that there are many faculty members who are doing work in global health," says Mr. Bridgman-Packer. "The difficulty for us was creating a centralized place where students could identify potential opportunities and mentors to work with." Out of those conversations with Dr. Nicholas emerged a committee that included faculty as well as Mr. Brand, Mr. Bridgman-Packer, Ms. Criswell, and other students who worked to create a new course.

The Dr. Edgar Housepian Global Health Lecture Series launched last September with a keynote lecture by Elaine



Stephen Nicholas, MD, and Wafaa El-Sadr, MD

Abrams'82, professor of epidemiology at Mailman and professor of pediatrics at P&S and senior director for research at ICAP. It concluded in December with a finale by Dr. Nicholas, the course director, on how to bring the lessons of global medicine back to local communities. In the weeks between, the course covered issues of global emergency medicine and trauma; maternal health, family planning, and abortion care; diseases of poverty and challenges to health and survival; global surgery and anesthesia; global nutrition and obesity; global mental health; global tobacco epidemic; noncommunicable diseases; and HIV, TB, and malaria. One evening in late September, Stephen Morse, MD, professor of epidemiology at Mailman and director of the infectious disease epidemiology certificate program, was scheduled to give the lecture "Ebola—A Surprise?" That day the Centers for Disease Control and Prevention confirmed the first case of Ebola diagnosed in the United States, in Dallas, Texas, and Dr. Morse had spent hours fielding calls from reporters. To speak to students uninterrupted that night, he had to turn off his phone.

When a new mosquito-borne virus first appeared in the Caribbean, P&S students who had seen the virus when they worked in the Dominican Republic were able to recognize it when it appeared in the ER at Columbia. ●

The optional course, with its lectures, break-out sessions, and required readings, gave students a grounding in the literature and topics. “It provided a foundational body of information to the students that has been complementary to the core curriculum,” Dr. Mellman says, and it has provided “a list of really wonderful faculty who will come and talk about the work they’re doing and, in that formal way, further expose students to their work.” Another goal for the students, says Mr. Brand, was to identify faculty who might serve as mentors, and the lecture series was a successful initiative in facilitating the process of linking interested students with potential mentors working in global health.

While the lecture course was in development, Dr. Nicholas said, organizers did not know if the course would attract even 20 students. But 180 students applied and 60 were accepted. Those enrolled came predominantly from P&S but also included students from Mailman, the College of Dental Medicine, the School of Nursing, and the School of International and Public Affairs.

In addition to mastering a foundational body of knowledge in global health, students must be culturally, psychologically, and practically prepared for work abroad. The process is extensive—with an emphasis on cultural competence, as well as such nitty-gritty concerns as pre-departure orientation and security briefings. The process does not end when students depart the United States. Like any health care professional who has worked in difficult locations around the world, students face a sometimes difficult transition when they return home. Dr. Nicholas likens it to when he, a self-described pale-faced cowboy from Wyoming, began working in New York City in the 1980s: “What did I know about Harlem? Well, all I knew was I didn’t know anything. That was a useful thing to know.”

Medical students going abroad must start with the premise of, first, do no harm, he says. And they need to know that they can do harm simply by their presence, by requiring time of their hosts, or by being judgmental or dismissive, even if those responses are unintended. It is easy for visitors to say, for example, “I can’t believe you don’t have this medicine or that diagnostic test,” Dr. Nicholas notes. “We can’t help it because we come from such different places.”

Frustrations can accrue when one works in a resource-limited setting, and students need to be trained on how to manage that frustration before it calcifies as anger or depression. But frustration, Dr. Nicholas says, “can also be part of the richness of learning how to problem-solve amidst challenges and limitations”—lessons that are invaluable to students of medicine, regardless of whether they plan careers in global health.

Dr. Nicholas learned of the unintended benefits of global experience firsthand. At the peak of the epidemic in 1990, when AIDS was the leading killer of children in Harlem, he was head of pediatrics at Harlem Hospital. By the late 1990s, as transmission rates in the United States plummeted, Dr. Nicholas—who had never thought about working in international health—“felt a moral obligation in a world filled with HIV to think beyond our own shores,” he says. At the time the Caribbean had the second-highest rate of HIV infection in the world, second to sub-Saharan Africa, and 85 percent of all infected individuals resided on one island, Hispaniola, shared by Haiti and the Dominican Republic. He launched IFAP in 1999, introducing the first AIDS treatment for pregnant women. In the province where the program is based, the rate of mother-to-child HIV transmission is now as low as New York’s. The clinic, which opened in 2004, is now one of the largest providers of care and treatment for children and adults in the country. IFAP started hosting P&S students there in 2002 and added students from other disciplines in 2008. Since then, about 500 students have done rotations in the Dominican Republic. “We’ve been able to bring the transmission rates

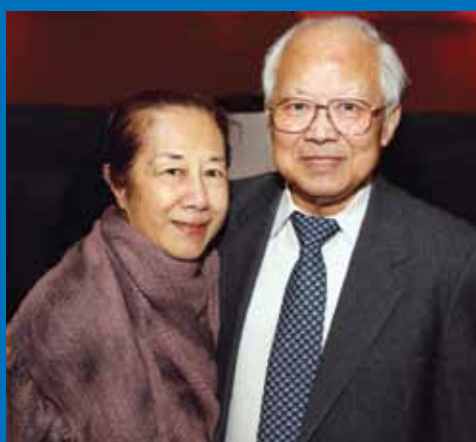


HELP FROM OUR FRIENDS

WU PHILANTHROPY EXTENDS GLOBAL REACH

Clyde Y.C. Wu ’56 has been working to advance health care in his native China since he left in 1949 to attend the College of Physicians and Surgeons. This mission began when Dr. Wu and his late wife, Helen, created the Clyde and Helen Wu Fellows Program, which selects fellows from the ranks of junior faculty at Beijing’s Peking Union Medical College for a year of training at Columbia. Many of the Wu Fellows have gone on to become senior leaders in China’s medical field, and Clyde and Helen Wu continued to build a remarkable philanthropic legacy at Columbia.

Married for more than 50 years, the couple shared a deep commitment to advancing medical training, research, and patient care. Together, they endowed the Clyde and Helen Wu Center for Molecular Cardiology and established five Clyde and Helen Wu Professorships. They also made a leadership gift to the University’s new Medical and Graduate Education Building. Before Helen passed away in June,



the Wus renewed their efforts to facilitate the exchange of clinical knowledge and expertise with major medical schools in China by establishing the Wu Family China Center, which supports collaborations between Columbia and leading global institutes in China. This new center also reinforces University efforts to increase Columbia’s global presence and impact.

“

The themes of inequality and their impact on health that we generally study in resource-poor settings are also highly relevant in New York.”

way down nationally,” Dr. Nicholas says. “In the province where we’re working, we’ve had no infected babies for the last two years.”

Those are results he set out to achieve. But after he began working in the country—immersing himself in its language, place, and culture—Dr. Nicholas was surprised to see that he was becoming a better doctor for his patients at home, too. “I thought I was a pretty good doctor for them, but I just didn’t realize how limited I was,” he says. When your patients are immigrants—newly arrived or even second-generation—understanding their culture of origin often makes a physician more empathetic, he says. “It gives you a more sophisticated way to interact with patients, and they then trust you more.”

Strengthening connections with local communities is an important goal in global medicine. Rafael Lantigua, MD, who has been instrumental in building CUMC’s partnership with UNPHU, puts it this way: “There’s an air bridge daily between New York and Santo Domingo that’s moving around 4,000 people every day one way and the other.” In addition, students have recently worked with patients in Chinatown, as well as with immigrant groups that settled in the outskirts of Beijing. Programs also seek to link students who care for people of the West African diaspora in Harlem to efforts in their countries of origin. As Mr. Bridgman-Packer says, “In New York City, we need to be sensitive to our patients’ vast range of different cultures, identities, and ideologies.”

Students understand how important this level of cultural awareness is for their future careers, no matter where they may be working. Students see the principles of global health as benefiting them as physicians working in the United States, Ms. Criswell says, because the issues at play around the world are relevant at home too. Moreover, as people, ideas, and products move across borders, so do diseases. What happens globally directly affects how medical professionals engineer their local health care systems.

Thus the benefit of broader experience is more than cultural, but clinical and technical as well. Resource-limited settings do not have the many tools and laboratories that physicians now typically rely on, so work in such an environment sharpens one’s skills. “Your differential diagnosis capacity goes way up because you’ve got to deduce what’s going on,” says Dr. Nicholas. And students are introduced to diseases they do not often see in the United States. When

students do a rotation at the children’s hospital at UNPHU in the Dominican Republic, says Dr. Lantigua, they see dengue fever, polio, and rheumatic heart disease. And when *chikungunya*, a new, mosquito-borne virus, first appeared in the Caribbean at the end of 2013, P&S students who had seen the virus when they worked in the Dominican Republic were able to recognize it when it appeared in the emergency room at Columbia. It is a perfect example, Dr. Nicholas notes, of how context and exposure make one a better doctor.

These wide-ranging benefits of global medicine, however important, are not ultimately what calls someone to work in locations around the world. Students say their desire lies in the impulse that made them want to care for others in the first place. For many students today, that urge is manifest in a broader call for social justice in medicine, a call in which the global and the local are intimately intertwined. Says Mr. Bridgman-Packer: “The themes of inequality and their impact on health that we generally study in resource-poor settings are also highly relevant in New York because in many ways the inequalities here operate on the same principles as inequalities existing anywhere else in the world.” ♦



Top: Rachel Criswell ’17 working with clinic staff and traditional midwives in Liberia to identify ways to encourage women to deliver babies with skilled birth attendants

Right: Ms. Criswell and a family medicine doctor pose with family planning informational materials in a clinic in Ukraine.

Left: Ms. Criswell in a park in Islamabad where she worked with the International Rescue Committee on a higher education development project



FROM PRINTER TO PATIENT

P&S CLINICIANS
USE 3-D PRINTERS
TO ENHANCE
PATIENT OUTCOMES

By Alla Katsnelson

Photographs by Jörg Meyer

The human heart is an engineering marvel. A two-sided pump, it coordinates the flow of blood into the lungs to pick up oxygen, and then out into the body to deliver it. In adults, the heart pumps 1.5 gallons of blood each minute and 1.5 million gallons over a lifetime. But in rare cases, babies are born with hearts so malformed and the vessels within them so abnormally routed that they cannot properly pump blood at all. Confronting such tough cases, surgeons like Emile Bacha, MD, director of congenital and pediatric cardiac surgery at NewYork-Presbyterian Congenital Heart Center, have two options: Repair the baby's heart by enlarg-

such a case to Dr. Bacha, the Calvin F. Barber Professor of Surgery. Her patient, still unborn at 35 weeks of gestation, had a rare form of a congenital heart malformation called double outlet right ventricle. Based on the maze of holes and abnormally connected vessels within, Dr. Bacha doubted that he would be able to fully repair the baby boy's heart.

Dr. Chelliah came bearing a solution, however: What if they could use a 3-D printer to generate a perfect model so that Dr. Bacha could literally hold the infant's heart in his hand, study its ins and outs, make some test cuts, and design a clear plan for the procedure before the baby entered the operating room? That prospect could revolutionize the outcome for these babies, Dr. Bacha says. "The technology is such an obvious marriage with what we need."

3-D printing—essentially printing with a solid substance rather than with ink to generate an object you can hold in your hand—is not a new technology. Invented in 1983, it was initially embraced by industrial designers as a bold, quick way to prototype new ideas. But it was not long until researchers began to explore its promise in medical applications. Today, 3-D printing has spread so widely that anyone can buy a basic device on Amazon.com for less than \$1,000. Meanwhile, biomedical researchers are using ever more sophisticated printers to address clinical needs, devising ways to print everything from custom-made blood vessels and bone segments to scaffolds that release proteins and hormones to boost the body's own regenerative potential. The beauty is that these materials can be custom-formulated to address the distinct needs of a specific individual. "All of this is part of the overall movement toward personalized medicine," says Dr. Chelliah.

Dr. Chelliah first saw the benefits of using 3-D printed models in pediatric cardiac interventions during her fellowship at the Children's National Medical Center in Washington, D.C., and she was excited to bring the technique to P&S when she joined the faculty in 2013. "Columbia has a larger-than-usual pediatric congenital heart disease patient volume as well as a pretty complex mix of patients," she says. "I thought it would be a very exciting project to bring here."

Dr. Chelliah's timing was fortuitous: Not long after her arrival at Columbia Marie Hatcher, president and founder of Matthew's Hearts of Hope, a foundation for children with congenital heart defects, decided to offer small research grants to pediatric cardiology fellows. Ms. Hatcher's son, Matthew, now 7 years old, was born with double outlet right ventricle and had already had three surgeries. When Ms. Hatcher received an application for a \$5,000 grant from Dr. Chelliah's

ing narrowed areas, closing errant holes, and realigning vessels, or conduct a palliative operation known as a Fontan procedure that leaves the infant with much-reduced heart function. The trouble is, a baby's heart is difficult to image and the convolutions inside this pingpong ball-sized structure add to the complication. "You pretty much have to figure it out on the table," Dr. Bacha says. When you do not know what you are getting into before you start, he adds, the chance for achieving a full repair is lessened.

Last summer, pediatric cardiologist Anjali Chelliah, MD, assistant professor of pediatrics, brought just



Emile Bacha, MD
Anjali Chelliah, MD
Hannah Fraint, MD

colleague, then pediatric cardiology fellow Hannah Frint, MD, to use a novel 3-D technique to create a model in advance of surgery, Ms. Hatcher and the board members reviewing the applications gave it top marks for potential impact for a modest sum.

With the funding in hand, it did not take long for Dr. Frint and Dr. Chelliah to identify the unborn boy with the maze for a heart as a clear candidate for the procedure. His congenital heart malformation had been diagnosed five months into gestation at a different facility and when his parents came to Dr. Chelliah, a fetal cardiogram revealed just how complex his heart anatomy was.

Having identified their first patient, the team turned its attention to obtaining the most precise possible 3-D image of the infant's heart. To get it, Dr. Chelliah partnered with cardiologist Andrew Einstein, MD, associate professor of medicine (in radiology) and director of cardiac CT research. A number of imaging techniques exist that can shed light on the shape—or the mis-shape—of a baby's heart. Echocardiography and cardiac MRI provide a complete enough picture in many cases, but cardiac computed tomography is often the best modality for visualizing cross-sections of the 3-D relationships among cardiac structures. Yet doctors generally hesitate to use cardiac CT in children so young, says Dr. Einstein, because it essentially involves taking a series of X-rays, thus exposing young patients to potentially dangerous doses of radiation.



Andrew Einstein, MD

Over the past year, Dr. Einstein and Dr. Chelliah have developed a protocol for cardiac CT in babies that uses lower-energy X-rays and fewer of them, localized to as small an area as possible, effectively reducing the radiation dose to the equivalent of a few chest films. “I don’t know of anyone doing CT scans of the heart with doses as low as we’ve been able to do, in the smallest children,” says Dr. Einstein. The duo’s first effort to scan Dr. Chelliah’s patient, on the day he was born at 39 weeks’ gestation, didn’t go well; the baby was moving and crying too much. “We brought him back on day two and repeated the scan with general anesthesia,” says Dr. Einstein. “I had no worries about repeating the scan and the second time worked like a charm.”

As the baby lay in Morgan Stanley’s neonatal intensive care unit, receiving a continuous infusion of medication to keep his aorta open, his cardiac CT data traveled to the offices of a small Belgian 3-D printing company called Materialise to be turned into a tiny clear plastic replica of his heart. Two days later, Dr. Bacha had a model in hand. “For us, these complex cases have always been high stakes, high drama; only the best surgeons did them because you had to think on your feet and make the right decisions quickly,” says Dr. Bacha. “Having practiced for the last 18 years under this kind of pressure, I appreciate being able to look at [the heart] at my leisure.”

When the baby was a week old, Dr. Bacha was able to perform a complete repair in a surgery that lasted less than six hours, averting what otherwise would have been three procedures spread over the next three years. After 10 days of recovery, the infant was able

“WE DON'T ANTICIPATE THAT THIS BABY IS EVER GOING TO NEED ANOTHER SURGERY.”



A 3-D printed heart model

to go home to his family. “We don’t anticipate that this baby is ever going to need another surgery,” Dr. Chelliah says.

One of the most heartwarming features of the baby’s case, Dr. Chelliah says, is how grateful the baby’s parents were for the piece of plastic that had so drastically changed their son’s prognosis. Just a few days before the infant’s family was able to take him home, Dr. Chelliah and Dr. Frint learned that Marie Hatcher and her son, Matthew, were in the hospital.

With the moms’ permission, the two pediatric cardiologists arranged to have the families meet. Ms. Hatcher recalls making her way to the NICU to find the baby’s mom standing over an infant who, with his dark hair and round face, looked uncannily like her own son had at that age. After the mothers embraced, the baby’s parents got a chance to meet Matthew and thank him for what he does to help other babies.

“Matthew went through three surgeries,” says Ms. Hatcher. “Knowing that another mom’s baby was only going to have to go through one was huge. You know you’re doing good work but when you actually see that person and their baby and you know that you have had a big impact on their lives, it’s very humbling and very gratifying.”

Over the past year, four other young patients have had surgeries. The first was a 4-year-old girl who underwent two palliative surgeries shortly after her birth and on whom Dr. Bacha too managed to do a complete repair. Following her, a 4-year-old, a 5-month-old, and a 3-year-old—all of whom had already undergone at least one palliative surgery—also received a complete repair.

Although the Matthew’s Hearts of Hope pilot study has ended, Dr. Chelliah has secured additional funding to extend the 3-D work and the doctors are hoping to join two upcoming multicenter trials to collect further data. “We want to show that this really does have a major impact,” she says. “Anything that can help pediatric patients avoid multiple surgeries is obviously not just beneficial for them, but should persuade insurers to cover it as well.”

She and her colleagues are convinced that the procedure will soon become routine. They are also exploring other ways that the technology could be leveraged. “This is just where we chose to start,” Dr. Chelliah says. “We know it can be applied in many, many kinds of patients.”

Jeremy Mao, DDS, PhD, the Edwin S. Robinson Professor of Dentistry (in Orthopedic Surgery), has devoted much of his research career to the meniscus, a C-shaped piece of cartilage in the knee. As with other tissues comprised of fibrochondrocytes—present only in the spine and in places where tendons connect to bone—the meniscus heals poorly. Dr. Mao and his team identified the protein cues that push stem cells to differentiate into fibrochondrocytes, then used a 3-D printer to produce custom-tailored, meniscus-shaped bioscaffolds loaded with the proteins to implant in animals. “In just about all the ways we look at this, the regenerated menisci were similar to the native ones,” says Dr. Mao, who hopes to start human testing in the next year.



Scott Roskind, left,
and John Minio



HELP FROM OUR FRIENDS

ROSKIND AND MINIO FAMILIES LEAD BABIES HEART FUND GALA TO RECORD YEAR

As the longest-running fundraising event at Columbia University Medical Center, the Babies Heart Fund Gala is a uniquely important and steady source of support for the Division of Pediatric Cardiology. Its success owes a great deal to the Roskind family, which helped found the Babies Heart Fund in 1986 to advance research and treatment for congenital heart disease. For Robert Roskind, the Babies Heart Fund was a way of thanking Columbia faculty for the excellent care they provided his son, Scott, who was born with a congenital heart defect. Now a healthy adult with his own family, Scott Roskind is continuing his family’s philanthropic legacy as a co-chair of the fund, along with John Minio, a grateful parent whose son was treated at Columbia 24 years ago. Together, Scott Roskind and John Minio helped guide the fund to another outstanding year. On March 5, the 28th annual Babies Heart Fund Gala was held at the Pierre Hotel in New York City and raised more than \$600,000, the highest fundraising total in the gala’s history, to advance research in congenital heart disease at Columbia.



A 3-D printed meniscus scaffold

Dr. Mao believes this work just barely scratches the surface of the potential for 3-D printing to improve patients' lives. He is collaborating with Michael Shen, PhD, professor of medical sciences (in medicine), of genetics & development, and of urological sciences (in urology), to print 3-D hydrogels that model the niche in which cancer cells live. The most obvious applications, however, lie in the field of regenerative medicine. Michael Kazim, MD, clinical professor of ophthalmology and of surgery, has recreated the orbital structure of the eye, an application for which the materials currently used are outdated and not biocompatible. Francis Lee, MD, the Robert E. Carroll and Jane Chace Carroll Laboratories Professor of Orthopedic Surgery, is testing simple 3-D implants to correct bone defects.

While research continues to identify other uses for 3-D printing in health care, Dr. Einstein, whose exper-

tise in cardiac CT was vital for the Matthew's Hearts of Hope pediatric patients, has started to examine the possibility of creating high-precision models for adult heart patients, such as those who have atrial fibrillation. And much more can be done for the youngest critically ill cardiac patients, as well, says Dr. Chelliah. "A major problem in pediatrics is that it is hard to get devices made in pediatric sizes," she says. "There just aren't that many children who need them, and children are variable sizes while adults are closer to one size." To stent a child's heart, for example, cardiologists often use liver stents created for adults. Says Dr. Chelliah: "We see a world where, a few years from now, when we see a patient with a hole in his or her heart, we will be able to visualize it and maybe even print a device that will go into the child's heart, sized exactly as needed." ♦



**CLINICIANS AND
RESEARCHERS
ARE STUDYING
MANY USES FOR
3-D PRINTING IN
PATIENT CARE.**

■ 2015

Clinical and Research



Highlights

TEAMWORK AND INGENUITY are hallmarks of work done by P&S clinicians and investigators who delved ever deeper this year in their quest for insights to guide clinical care and precision medicine, as evidenced in the following pages that highlight research conducted and clinical advances made during the course of the year.

The results—a testament to the participation of patients who furnish tissue samples and participate in clinical research—revealed new insights into transplant tolerance and lung cancer, as well as the mechanisms by which the human immune system protects the body against invading pathogens.

Genetically modified animals, too, have played a key role in advancing the work of P&S scientists. Pediatric oncologists designed mouse avatars to test individualized cancer protocols before treating their human patients. A mouse model of autism revealed a protein implicated in irregular synaptic development. And observations in mice helped scientists identify the stem cells that contribute to healing after a bone breaks; their findings may hold the key to bone regeneration.

Only a few achievements are described on the following pages. Many more were reported during the year, including work that



touches nearly every part of the human body and mind: obesity, diabetes, kidney disease, schizophrenia and other mental illnesses, children's vaccinations, Alzheimer's disease, retinitis pigmentosa and color blindness, and emphysema. Data scientists developed a computational method to investigate the relationship between birth month and disease risk. Another team found that a unique array of sensory receptors in a bat's wing provides feedback during flight; a better grasp of the process could inform aircraft design and new sensors for monitoring airflow. A vital advance in clinical care was reported in the *New England Journal of Medicine*: Full implementation of new hypertension guidelines could prevent 56,000 cardiovascular disease events and 13,000 deaths each year, without increasing overall health care costs. In March, the Food and Drug Administration approved a smaller, safer heart valve developed by a member of the P&S faculty. In June, researchers revealed the role of acid-reducing medications in pediatric cases of *Clostridium difficile* infection. Last fall, scientists reported on the memory-boosting power of cocoa. Read more about these and many other research and clinical highlights in the CUMC online newsroom (newsroom.cumc.columbia.edu).

Photographs by Jörg Meyer



Following Biology's Lead

Every year, 50,000 infants are born in the United States with a constellation of symptoms that boils down to a genetic glitch. For many, doctors can offer a diagnosis: Tay-Sachs, a neural tube defect, a metabolic disorder. Even if the news is not good, health care professionals have enough insight to help families prepare for what's to come.

Some conditions, though, are so rare and so poorly understood that doctors have little to offer by way of diagnosis or consolation, and families spend years on a painful and expensive quest for

answers. Increasingly, however, clinician-scientists at academic medical centers are offering whole exome sequencing (WES), a technique for analyzing all of a patient's protein-encoding genes using a few vials of blood. Developed for research applications, the technique is now frequently covered by insurance and available as a diagnostic tool.

A Columbia team in 2014 reported on the results of WES for 115 patients. "Our experience should assist other clinicians in implementing WES into their clinical practice because we have addressed

practical concerns including patient education in pretest counseling, consent, insurance coverage, turnaround time, yield of testing, updates of test results, and impact on clinical care," the researchers wrote. "We have found that WES significantly improves our diagnostic ability; we have addressed many of the practical problems of its clinical implementation and routinely use WES as a primary test in patients' genetic evaluation."

The individuals who received WES all had an undefined genetic disorder and were patients of Wendy Chung, MD, PhD, who directs the clinical genetics program at Columbia University Medical Center, and two members of the Division of Clinical Genetics in the Department of Pediatrics, Kwame Anyane-Yeboah, MD, and Alejandro Iglesias, MD. WES yielded a definitive genetic diagnosis for 32 percent of the patients, and in many cases helped inform families about better treatment options.

WES is particularly valuable for the youngest patients, the team noted, because diagnostically relevant symptoms and signs may take time to emerge, delaying effective treatment. "A diagnosis made early can be particularly valuable to identify additional associated features of clinical syndromes before they become symptomatic to prevent or ameliorate the manifestations and to minimize the diagnostic evaluation of new symptoms." Such was the case for three of the patients in the study.

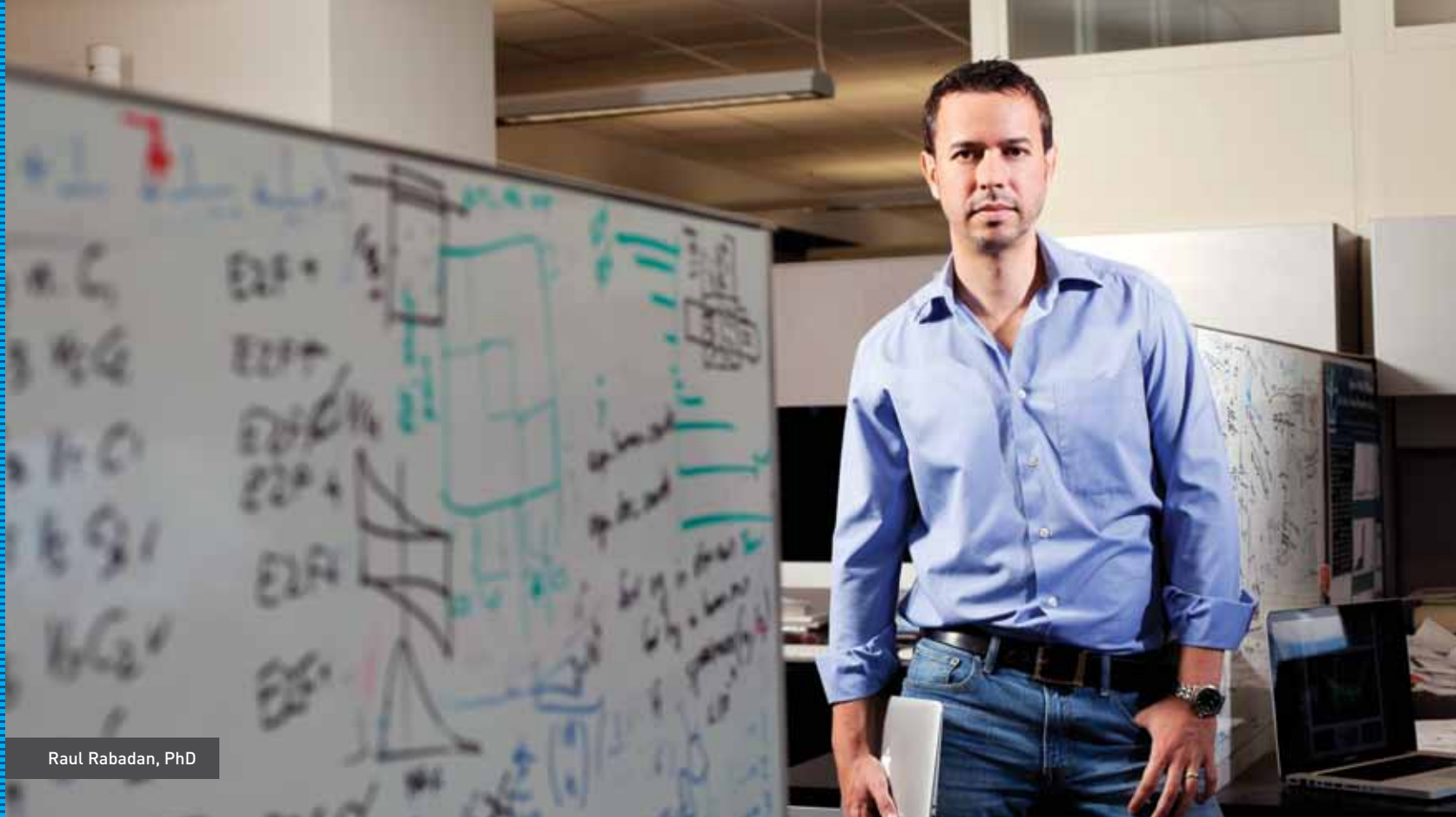
Diagnoses based on WES allowed all of the patients to avoid more invasive diagnostic procedures, such as muscle biopsy. Results also helped several families alter medical management, access social and educational services available only to individuals with a clear diagnosis, identify other family members at risk for the condition, and make informed decisions about reproductive planning.

"When we've exhausted the routine clinical diagnostics, we go beyond clinical care and use novel research methods," says Dr. Chung. "Genomic sequencing, with the purpose of being comprehensive, answers a very relevant clinical question using the most advanced genomic tools to get at the answer. We go into it without preconceived notions and just go where the biology takes us."

*This is a summary of research published in *Genetics in Medicine*, December 2014.*



Alejandro Iglesias, MD
Kwame Anyane-Yeboah, MD
Wendy Chung, MD, PhD



Raul Rabadan, PhD

Scientists Identify Lymphoma Gene

The first-ever systematic study of the genomes of patients with ALK-negative anaplastic large cell lymphoma (ALCL), a particularly aggressive form of non-Hodgkin's lymphoma, shows that many cases of the disease are driven by alterations in the JAK/STAT3 cell signaling pathway. The study, done with Weill Cornell Medical College, also demonstrates, in mice implanted with human-derived ALCL tumors, that the disease can be inhibited by compounds that target this pathway, raising hopes that more effective treatments might soon be developed.

"Current therapies for this form of lymphoma fail to work in the majority of cases," says co-study leader Raul Rabadan, PhD, associate professor of systems biology and of biomedical informatics. "However, now that we know the mutations that drive a significant percentage of cases, we can envision a new, personalized genomic approach to the treatment of ALK-negative ALCL."

About 70,000 cases of non-Hodgkin's lymphoma are diagnosed each year; ALCL accounts for about 3 percent of them. Patients with ALCL that has spread to multiple body sites fall into two groups, depending on whether their cells express an abnormal form of the ALK (anaplastic lymphoma kinase) protein. ALK-positive lymphomas tend to respond well to chemotherapy, with a long-term disease-free survival rate of more than 70 percent. These lymphomas are due to the fusion of two genes producing an abnormal protein that activates the gene STAT3. Patients with ALK-negative lymphomas have a poorer prognosis, with a long-term survival rate of less than 50 percent. Very little is known about the cause of this form of the disease.

To learn more about the genetics of ALCL, Dr. Rabadan's team sequenced the exomes and the RNA of tumor cells from 155 patients with ALCL and 74

patients with other forms of lymphoma. The team found mutations in either JAK1 or STAT3 in about 20 percent of the patients with ALK-negative ALCL. Of those 20 percent, 38 percent had mutations in both genes.

Either JAK1 or STAT3 mutations can cause abnormal activation of the JAK/STAT3 signaling pathway, which transmits chemical signals from outside the cell to genes in the cell nucleus. Overactivation of this pathway has been implicated in various forms of cancer.

The researchers also detected several novel gene fusions, some of which appear to activate the JAK/STAT3 pathway. Patients with these gene fusions did not have JAK1 or STAT3 mutations, suggesting that the fusions are an independent cause of ALK-negative ALCL.

To confirm whether JAK1 and STAT3 mutations can cause ALK-negative ALCL, the researchers induced these mutations in normal human cells. The mutations led to diseased cells.

The researchers also tested JAK/STAT3 pathway inhibitors in mice implanted with tumors derived from patients with ALK-negative ALCL. Tumor growth was significantly inhibited, compared with controls. "Our findings demonstrate that drugs targeting the JAK/STAT3 pathway offer a viable therapeutic strategy in a subset of patients with ALCL," says Dr. Rabadan. "A couple of JAK/STAT3 inhibitors have been approved by the FDA for the treatment of psoriasis and rheumatoid arthritis, and several more are currently in clinical trials. These could be tested in patients whose genetic profile matches those we identified in our study."

This is a summary of research published in Cancer Cell, April 13, 2015.

Tailored Clinical Care for Bone Marrow Transplant

Bone marrow transplant patients at NewYork-Presbyterian/Columbia now have a unit of their own. The Irving Bone Marrow Transplant Unit is a state-of-the-art facility for comprehensive bone marrow transplant care.

The unit features 18 inpatient rooms, a high-tech nurses' station for individual patient monitoring, and a specialized airflow system to help protect patients with weakened immune systems. The unit is supported by a \$20 million gift from Herbert and Florence Irving.

The Irving Bone Marrow Transplant Unit is designed to deliver patient-centered care for bone marrow transplant recipients and to advance research to make BMT a safe and viable lifesaving therapy for a wide range of patients. Bone marrow, the body's factory for making all types of blood cells, can be affected by benign blood disorders, such as severe aplastic anemia and sickle cell anemia, and malignant blood disorders, such as acute leukemias, lymphoma, and myeloma. BMT replaces damaged or diseased bone marrow with

healthy donor cells and—because of the ability of the donor immune cells to attack the blood cancer cells—it is a potent form of immunotherapy. In many cases, the treatment reverses conditions that were once thought to be incurable.

In addition to its use in blood cancer treatment, BMT and other forms of cellular therapies can be used to custom-tailor a patient's immune system. Megan Sykes, MD, director of the Columbia Center for Translational Immunology, has demonstrated that combining BMT and organ transplantation can induce tolerance and allow acceptance of the donor organ without the use of long-term immunosuppressant therapy. NewYork-Presbyterian has the largest solid organ transplant program in the country, putting the BMT unit at the forefront of efforts to make these novel combined transplant procedures the clinical standard.

The unit is directed by Markus Mapara, MD, PhD, director of the blood and marrow transplantation program at NewYork-Presbyterian/Columbia and professor of medicine. In addition to his interest in combined bone marrow and solid organ transplantation, Dr. Mapara is developing new approaches to improve the outcomes of patients undergoing autologous and allogeneic hematopoietic stem cell transplantation by preventing and/or reducing treatment-related complications such as graft-versus-host disease and preventing recurrence of the underlying disease.

Dr. Mapara primarily cares for patients with hematologic malignancies who need blood or marrow transplantation. A particular focus of his research is the ability to perform transplants in patients without matched donors. Approximately 25 percent of people who need a bone marrow transplant have a matching donor in their family. Those without a familial donor must be matched through national and international registries. The chance of finding a match in these registries is about 70 percent for Caucasians. For ethnic minority patients, who are underrepresented in the donor banks, the match rate is much lower. Partial matches from first-degree relatives, called haploidentical matches, have made BMT possible, especially in patients from ethnic minorities who are unable to find a matched unrelated donor.



Markus Mapara, MD, PhD

Going Local

The human immune system—popularly conceived along the lines of a roaming national defense force, poised to combat pathogens—has its own variation on the mantra *location, location, location*.

“By mapping the locations of T cells throughout the body, we’ve found that each organ has its own set of resident T cells that are specifically adapted to the local pathogens and conditions,” says Donna Farber, PhD, professor of surgical sciences (in surgery) and of microbiology & immunology in the Columbia Center for Translational Immunology. Such specialization has not been appreciated, Dr. Farber says, because most of what is known about T cells comes from studies of those circulating in the blood. T cells also populate such organs as lungs, intestines, and skin, which are constantly exposed to pathogens. “We need immune cells at these sites, too,” she says. “Blood contains only a very small fraction—2 percent—of our T cells.”

Blood, of course, is relatively easy to obtain for research purposes. For T cells from other body systems, Dr. Farber turned to the New York Organ Donor Network (LiveOnNY), which granted Dr. Farber’s team access to biological samples from organ donors for which consent for use of tissues for research was obtained. The team analyzed T cells from 56 individuals, with ages spanning six decades.

In the lab, graduate students and first authors Joseph Thome and Naomi Yudanin identified the type of T cells in each organ. These types include naïve cells that respond to new pathogens and memory cells that retain information on previously encountered pathogens and can mediate protective immunity to pathogens.

They found that each organ had its own unique collection of T cell types that proved surprisingly similar among all individuals. “The immune systems in different lungs were more similar to each other than to another organ in the same person,” says Dr. Farber. “These individuals were as diverse as New York City, but each tissue had a similar complement of T cells adapted in the same way.” Sites such as lungs and intestines, the point of entry for many pathogens, contain complements of memory T cells

constantly on alert to maintain health in these sites. These “localized militias” of the immune system establish themselves early in life and persist in stable form for decades.

A finer analysis looked at the antigen-specific receptors expressed by memory cells in each organ, investigating whether the same T cell clone (which would recognize the same antigen) was present in different organs. Here, too, organs were unique. “Within a person, you store up memories that are specific to each site,” Dr. Farber says. That degree of compartmental-

ization of the immune system’s T cells will be surprising to most immunologists, she adds. And the findings are sure to inform clinical applications. “We need to understand what’s happening locally. For a vaccine, if you know that a pathogen is always going to enter the lung, that’s where you want to beef up immunity. For cancer therapy, tumors appear in tissues; you need to understand the local tissue.”

This is a summary of research published in Cell, Nov. 6, 2014.



Joseph Thome, Naomi Yudanin,
Donna Farber, PhD



Ronald Wapner, MD



Mary E. D'Alton, MD

Detecting Down Syndrome

During pregnancy, maternal blood flows against the placenta, allowing the exchange of nutrients, blood gases, and cellular and genetic material. Simultaneously, placental cells are being shed into the maternal circulation, resulting in small fragments of fetal DNA circulating in the maternal blood and accounting for approximately 10 percent of the total DNA in the mother's plasma. Newer genetic techniques now allow for the genetic evaluation of the origin of this DNA to detect alterations in the number of fetal chromosomes without requiring a diagnostic procedure, such as amniocentesis or chorionic villus sampling.

By analyzing those fragments, obstetricians can detect evidence of such conditions as Down syndrome; other chromosomal anomalies, including trisomy 18, also known as Edward syndrome, or trisomy 13 (Patau syndrome); sex-linked conditions; and Rh incompatibility between woman and fetus.

In a study of 18,500 pregnancies, researchers at Columbia and the University of California, San Francisco, found that one such test is more accurate than conventional screening at identifying Down syndrome.

"This study supports the use of noninvasive prenatal testing as a first-line screening option for any pregnant woman, regardless of the patient's age or whether the patient is low, average, or high risk," says Ronald Wapner, MD, director of reproductive genetics at Columbia and one of the principal investigators of the study. Dr. Wapner led the study with Mary E. Norton, MD, at UCSF.

Tests that detect fetal DNA in maternal blood were first introduced in 2011 but have been investigated mostly in high-risk women—those who are over age 35 or who have genetic risk factors. This study supports the use of noninvasive prenatal testing as a first-line screening option for any pregnant woman.

The new study is the first in the general pregnant population that is large enough to compare the performance of the new DNA test with con-

ventional screening. The researchers tested a DNA test offered by Ariosa Diagnostics, but other companies market similar tests.

The researchers found that the new test correctly identified more Down cases—with far fewer false positives—than standard screening that combines blood tests with an ultrasound exam.

The DNA test identified all 38 cases of Down syndrome and produced only nine false positives (0.06 percent). Standard screening identified 30 of the 38 cases of Down syndrome and produced 854 false positives (5.4 percent).

About 3 percent of the DNA tests did not produce a result, often because the fraction of fetal DNA in the blood sample was too low. These participants had a higher frequency of Down syndrome cases as well as other chromosomal abnormalities, and further study is needed to determine the best approach for these patients.

Before the DNA test can be widely used in patient care, people's expectations of the test should be carefully considered, the authors say. The test is highly accurate at detecting Down syndrome and other conditions with extra chromosomes, but standard screening and diagnostic testing can identify a broader array of abnormalities not detectable with the cell-free DNA test.

Mary E. D'Alton, MD, the Willard C. Rappleye Professor of Obstetrics & Gynecology and chair of the Department of Obstetrics & Gynecology, is an expert in maternal fetal medicine and has long promoted monitoring and technology that will improve pregnancy outcomes. "This research is further evidence of Columbia's unique ability to identify ways to give parents an accurate picture of their baby's medical condition and create the best management plan," says Dr. D'Alton.

This is a summary of research published in the New England Journal of Medicine, April 23, 2015.

Boning Up

A stem cell capable of regenerating both bone and cartilage has been identified in the bone marrow of mice. Known as osteochondroreticular—OCR—stem cells, the newly identified type of bone stem cell appears to be vital to skeletal development and may provide the basis for novel treatments for osteoarthritis, osteoporosis, and bone fractures.

OCR cells were discovered by tracking a protein expressed by the cells. Using this marker, researchers found that OCR cells self-renew and generate key bone and cartilage cells, including osteoblasts and chondrocytes. Researchers also showed that OCR stem cells, when transplanted to a fracture site, contribute to bone repair.

“We are now trying to figure out whether we can persuade these cells to specifically regenerate after injury,” says Siddhartha Mukherjee, MD, DPhil, assistant professor of medicine. “If you make a frac-

ture in the mouse, these cells will come alive again, generate both bone and cartilage in the mouse, and repair the fracture. The question is, could this happen in humans?” The researchers believe that OCR stem cells will be found in human bone tissue, as mice and humans have similar bone biology.

“Our findings raise the possibility that drugs or other therapies can be developed to stimulate the production of OCR stem cells and improve the body’s ability to repair bone injury—a process that declines significantly in old age,” says Timothy C. Wang, MD, the Dorothy L. and Daniel H. Silberberg Professor of Medicine, who initiated the research. Previously, Dr. Wang found an analogous stem cell in the intestinal tract and observed that it was also abundant in the bone.

“These cells are particularly active during development, but they also increase in number in adulthood after bone injury,” says Gerard Karsenty,

MD, PhD, the Paul A. Marks Professor of Genetics & Development, professor of medicine, chair of genetics & development, and a member of the research team. The study also showed that adult OCRs are distinct from mesenchymal stem cells—MSCs—which play a role in bone generation during development and adulthood. Researchers had presumed that MSCs were the origin of all bone, cartilage, and fat, but recent studies have shown that these cells do not generate young bone and cartilage. The Columbia study suggests that OCR stem cells actually fill this function and that both OCR stem cells and MSCs contribute to bone maintenance and repair in adults. The researchers also suspect that OCR cells may play a role in soft tissue cancers.

This is a summary of research published in Cell, Jan. 15, 2015.



Gerard Karsenty, MD, PhD, Timothy C. Wang, MD, Siddhartha Mukherjee, MD, DPhil

Transplant Tolerance

Columbia researchers have pinpointed the immune system mechanism that allows a kidney transplant to be accepted without lifelong immunosuppressant drugs, a significant step toward reducing or eliminating the need for the costly and potentially toxic immunosuppressant drugs and improving long-term transplant success.

Using a new technique for identifying and tracking specific cells, combined with advanced genetic sequencing, the researchers found a set of patient-specific T cells that react to the donor tissue. In patients who reject the organ, these cells increase in number. The cells gradually disappear, however, in patients who accept the organ without immunosuppression; those patients are considered to be immunologically “tolerant” of their donors.

“This new technique has the potential to predict and identify rejection and tolerance in different types of transplant patients,” says study leader

Megan Sykes, MD, the Michael J. Friedlander Professor of Medicine, professor of microbiology & immunology and surgical sciences (in surgery), and director of the Columbia Center for Translational Immunology.

When a patient receives a transplant, a unique population of lymphocytes, donor-reactive T cells, emerge to reject the foreign organ. Immunosuppressant medication is almost always required to prevent rejection of the donor tissue.

Earlier studies suggested that a unique subset of T cells, called regulatory cells, play a role in inducing tolerance, but they seemed not to be involved in maintaining tolerance later on. Furthermore, it was unclear whether donor-reactive T cells actually disappeared or were still present but inactive in long-term tolerant recipients. To learn more, the Columbia team devised a new technique for identifying and tracking these cells.

The researchers used their technique on blood samples taken from six kidney transplant patients. Two of the patients had undergone conventional kidney transplants. The other four received combined kidney and bone marrow transplantation (CKBMT) in a clinical trial and stopped taking immunosuppressants eight months after surgery. CKBMT, an experimental therapy, produces an immune state that combines elements of both the recipient’s and donor’s immune systems. “Our studies have shown that CKBMT induces tolerance of the transplanted organ without the need for long-term immunosuppressants. But we didn’t understand the mechanism behind this tolerance,” says Dr. Sykes, who helped develop CKBMT in the early 2000s as part of a Harvard University–Massachusetts General Hospital team.

In the new study, Columbia researchers identified the donor-reactive T cells in each patient’s blood before transplant and repeated the test after transplant at six, 12, and 18 months. Three of the four patients who underwent CKBMT showed a decrease in donor-reactive T cells and tolerated the transplant. In the fourth CKBMT patient, the donor-reactive cells did not significantly decline over time and the patient rejected the donor kidney. The two patients who had the kidney transplant alone had an increase in donor-reactive T-cell receptors.

“Our findings suggest that deletion of a specific set of donor-reactive T cells is a major mechanism governing tolerance of donor tissue,” says Dr. Sykes. “The study also supports the approach of combining kidney transplants with bone marrow transplants, with its resultant elimination of donor-reactive T cells. This approach needs further study, but so far, all signs indicate that it could eliminate the need for lifelong immunosuppression.”

Immunosuppressant drugs have dramatically increased transplant success, but they have notable drawbacks, including significant side effects and increased risk of cancer, opportunistic infections, hypertension, elevated cholesterol, and other conditions. “On top of all that, the transplants often do not survive permanently because of the drugs and the constant attacks of the recipient’s immune system,” says Dr. Sykes.

The team is planning a trial of CKBMT at Columbia.

This is a summary of research published in Science Translational Medicine, Jan. 28, 2015.



Megan Sykes, MD

Picture Perfect

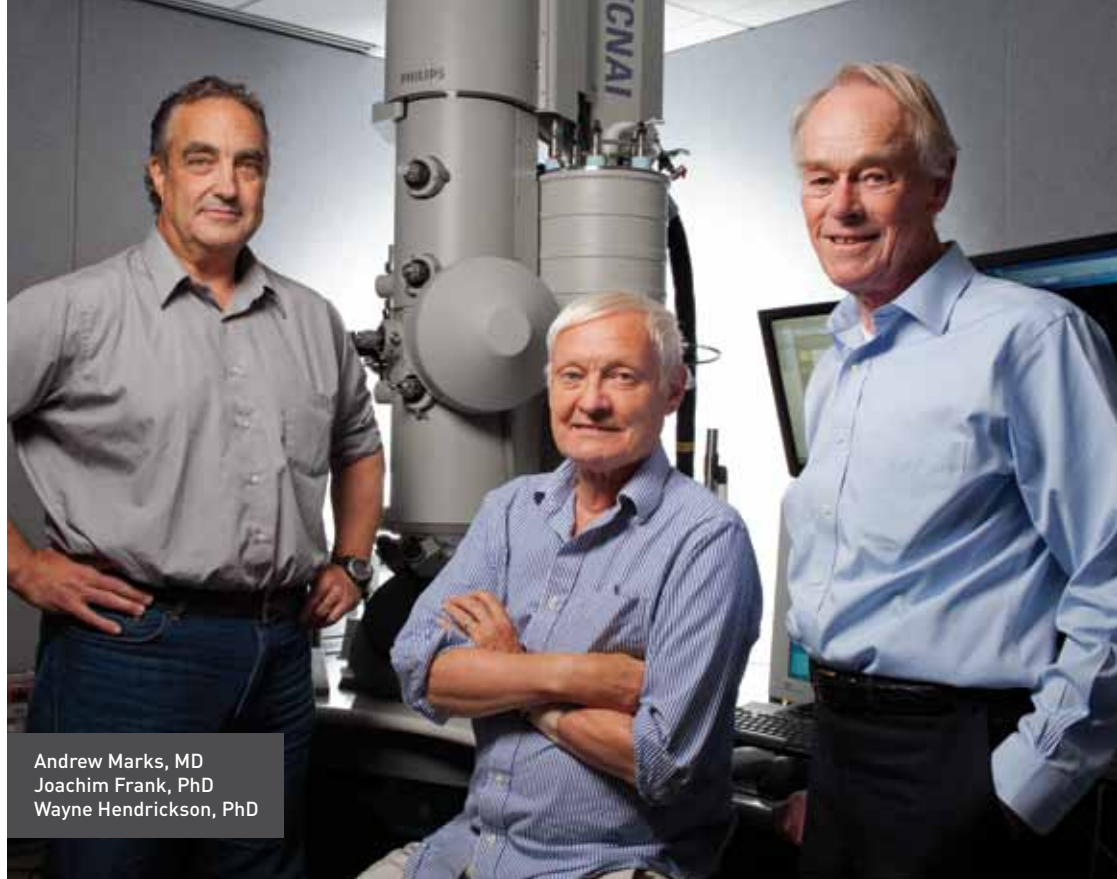
Using the same technology available in smartphone cameras, Columbia scientists are capturing images of individual molecules at a level of detail never before possible—including images of a molecule implicated in heart failure, age-related muscle weakness, and muscular dystrophy.

The new images of the ryanodine receptor, a membrane protein that functions as a channel for the passage of calcium ions in muscle cells, have led to the determination of its 3-D structure in unprecedented detail. The newly discovered structure will help researchers understand how the molecule works, why it fails in heart and skeletal muscle disease, and how to design drugs to improve the function of faulty receptors.

The findings emerged from a collaboration among the laboratories of Andrew Marks, MD, an expert in the physiology of ryanodine receptors; Joachim Frank, PhD, an expert in electron microscopy; and Wayne Hendrickson, PhD, an eminent X-ray crystallographer.

Biological molecules are tiny, with even the largest molecules only 1/10,000th as large as the width of a human hair.

The highest resolution images of such molecules have traditionally been captured using X-ray diffraction from precisely arranged crystals of the molecule of interest. Unfortunately, making crystals of many of the biomolecules of most interest to biologists and pharmaceutical companies is challenging and, for some, nearly impossible.



Andrew Marks, MD
Joachim Frank, PhD
Wayne Hendrickson, PhD

A wider variety of biomolecules can be imaged with electron microscopy, which does not require crystals. But until the advent of new cameras, the resolution of such images was often too low to obtain the exquisite details required by drug designers.

One of the first of the new cameras was deployed in 2012 in the lab of Dr. Frank, professor of biochemistry & molecular biophysics, who developed the approach of determining the structure of molecules from many single images.

Like its smartphone counterpart, the camera uses active pixel sensor technology, which pro-

vides superior resolution, higher contrast, and fewer image artifacts than the charged couple device-based cameras used previously.

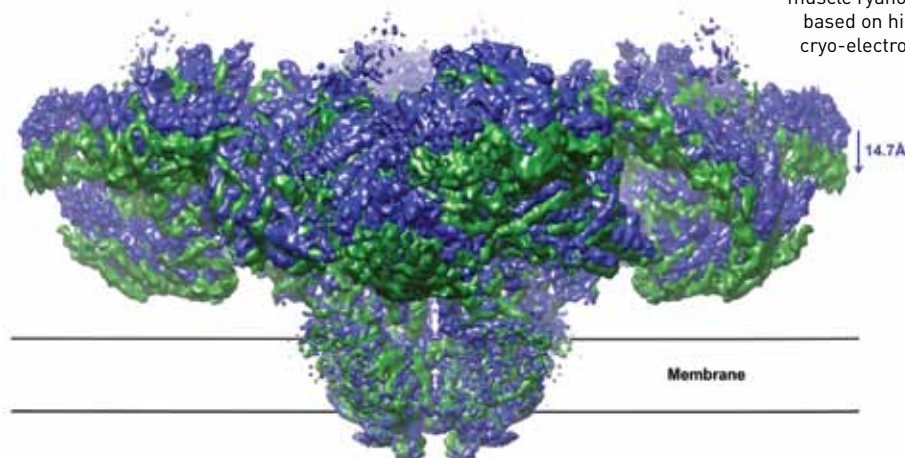
When the ryanodine receptor channel works correctly, the molecule regulates contractions in heart and skeletal muscle by controlling the passage of calcium ions through its central pore. When the channel malfunctions, calcium leaks through the pore, exacerbating heart failure or causing muscle weakness.

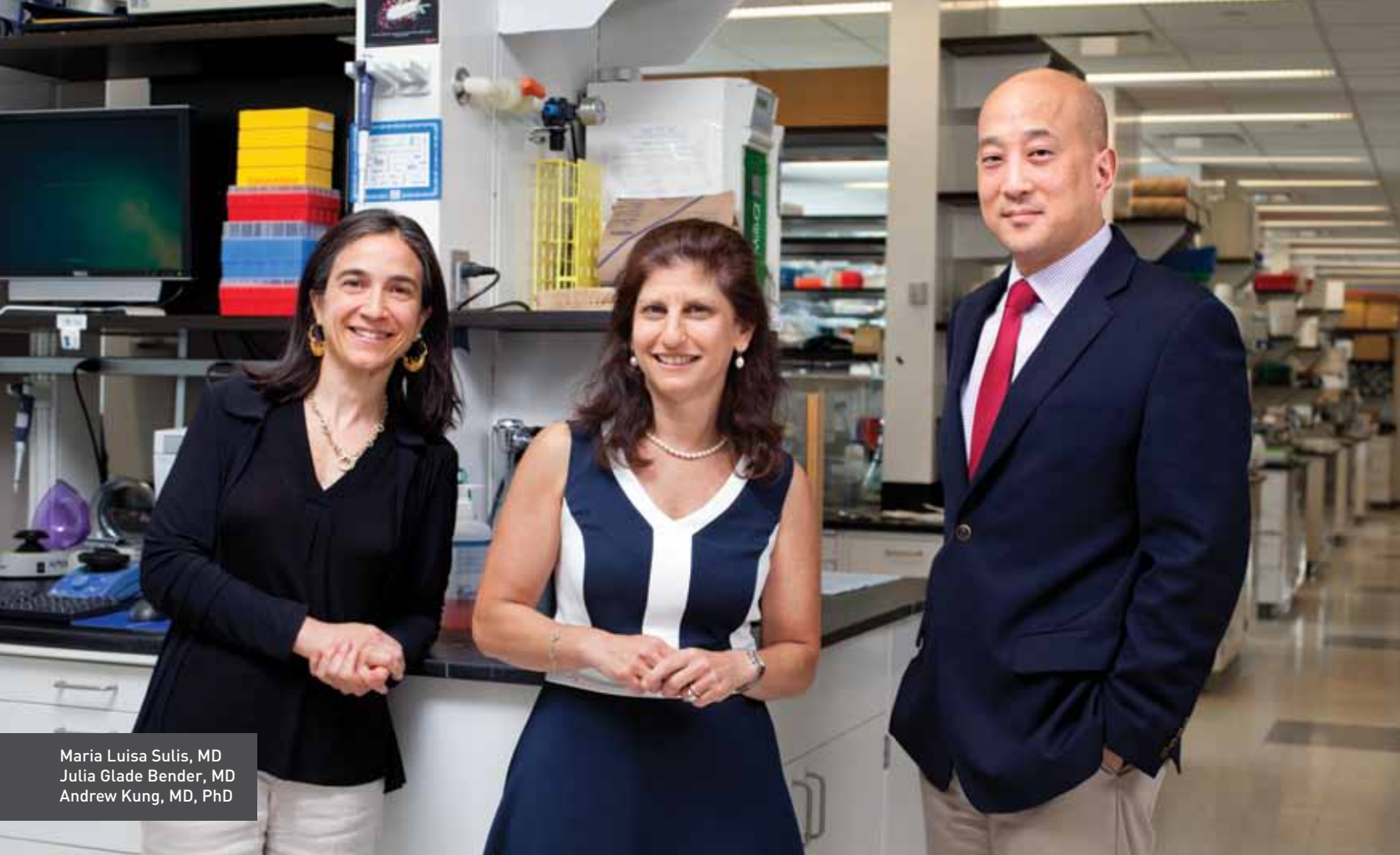
Previous attempts by Dr. Frank to uncover the ryanodine receptor's shape in the early 90s revealed the general outlines of the molecule, including the pore. But details vital to understanding how the molecule works and how defects in it cause disease remained obscure.

The new camera model reveals these details, as well as some that had not been anticipated. Biologists can now see where mutations in the ryanodine receptor channel occur, understand how those mutations affect the functioning of the channel, and model how the receptor channel opens and closes. "Having the structure in hand will completely change the field of ryanodine receptor channel research," says Dr. Marks. "It will give us new insights into how the drugs work and how to make them work better."

This is a summary of research published in Nature, Jan. 1, 2015.

3-D model of the skeletal muscle ryanodine receptor based on high-resolution cryo-electron microscopy





Maria Luisa Sulis, MD
Julia Glade Bender, MD
Andrew Kung, MD, PhD

Precision Cancer Medicine for Pediatric Patients

At Columbia University Medical Center, all pediatric cancer patients now have access to genome sequencing of their tumors. Using technologies that have until now been largely restricted to research use and have taken many months to process, the Precision in Pediatric Sequencing—PIPseq—program provides results to a patient's doctor in less than three weeks.

"We recognize that a diagnosis of cancer or a blood disorder is a frightening prospect that affects not only the child, but the entire family," says Andrew Kung, MD, PhD, chief of the pediatric hematology, oncology, and stem cell transplantation division and the Robert and Ellen Kapito Professor of Pediatrics. "There have been dramatic advances in the way we manage pediatric cancers and blood disorders, and today patients are reaping the benefits of decades of research."

While tremendous progress has been made in the treatment of pediatric cancers, oncologists are still challenged by cancers that fail to respond or develop resistance to treatment. The key to success in the battle against these cancers lies in the biology of each child's cancer. What mutations are driving its growth or rendering it invulnerable to the standard treatments?

PIPseq strives to identify the molecular drivers of each patient's cancer and use that information to personalize treatment with novel biologically targeted investigational agents. "With next-generation sequencing," says Julia Glade Bender, MD, medical director of PIPseq,

"we can delve deeper into the genetic basis of cancer to pinpoint novel therapeutic targets."

In early 2014, with support from the Herbert Irving Comprehensive Cancer Center, the division started performing genome sequencing of tumors in patients with high-risk or relapsed cancers, and the sequencing is now offered to all pediatric cancer patients. "No other pediatric cancer program is applying precision medicine to the problem of childhood cancers the way we are," says Maria Luisa Sulis, MD, head of hematologic malignancies for PIPseq. "We are one of the only programs prospectively sequencing cancers and using the results to make clinical decisions for our patients."

As part of the PIPseq program, investigators also use biopsy or resection samples from patients to grow the tumors in mice, creating what are termed patient "avatars." One centimeter of tumor tissue can be used to generate 50 to 100 avatars. Coupled with the identification of gene mutations through PIPseq, the avatar models can be used to determine whether the identified mutations contribute to the cancer's development. With that information, clinician-scientists can identify target drugs that might be relevant for treating a particular child's tumor. "Columbia's program is rooted in science," says Dr. Kung, "and the rich connection between basic science and clinical care allows us to provide cutting-edge care for children with cancer. We are using tomorrow's technologies and leveraging advances in genomics, molecular biology, and cancer biology to identify more precise methods to treat patients today."

New Autism Insights

Two studies investigating facets of autism have honed in on underlying mechanisms of the disease.

In one, David Sulzer, PhD, professor of neurobiology in psychiatry, neurology, and pharmacology, focused his attention on a neurological process akin to that of orchardists pruning the lush spring growth produced by their apple trees. During infancy, synapses—the structures responsible for neural communications—form at a brisk pace. Over the next two decades, biological processes “prune” them by half to optimize cognitive function. “While people usually think of learning as requiring formation of new synapses,” says Dr. Sulzer, “the removal of inappropriate synapses may be just as important.”

Dr. Sulzer and co-author Guomei Tang, PhD, assistant professor of neurology, have a theory of the role of slowed synaptic pruning in autism. They demonstrate evidence of slowed pruning in the brains of children with autism who died of other causes and identify evidence of the underlying mechanism. In children with autism, they found that autophagy—the cell’s recycling and waste management process—seemed impaired. Using a mouse model of autism, the team identified the protein—mTOR—that impedes pruning and tested a drug that ameliorates its effect.

Because large amounts of overactive mTOR were found in almost all of the brains of the autism patients, the scientists hypothesize that the same processes may occur in children with autism. “Hundreds of genes have been linked to autism,” says Dr. Sulzer, “but almost all of our human subjects had overactive mTOR and decreased autophagy, and all appear to have a lack of normal synaptic pruning. Overactive mTOR and reduced autophagy, by blocking normal synaptic pruning that may underlie learning appropriate behavior, may be a unifying feature of autism.”

Dennis Vitkup, PhD, associate professor of systems biology and of biomedical informatics, has conducted a large-scale genomic analysis of hundreds of people with autism spectrum disorder—ASD—to discover how diversity among disease traits can be traced to differences in patients’ genetic mutations.

More damaging genetic mutations usually lead to worse disease outcomes, Dr. Vitkup found. Patients with low verbal or nonverbal IQs usually have



David Sulzer, PhD
Dennis Vitkup, PhD

mutations in genes that are more active in the brain. Individuals with high IQs are less likely to have mutations that completely shut down genes. In fact, mutations that only partially damage normal gene function in the brain appear to be predominantly associated with high-functioning autism cases.

Behavioral variability in autism patients may stem from the types of brain cells affected, and the Columbia researchers have taken the first steps in determining which cell types in the brain are most affected by autism mutations. Dr. Vitkup and colleagues identified these cells by looking at the normal activity of autism-related genes in dozens of similar cell types in mouse brains. The analysis showed that many different types of neurons throughout the brain are affected by mutations in autism genes.

“The idea that eventually all autism mutations would converge onto a single type of neuron or single brain area isn’t what we see in the data,” Dr. Vitkup says. “Instead, an autism mutation usually affects multiple brain areas simultaneously.” Certain neurons, however, appear to be more affected than others. The Columbia researchers found strong effects in cortical and striatal neurons that form a circuit that controls repetitive motions and behaviors, such as rocking, an insistence on sameness, and restricted interests, which are common in people with ASD.

This is a summary of research by Dr. Sulzer published in Neuron, Sept. 3, 2014, and by Dr. Vitkup in Nature Neuroscience, Dec. 22, 2014.



HELP FROM OUR FRIENDS

SIMONS FOUNDATION PLEDGE ADVANCES AUTISM RESEARCH

The Simons Foundation has committed \$7.5 million to support research in autism and developmental disorders. The research will be led by Wendy Chung, MD, PhD, associate professor of pediatrics (in medicine). Dr. Chung is a highly regarded clinical and molecular geneticist and director of Columbia’s clinical genetics program. She will draw on state-of-the-art genomic techniques to pursue a better understanding of the cause of autism and how to treat and support individuals and families with autism spectrum disorder. The gift extends a generous record of support by the Simons Foundation for autism research at Columbia.

Faculty Receive Diversity Grant Awards

Eight P&S faculty members received funding in 2014-15 through the Columbia Provost's Grants Program for Junior Faculty Who Contribute to the Diversity Goals of the University. The program is a component of Columbia's ongoing commitment to faculty diversity.

Columbia announced the commitment of an additional \$33 million this year to continue the expansion of faculty diversity efforts to recruit faculty from underrepresented groups to more closely reflect the composition of the national pool of qualified candidates.

The junior faculty grants program is designed to contribute to the career success of junior faculty who contribute to Columbia's diversity goals. The program has supported 53 projects throughout Columbia since 2013. Applications

are reviewed by a committee of faculty from the Morningside and medical center campuses.

"This program provides pilot grants to help junior faculty on their pathway to tenure and/or promotion," says Dennis Mitchell, DDS, MPH, the University's vice provost for faculty diversity and inclusion. "P&S faculty did spectacularly this year in the competition for these grants, and we are confident that the work being done will benefit the faculty members, our patients, and our diversity goals."

The 25 projects funded during the two 2014-15 funding cycles included eight projects by P&S junior faculty, two of whom joined the Department of Pediatrics this year: Stephanie Lovinsky-Desir, MD, and Jenny K. Rodriguez Francis, MD.

The full list of P&S research projects supported by 2014-15 grants:

Probing Human Islet Alpha Cell Biology With Single-Cell Gene Expression

Xiaojuan Chen, MD, PhD
assistant professor of surgical sciences (in surgery)

Hispanic Adolescent and Parent Discordance about Reproductive Health Trials

Jenny K. Rodriguez Francis, MD, MPH
assistant professor of pediatrics at CUMC

Breast Cancer Among Thyroid Cancer Survivors

Jennifer H. Kuo, MD
assistant professor of surgery

The Impact of Physical Activity Level on Environmental and Epigenetic Mechanisms in Asthma

Stephanie Lovinsky-Desir, MD
assistant professor of pediatrics

The Effects of Inhaled Glucocorticoids on Central Skeleton Structure and Strength in Postmenopausal Latina Women

Emily Stein, MD, MS
assistant professor of medicine

The Role of Ubiquitination in Neurotransmitter Release

Clarissa Waites, PhD
assistant professor of pathology & cell biology and of neuroscience (in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain)

Understanding Gender Differences in Atrial Fibrillation Using a Novel Transgenic Mouse Model

Elaine Wan, MD
Esther Aboodi Assistant Professor of Cardiology (in Medicine)

The Role of Selective Macroautophagy in Neurodegeneration

Ai Yamamoto, PhD
assistant professor of neurology and of pathology & cell biology



Stephanie Lovinsky-Desir, MD

Jenny K. Rodriguez Francis, MD

Booster Shot

The case was dire: An inoperable sarcoma had invaded 16-year-old John Ficken's abdominal wall, pelvis, and bladder. The boy's belly protruded with the growth, and the pain was unrelenting. Yet Mr. Ficken's young surgeon and oncologist, William Coley, harbored cause for optimism: an eponymous (and experimental) bacterial cocktail intended to jumpstart his patient's immune system and eradicate the cancer. Over the course of four months, the New York City physician injected Mr. Ficken's tumor with an increasingly potent dose of Coley vaccine. Each treatment induced inflammation, chills, and fever, but slowly, the tumor shrank. By the time Mr. Ficken's treatment ended in May 1893, the cancer had shrunk by 80 percent. As that summer drew to a close, the tumor was barely perceptible. Mr. Ficken lived another quarter century, until a heart attack killed him in 1919.

A century after Dr. Coley's pioneering work was eclipsed by sterile surgical techniques, radiation, and chemotherapy, scientists have again turned their attention to the role of the immune system in fighting cancer. One of the latest immunotherapies to reach the market is nivolumab, a drug approved by the FDA for the treatment of patients with advanced squamous non-small cell lung cancer, or NSCLC.

Nivolumab rehabilitates the immune system's delicate balance by restoring activity of the T cells. Specifically, the drug disables the PD-1 protein, which suppresses T cell activity. When this "checkpoint" protein is inhibited, T cells can go about their business.

"Groundbreaking" and "revolutionary" often overstate the case, says Naiyer A. Rizvi, MD, director of thoracic oncology and immunotherapeutics, but the words truly apply to the impact of the new immunotherapy agents that target the PD-1 pathway for NSCLC.

Work by Dr. Rizvi was key to approval of nivolumab for squamous lung cancer. "When I first started treating patients with nivolumab in 2008, it was hard to imagine how dramatically this could help patients who were resistant to all of our standard treatments," says Dr. Rizvi. "We have some patients who are still alive many years after taking this drug, with no evidence of



Naiyer A. Rizvi, MD

cancer. This has never been seen with standard lung cancer treatment."

While some patients with NSCLC respond well to PD-1 inhibitors, others do not. Dr. Rizvi and his former colleagues at Memorial Sloan Kettering Cancer Center thought that the cancers that had accumulated the most DNA damage were more likely to have worn out the immune system and would likely be helped the most by PD-1 inhibitors.

They tested their hypothesis by sequencing tumor DNA from both responders and nonresponders to treatment with pembrolizumab, a PD-1 inhibitor. Among their findings was that patients with extensive DNA damage were far more responsive to treatment than those with less

DNA damage. "We were able to use advances in sequencing technology to study the entire exome of tumors from patients with NSCLC who were treated with pembrolizumab. We found that the more genetically damaged the tumor was, the more likely the patient was to respond to PD-1 inhibitors.

"This is an important first step toward being able to predict who will respond to PD-1 inhibitors," says Dr. Rizvi, "and could be a new way to think about precision medicine based on the sequencing of tumor DNA."

This is a summary of research published in Lancet Oncology, March 2015, and Science, April 3, 2015.

Gifts Support Research and Treatment in Neuropathy, Alcohol and Substance Abuse, and Alzheimer's Disease

Taub Family Commits an Additional \$7 Million to Support Alzheimer's Research



The Taub Family

The Henry and Marilyn Taub Foundation has made a new pledge of \$7 million to advance the study and treatment of Alzheimer's disease and related neurodegenerative disorders, renewing the foundation's remarkable commitment to the Taub Institute for Research on Alzheimer's Disease and the Aging Brain.

The Taub Institute was established at Columbia through a gift from the Taub family. The latest gift will support the development and implementation of four core research platforms and an innovation grants program that will foster collaboration and increase efficiency within the institute's research program. These operational improvements will contribute to the continued stability and strong reputation of the Taub Institute as a nationally recognized research center.

\$7 Million Gift to Establish Alcohol and Substance Abuse Treatment Program

The Christopher D. Smithers Foundation has donated \$7 million to establish the Smithers Family Center for Alcohol and Substance Abuse at Columbia.

The center will support efforts by the Department of Psychiatry to advance clinical care, education, and research in alcohol and substance abuse treatment. With an emphasis on individualized clinical care, the center will draw on the latest scientific evidence, as well as training initiatives and new research, to improve the field's ability to treat patients with alcoholism and other substance abuse disorders.

Thompson Family Foundation Pledges \$15 Million to Launch Initiative in Chemotherapy-Induced Peripheral Neuropathy

The Thompson Family Foundation has committed \$15 million to the Department of Neurology to launch a new research initiative into chemotherapy-induced, idiopathic, and other forms of neuropathy. The Thompson Family Foundation Initiative in Chemotherapy-Induced Neuropathy and Sensory Neuroscience will draw on the efforts of physician-scientists across multiple disciplines, including anesthesiology, dermatology, genetics & development, medicine, neurology, neuroscience, pathology & cell biology, physiology & cellular biophysics, the Columbia Translational Neuroscience Initiative, the Herbert Irving Comprehensive Cancer Center, the Motor Neuron Center, and the Gertrude H. Sergievsky Center.

"This is an exciting and highly collaborative project that will illuminate the intersection of several fields, in particular neurology, neuroscience, and oncology," says Richard Mayeux, MD, chair of the Department of Neurology, who will co-lead the initiative along with Serge Przedborski, MD, PhD, and Ellen Lumpkin, PhD. "We are eager to lead this effort and grateful for the Thompson Family Foundation's tremendous generosity." The initiative honors the memory of Wade Thompson, co-founder of Thor Industries.

Cancer Biography: Documentary, Panel Discussion, and Emmy Nomination

Columbia oncologist Siddhartha Mukherjee's biography of cancer, "The Emperor of All Maladies," won a Pulitzer Prize in 2010 and was made into a six-hour PBS documentary this year.

The documentary has now been nominated for an Emmy in the Outstanding Documentary or Nonfiction Series category.

In the weeks leading up to the airing of the documentary on March 30 and 31 and April 1, Dr. Mukherjee, assistant professor of medicine at P&S, and other P&S faculty raised awareness of cancer prevention, treatment, and research. Along with Dr. Mukherjee, participants at a March 24 event in Low Library on the Columbia campus were the documentary's executive producer, Ken Burns; its director, Barak Goodman; journalist and cancer activist Katie Couric; and cancer researchers from Columbia, Johns Hopkins, and UCLA.

The cancer experts at the March 24 panel discussion, which was moderated by Stephen Emerson, MD, PhD, director of the Herbert Irving Comprehensive Cancer Center at Columbia and NewYork-Presbyterian, spoke about the future of cancer research. "In recent years we've learned cancer is not one disease, but hundreds of diseases," said Andrew Kung, MD, PhD, the Robert and Ellen Kapito Professor of Pediatrics and chief of pediatric oncology at Columbia. "Eighty percent of children with cancer are now cured. By sequencing every gene in the cancers of pedi-



Panelists discussing the future of cancer research, from left: Stephen Emerson, Siddhartha Mukherjee, Andrew Kung, Cory Abate-Shen, William Nelson, Gary Schwartz, and Dennis Slamon.

atric patients, we can start chipping away at the remaining 20 percent."

Researchers are looking not only at the genetics, but also at the cell biology of cancer. Dr. Mukherjee described his most recent work investigating the roles played by stem cells in various forms of cancer. The most exciting discovery to come out of his lab recently, he said, is that researchers will be able to find normal stem cells, including a stem cell that seems to build the entire vertebrate skeleton—a skeleton stem cell.

Dennis Slamon, MD, PhD, director of the UCLA Jonsson Comprehensive Cancer Center's clinical/translational research, said, "We are no longer focused on the organ in which a cancer originates. Identifying which genes are broken allows us to determine which pathways are broken. This sounds very logical now, but it represents a major change in thinking from just a few decades ago."

Cory Abate-Shen, PhD, the Michael and Stella Chernow Professor of Urological Sciences and professor of pathology & cell biology, said now that doctors are at the point of being able to identify many cancers at an early stage, the next step is to determine whom to treat. "For example, we've brought a systems approach to decide which prostate cancers need to be treated. We now can test biopsy samples to differentiate between aggressive and harmless tumors."

Gary Schwartz, MD, the Clyde and Helen Wu Professor of Oncology and chief of the division of hematology-oncology, said that the day will come when the physical exam of every cancer patient will include DNA sequencing. "We will have personalized medicine for every patient with cancer in the United States. Without this type of information, we are not giving patients the full benefit of treatment."

One highly promising path in cancer treatment is immunotherapy. Dr. Schwartz told how researchers had noticed that patients with autoimmune diseases do not get cancer. Through immunotherapy, he said, some formerly untreatable cancers go away. He noted the March approval by the FDA of the drug Opdivo (nivolumab) for treatment of advanced squamous non-small cell lung cancer.

William Nelson, MD, PhD, director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, predicted that a smart missile eventually will deliver drugs to where the biomarkers are. "You can see the beginning of precision medicine with the discovery of that first gene. One of the remarkable things about the documentary is that you can't watch it without thinking about where we are going."

A new website that combines information about cancer care and research at Columbia is available at www.columbia.edu/cancer.



Siddhartha Mukherjee and Ken Burns



About the Class of 2015

153 MD graduates,
54 percent of them women

13 also received PhD degrees

5 also have MPH degrees

6 also received MBA degrees
from Columbia

3 also have DDS degrees

1 also received an MS degree
in narrative medicine

28 took an extra year for research

37 percent took an extra year
for either research or to complete
a dual degree

22 percent went abroad for summer or
senior electives or scholarly projects,
mostly to developing countries

20 students got married during
medical school

10 babies were born to students in
the class during medical school

Graduates completed **43** triathlons
or full or half marathons

1/3 of the class volunteered as senior
mentors to incoming medical students

All the students have jobs
after medical school

51 percent will remain in New York state,
mostly in New York City

31 percent matched at Columbia

8 couples participated in the
match, including **5** in which both
were P&S students

New NeuroTechnology Center Fosters Interdisciplinary Neuroscience

The mission of Columbia's new interdisciplinary NeuroTechnology Center is to develop advanced optical, electrical, and computational technologies for the study of complex neurobiological systems. The center draws together researchers from the Kavli Institute for Brain Science, the Mortimer B. Zuckerman Mind Brain Behavior Institute, the Faculty of Arts and Sciences, and the Fu Foundation School of Engineering and Applied Science.

The center is led by Rafael Yuste, professor of biological sciences and of neuroscience and an authority on the development of optical methods in neuroscience. Dr. Yuste, co-director of the Kavli Institute, was the lead author of the initial Brain Activity Map proposal that gave rise to President Obama's BRAIN initiative.

The new center provides scientific and intellectual cohesion to an already existing group of independent researchers in the biological and physical sciences and in engineering and data sciences. It supports and facilitates the education and training

of undergraduates, graduate students, postdoctoral researchers, and faculty on the newest technologies. The center's initial activities are funded by a seed gift from the Kavli Foundation.

Examples of projects within the center's mission are the development of in vivo microelectrode technologies for use in neuroscience and of novel computational methods to analyze large-scale recordings of neuronal activity. These tools and technologies are developed in close integration with researchers in the Zuckerman Institute, who then become users of the technologies.

"The NeuroTechnology Center neatly captures the spirit of Columbia's interdisciplinary approach to the biomedical and physical sciences," says neurobiologist Thomas Jessell, co-director of the Zuckerman Institute. "By bringing together today's technical innovators, the center drives advances in many scientific fields, not least the strengths in the neural sciences represented in the Zuckerman Institute."

2014-15 Precision Medicine Lectures

Columbia's precision medicine initiative hosted a series of distinguished lectures in precision medicine this past year.

The inaugural lecturer, on Dec. 1, was David Goldstein, PhD, who joined Columbia Jan. 1 as director of the new Institute for Genomic Medicine. Dr. Goldstein joined Columbia from Duke University, where he was director of the Center for Human Genome Variation and the Richard and Pat Johnson Distinguished University Professor, with appointments in molecular genetics & microbiology and biology.

Dr. Goldstein spoke on "Genetics & Genomics of Precision Medicine."

The second lecturer in the series was Harold Varmus, MD, then director of the National Cancer Institute and former director of the National Institutes of Health and Memorial Sloan Kettering Cancer Center. He spoke Feb. 19 on "How Cancer Research is Transforming Cancer Control." Dr. Varmus, a 1966 graduate of P&S, shared a Nobel



Goldstein



Varmus

Prize in 1989 for discovery of the cellular origin of retroviral oncogenes.

Richard P. Lifton, MD, PhD, chair of genetics and the Sterling Professor of Genetics and Internal Medicine at Yale University, spoke March 19 on "Genes, Genomes, and the Future of Medicine." Dr. Lifton was named in March to co-chair the Working Group of the Advisory Committee to the NIH Director, a team of experts in precision medicine and clinical research studies who are charged with soliciting opinions and developing a vision for President Obama's precision medicine initiative.

New Chairs for Two Departments

New chairs were named this year for the Department of Urology and the Department of Pathology & Cell Biology.

James McKiernan, MD, a longtime member of the urology faculty at P&S, was named chair of the Department of Urology and the John K. Lattimer Professor of Urology. Formerly the George F. Cahill Professor of Urology, Dr. McKiernan served as interim chair for a year.

Dr. McKiernan, a graduate of P&S, trained at NewYork-Presbyterian and Memorial Sloan Kettering Cancer Center. He specializes in urologic oncology.

Kevin Roth, MD, PhD, has been named chair of the Department of Pathology & Cell Biology and pathologist-in-chief at NewYork-Presbyterian/Columbia University Medical Center, effective Sept. 1, 2015. Dr. Roth succeeds Michael Shelanski, MD, PhD, chair of the department for 28 years.



James McKiernan, MD



Kevin Roth, MD, PhD

Dr. Roth was recruited from the University of Alabama at Birmingham, where he chaired the Department of Pathology. His research focuses on neuronal cell death regulation and neuropathology, including attempts to define the molecular pathways regulating apoptotic and nonapoptotic neuronal cell death and neuron loss in Alzheimer's disease and Parkinson's disease. His MD and PhD degrees in neuroscience are from Stanford University.

New Degree: MD/MS in Biomedical Sciences

P&S students now have an opportunity to pursue a new dual degree, the MD/MS in Biomedical Sciences. The program was inspired by the success of the P&S curriculum's scholarly projects program that pairs medical students in their last phase of education with faculty mentors to conduct four or more months of scholarly work in one of six tracks. The new degree will allow students to take their scholarship farther by adding specific training in research to the students' medical education and crafting an original, publication-worthy thesis during a full year of research leading to the conferral of a master's degree with the MD.

"This program integrates research and clinical training," says Jennifer Punt, VMD, PhD, senior associate dean for student research during the degree's planning stages. "It doesn't replace the scholarly projects program; it fills a gap on the continuum between that and the MD/PhD program. It reflects our awareness of several cohorts of medical students who do not join MD/PhD programs but are still poised to contribute substantively and creatively to medical scholarship and advances."

Students may complete the 32-credit curriculum in four or five years, depending on the amount of clinical exposure they require. In addition to completing traditional medical studies and clinical rotations, students will join a medical scholars seminar to develop both research skills

and a community of scholarly peers. They also will engage in a distinctive didactic program that allows them to customize their training according to their developing interests. One feature of this is a unique open-campus requirement where students attend and report on a series of seminars of their choosing over a yearlong period. This encourages exposure to the breadth of talent, diversity of interests, and network of possible mentors throughout Columbia University.

A cornerstone of the new program is the master's thesis, a dissertation of original research each student will defend. After students commit to a mentor, they form a master's thesis committee that will review students' proposals, research progress, and thesis drafts. "A thesis is your product, even more than a paper," says Dr. Punt. "The ownership you feel is a different transformative experience intellectually."

The MD/MS program reflects the vision of Lee Goldman, MD, P&S dean. "It was Dean Goldman's intent to capture the research energy here to train the physician thinkers and scholars for the 21st century," says Dr. Punt. Curriculum planners first thought of reviving the MSD (doctor of medical science) degree, a program that was discontinued in the 1980s. "But after we reviewed the program, we realized it didn't really represent what was needed at the medical student level. So we started from scratch.

"This was a group effort," adds Dr. Punt. Over the course of a year she studied similar dual-degree programs around the country, worked with P&S education deans and scholarly project track directors, and consulted Columbia faculty members who represented a range of clinical and scholarly disciplines. The program proposed was presented to governing bodies at both CUMC and Columbia University, as required of any new degree program. "The review was lengthy because we wanted a program that was rigorous and that did not compromise the quality of content, the value of the experience for students, or the reputation of Columbia." The new degree was approved by New York's state education department in the spring of 2015 and only awaits the final approval for federal financial aid.

Program leaders expect 10 percent of each incoming class—about 15 students—to pursue the degree within five years. Other students will likely continue to choose an additional year of research, as about 20 percent of each class does now.

"There is a concern that the pool of physician-scientists is shrinking," says Dr. Punt. "This program allows students to think in a patient-oriented way while still doing in-depth research, without necessarily pursuing a PhD. It is designed to capture the intellectual energy and imagination of the remarkable students who join the P&S community."

Alliance Supports Genetic Discovery Research

Columbia University Medical Center and Biogen Idec, the world's oldest independent biotechnology company, have formed a \$30 million strategic alliance to conduct genetics discovery research on the underlying causes of disease and to identify new treatment approaches. As part of this agreement, a sequencing and analysis facility and shared post-doctoral program will support collaborative genetics research. The agreement integrates genomics research conducted at Columbia with Biogen Idec's

understanding of disease mechanisms and pathways and the company's expertise in discovering new medicines.

The collaboration enables Biogen Idec and Columbia to investigate the genomes of patients showing unusual treatment responses or unique disease presentations and to explore the connections among genes, pathways, and disease processes. The ultimate goal is to provide multiple qualified targets for new therapeutic

approaches, increasing the potential for the development of new treatments.

The new facility will have broad genetic research capabilities and the capacity to launch and complete whole-genome sequencing projects rapidly. It will allow for rapid population-scale DNA sequencing across a broad range of disease areas, focusing on diseases with significant unmet clinical need such as amyotrophic lateral sclerosis and idiopathic pulmonary fibrosis.



Dalla-Favera



Rothstein



Karsenty



Shadlen



Vunjak-Novakovic



Cimino

Faculty Elected to National Academies

Two P&S faculty were elected in April to the National Academy of Sciences, and three other full-time faculty members were elected to the National Academy of Medicine (formerly known as the Institute of Medicine).

Riccardo Dalla-Favera, MD, and Rodney Rothstein, PhD, were elected to the National Academy of Sciences.

Dr. Dalla-Favera is the Joanne and Percy Uris Professor of Clinical Medicine and professor of pathology & cell biology, genetics & development, and microbiology & immunology. He also is director of the Institute of Cancer Genetics. A distinguished investigator in the molecular genetics of cancer, Dr. Dalla-Favera has been an international leader in the field of lymphoid neoplasia for the past 30 years. He is also a member of the National Academy of Medicine.

Dr. Rothstein is professor of genetics & development and of systems biology. He has pioneered the use of recombination to alter genomes and has used these methods to isolate novel genes involved in the maintenance of genome stability. He is also a fellow of the American Academy of Arts & Sciences.

Three full-time faculty members—Gerard Karsenty, MD, PhD, Michael Shadlen, MD, PhD, and Gordana Vunjak-Novakovic, PhD—were elected to the National Academy of Medicine, known as the Institute of Medicine until a name change this year. Adjunct professor James J. Cimino, MD, also was elected.

Dr. Karsenty is the Paul A. Marks Professor of Genetics & Development, professor of medicine, and chair of the Department of Genetics & Develop-

ment. He has used clinical data, evolutionary history, and mouse genetics to study all aspects of skeletal biology.

Dr. Shadlen, professor of neuroscience, is also an investigator of the Howard Hughes Medical Institute and a member of Columbia's Mortimer B. Zuckerman Mind Brain Behavior Institute. He investigates the neural basis of decision-making and cognition by studying neurons that process information to give rise to interpretations, decisions, and plans for behavior.

Dr. Vunjak-Novakovic is the Mikati Foundation Professor of Biomedical Engineering and professor of medical sciences (in medicine). She also directs the Laboratory for Stem Cells and Tissue Engineering, which works on engineering human tissues for application in regenerative medicine, stem cell research, and disease modeling. She was the first woman from Columbia University to be elected to the National Academy of Engineering.

Dr. Cimino, adjunct professor of biomedical informatics, is a former professor of biomedical informatics and medicine at P&S. He is now chief of the Laboratory for Informatics Development at the NIH Clinical Center and the National Library of Medicine.

On July 1, 2015, the National Academy of Medicine joined the National Academy of Sciences and the National Academy of Engineering as the third academy overseeing the program units of the National Academies of Sciences, Engineering, and Medicine ("the Academies"). Election to the National Academy of Sciences, National Academy of Engineering, or National Academy of Medicine is considered to be among the highest professional honors for scientists, engineers, and health professionals.

Medical and Graduate Education Building

Even before the foundation was poured, the new Medical and Graduate Education Building rising on Haven Avenue attracted attention and awards. The glass tower has entered its final year of construction and is on schedule to open in 2016 in time for the Class of 2020 to use its high-tech classrooms, advanced simulation center, anatomy lab, collaborative and quiet study spaces, student commons areas, and surrounding green space.

As the building has gone up this past year, members of the P&S community participated in the project by signing two beams that were used to top off the building last October to complete the facility's superstructure. Installation of the building's façade has continued since then.

Several P&S students signed the beams and also participated in the project by trying out chairs being considered for the building's auditorium. Facilities Management set up a row of six cushioned, classroom-style chairs for students to try on for size and comfort. The students sat down, stretched out their legs, and gave feedback on the feel of the cushions, the leg room between rows, and the fold-out desks where students will set up notebooks and laptops.

More than 100 individuals representing more than 30 contracted firms have been working on the building since late summer 2013. The building's 14 stories will tower approximately 223 feet above ground. In addition to classrooms, simulation center, and learning spaces, the 100,000-square-foot interior will have lounges and a café.

The cutting-edge building with its cascading glass façade will act as a social/gathering space for student life and as a campus and neighborhood beacon. Its pioneering design, featured in



Construction as of July 2015

a number of publications, has been described as “eye-catching” and “a major landmark in the skyline of northern Manhattan.” The building also has been applauded for its green construction: The construction allows optimal daylight into classroom and public spaces and uses sustainable features, including light pollution reduction, conservation of a site's natural elements, water savings, and indoor environmental quality.

The building is located at the intersection of Haven Avenue and West 171st Street.

In December the building received the 53rd Annual Roger H. Corbetta Award from the

Concrete Industry Board. The award is given for projects that exemplify excellence in concrete in their architectural design, engineering design, general construction, and workmanship. The award was presented to the CUMC Capital Project Management team, design architect Diller Scofidio + Renfro, executive architect Gensler, structural engineer Leslie E. Robertson Associates, and construction manager and general contractor Sciam Construction.

Monthly updates on construction are provided at the building's website, www.educationbldg.cumc.columbia.edu/.





**Columbia University Trustees
Committee on the Health Sciences**

Kenneth A. Forde, MD, *Chair*
Rolando Acosta
Andrew Barth
Noam Gottesman
Mark Kingdon
Vikram Pandit
Michael Rothfeld

CUMC Board of Advisors

Keith T. Banks
Michael Barry
Stanley M. Bergman
Gary B. Bettman
E. Garrett Bewkes III
Eugene Braunwald, MD
Dana Buchman
John A. Catsimatidis
Neil L. Cohen
F. Jonathan Dracos
John L. Eastman
Loren Eng
Daniel D. Federman, MD,
Emeritus Member
Marjorie Harrison Fleming
Kenneth A. Forde, MD
Carl Frischling
Lee Goldman, MD
Marc D. Grodman, MD
Gerald L. Hassell
Ara K. Hovnanian
Michael Jaharis
Ilan Kaufthal
Thomas L. Kempner Jr.
Karen A. Kennedy, MD
Jonathan S. Leff
Ellen Levine
A. Michael Lipper
Paul J. Maddon, MD, PhD
Robert F. Mancuso
Paul A. Marks, MD,
Emeritus Member
Philip L. Milstein
Joseph M. Murphy
Lawrence Neubauer
Mark H. Rachesky, MD
John W. Rowe, MD
Kathe A. Sackler, MD
Peter Sacripanti
Thomas P. Sculco, MD
G. Lynn Shostack
Frank V. Sica
Richard Silverman
Dinakar Singh
Andrew Solomon, PhD
Sarah Billingham Solomon
Leonard Tow, PhD
Savio Tung

P. Roy Vagelos, MD
Joseph A. Walker
Deborah Weinberg
Peter A. Weinberg
Torsten Wiesel, MD
Richard E. Witten
Clyde Y.C. Wu, MD
George D. Yancopoulos, MD, PhD

Cancer Advisory Council

Richard E. Witten, *Chair*
Jacques Brand
Susan Brecker
Neil L. Cohen
Thomas W. Cornacchia
Dina Dublon
Joseph M. Forgione
Betsy Hilfiger
Marc Hurlbert, PhD
Lisa Keller
Marjorie Magner
Susan S. Mirza
Lisa Witten

Cardiac Council

Peter Sacripanti, *Chair*
E. Garrett Bewkes III
Jerome Chazen
Maurice Cuniffe
Gerald L. Hassell
Michael Jesselson
Kenneth Lerer
Bryan Marsal
Philip L. Milstein
Arthur Pergament
Jacob Richter, PhD
Jay L. Schottenstein
David Stern

Children's Board at Columbia

Karen A. Kennedy, MD, *Chair*
Gail Albert-Halaban
Lisa Applebaum Haddad
Dana Baumgarten
Joshua Baumgarten
Deanna Berkeley
James Berkeley
Tania Brief
Bhanu Choudhrie
Dhairya Choudhrie
Karina Choudhrie
Simrin Choudhrie
Leo T. Clark
Jennifer Tarr Coyne
John F. Crowley
Mark F. Dehnert
Mindy Nam Dehnert
Erica Dewan

Andrew Ehrlich
Dana Farrington
Lee Galvis
A. Drew Goldman
Boaz Halaban
Lee Helman
Andrea Hsu
Dana Roberson Johnson
Joseph J. Johnson III
Cynthia Kempner
Jamie Kempner
Kevin W. Kennedy
Pamela W. Kernie
Erica Alexander Martini
Ariane Matschullat
Clare Matschullat
Robert Matthews
Sue Matthews
Amy Mulderry
Jillian Neubauer
Lawrence Neubauer
Colleen Olson
Tagar Olson
Ellen Oppenheim
Jeffrey A. Oppenheim
Daphne Oz
Gabriela Palmieri (*for the
Choudhrie Family*)
Katherine Phillips, PhD
Jennifer I. Ratner, MD
Allan Reine
Amy Schulhof
Alex Silver
Brian Silver
Jamie Silver
Donna Vitale
John Workman
Susan York
Tucker York

**Columbia-Presbyterian
Health Sciences Advisory Council**

Jeremiah A. Barondess, MD
Gerard Bilotto, PhD, Esq.
Joan O. Camins
John K. Castle
Rhoda B. Cohen
Ron Cohen, MD
Sue E. Dalsemer
James J. Daly
Robert K. Dresing
Joanne Duhl
Josephine M. Eastman
Katama Eastman
Burt Ehrlich
Abigail Black Elbaum
Richard A. Elias, MD
Loren Eng
Gloria Farber, EdD

John H. Friedman
Susan Fuirst
Louis R. Gary
David A. George
Philip Goelet, PhD
Sandra O. Gold, EdD
Jay S. Goldsmith
Gloria F. Gottlieb
Martin B. Greenberg
Stuart P. Greenspon
Ernest L. Haas
Robert M. Harris
Daniel O. Hauser, PhD
Helen Skade Hintz
Burton P. Hoffner, MD
Marc Hurlbert, PhD
Herbert Irving
Thomas Campbell Jackson
Barbara Jonas, MSW
Janis W. Jones
Patsy L. Kahn
Albert Kalter, Esq.
Cindie D. Kastenbaum
Henry L. King
E. Peter Krulewitch
Missy Chase Lapine
Deanna Levine
Constance E. Lieber
Richard M. Lipkin
Phyllis Mailman
Lloyd A. Mallah
John H. Manice
Paul A. Marks, MD
Ariane M.H. Matschullat
Guri McKinnell
James B. Metzger
Constance J. Milstein, Esq.
Gerald Modell
Shelby Modell
Jo Ann Mazzella Murphy
Joseph M. Murphy
Fred F. Nazem
Lawrence Newman
Peter Norton
Gordon B. Pattee
Ponchitta Pierce
John H. Pinto
Stuart J. Rabin
Arlene Radbell
Audrey Schein
Mark Schwartz
Steven Segal
G. Lynn Shostack
Wilma Bulkin Siegel, MD
Robert Silbey, MD
Amy Shorin Silverstein
Ellen Strahl
Lynn Chernow Streim
Suzanne Sunshine
Leonard J. Tanzer

Jeff C. Tarr
 Vincent S. Tese
 John N. Tognino
 Doris F. Tulcin
 Gerard M. Turino, MD
 Tom Valenti
 George A. Violin, MD
 Kathleen Walas
 Robin L. Walters
 Susan Granat Weil
 Dayna J. Wilkinson
 Joseph D. Williams
 Clyde Y.C. Wu, MD

SENIOR ADMINISTRATION, COLUMBIA UNIVERSITY MEDICAL CENTER

Columbia University

Lee C. Bollinger, JD
President of the University

John H. Coatsworth, PhD
Provost of the University

Lee Goldman, MD
*Executive Vice President and
 Dean of the Faculties of Health
 Sciences and Medicine and
 Chief Executive of Columbia
 University Medical Center*

G. Michael Purdy, PhD
Executive Vice President for Research

Columbia University Medical Center

Lee Goldman, MD
*Dean of the Faculties of Health
 Sciences and Medicine and
 Chief Executive of Columbia
 University Medical Center*

Bobbie Berkowitz, PhD, RN
*Senior Vice President, CUMC
 Dean, School of Nursing*

Linda P. Fried, MD, MPH
*Senior Vice President, CUMC
 Dean, Mailman School of
 Public Health*

Christian S. Stohler, DMD,
 DrMedDent
*Senior Vice President, CUMC
 Dean, College of Dental Medicine*

Development

Lynne Roth, BA
Senior Vice President

Finance

Joanne M.J. Quan, MA
*Senior Vice President/
 Chief Financial Officer*

Wil McKoy, MBA
Vice President, Budget and Planning

Francine Caracappa, MBA, CPA
Controller

Operations

Mark McDougale, MPH
*Senior Vice President/
 Chief Operating Officer*

Amador Centeno, MS
*Vice President, Facilities
 Management and Campus Services*

Ross Frommer, JD
*Vice President, Government and
 Community Affairs*

William Innes, MS
Chief Human Resources Officer

Douglas Levy, JD, MS
Chief Communications Officer

Robert V. Sidel, MD
Chief Information Officer

General Counsel

Patricia Sachs Catapano, JD
Associate General Counsel

Senior Administration, College of Physicians & Surgeons

Lee Goldman, MD
Dean

Anne Taylor, MD
Vice Dean, Academic Affairs

Martha Hooven, MPA
Vice Dean, Administration

Steven Shea, MD
Senior Vice Dean, Affiliations

George A. Cioffi, MD
*Vice Dean, Clinical Affairs, and
 President, ColumbiaDoctors*

Education

Ronald E. Drusin, MD
Vice Dean

Lisa Mellman, MD
*Senior Associate Dean for
 Student Affairs*

Hilda Y. Hutcherson, MD
*Senior Associate Dean for Diversity
 and Multicultural Affairs*

Maurice Wright, MD
*Senior Associate Dean,
 Harlem Hospital*

Jonathan Amiel, MD
Associate Dean for Curricular Affairs

Stephen Nicholas, MD
Associate Dean for Admissions

Arthur G. Palmer III, PhD
Associate Dean for Graduate Affairs

Jennifer Punt, VMD, PhD
Associate Dean for Student Research

Noel Robin, MD
*Associate Dean,
 Stamford Health System*

Henry Weil, MD
*Associate Dean,
 Bassett Healthcare*

Research

Robert Kass, PhD
Vice Dean

Joanne Berdebes, MPH
*Associate Vice Dean for Research
 Administration and Finance*

Alumni Relations and Development

Anke Nolting, PhD
*Associate Dean and
 Executive Director*

Executive Committee of the Faculty Council, 2014-2015

Andrew Eisenberger, MD
*Assistant Professor of Medicine
 at CUMC*

Vincent Ferrera, PhD
*Associate Professor of Neuroscience
 (in Psychiatry)*

Mary Flood, MD, PhD
*Associate Professor of Medicine
 at CUMC*

Ivaylo Ivanov, PhD
*Assistant Professor of
 Microbiology & Immunology*

Donald Landry, MD, PhD
*Samuel Bard Professor of Medicine
 and Chair, Medicine*

Jennifer Levine, MD
*Assistant Professor of Pediatrics
 at CUMC*

William Levine, MD
*Frank E. Stinchfield Professor of
 Orthopedic Surgery at CUMC
 and Chair, Orthopedic Surgery*

Richard Mayeux, MD
*Gertrude H. Sergievsky Professor of
 Neurology, Psychiatry, and
 Epidemiology (in the Gertrude H.
 Sergievsky Center and in the Taub
 Institute for Research on Alzheimer's
 Disease and the Aging Brain) and
 Chair, Neurology*

Michael Shelanski, MD, PhD
*Delafield Professor of Pathology
 & Cell Biology (in Neuroscience
 and in the Taub Institute for Research
 on Alzheimer's Disease and the
 Aging Brain) and Chair, Pathology
 & Cell Biology*

Robert Sidel, MD
*Associate Professor of Biomedical
 Informatics at CUMC*

Karen Soren, MD
*Associate Professor of Pediatrics
 and Population and Family Health
 at CUMC*

Department Chairs

Anesthesiology
 Margaret Wood, MD

Biochemistry &
 Molecular Biophysics
 Tom Maniatis, PhD

Biomedical Informatics
 George Hripcsak, MD

Dermatology
 David R. Bickers, MD

Genetics & Development
 Gerard Karsenty, MD, PhD



Medicine
Donald W. Landry, MD, PhD

Microbiology & Immunology
Sankar Ghosh, PhD

Neurological Surgery
Robert A. Solomon, MD

Neurology
Richard Mayeux, MD

Neuroscience
Steven A. Siegelbaum, PhD

Obstetrics & Gynecology
Mary E. D'Alton, MD

Ophthalmology
George A. Cioffi, MD

Orthopedic Surgery
William N. Levine, MD

Otolaryngology/Head & Neck Surgery
Lawrence Lustig, MD

Pathology & Cell Biology
Michael L. Shelanski, MD, PhD

Pediatrics
Lawrence R. Stanberry, MD, PhD

Pharmacology
Robert S. Kass, PhD

Physiology & Cellular Biophysics
Andrew R. Marks, MD

Psychiatry
Jeffrey A. Lieberman, MD

Radiation Oncology
Lawrence H. Schwartz, MD
Interim Chair

Radiology
Lawrence H. Schwartz, MD

Rehabilitation &
Regenerative Medicine
Joel Stein, MD

– Programs in Occupational Therapy
Janet Falk-Kessler, EdD
Director

– Program in Physical Therapy
Debra Clayton-Krasinski, PhD
Director

Surgery
Craig R. Smith, MD

Systems Biology
Andrea Califano, PhD

Urology
James M. McKiernan, MD

University Centers and Institutes and Directors

Naomi Berrie Diabetes Center
Robin S. Goland, MD
Rudolph L. Leibel, MD

Center for Computational Biology
and Bioinformatics (C2B2)
Andrea Califano, PhD
Barry Honig, PhD

Center for Family and
Community Medicine
Richard Younge, MD

Center for Motor Neuron
Biology and Disease
Darryl De Vivo, MD
Serge Przedborski, MD, PhD
Hynek Wichterle, PhD

Translational Neuroscience Initiative
Serge E. Przedborski, MD, PhD

Center for Psychoanalytic
Training and Research
Eric R. Marcus, MD

Center for Radiological Research
David Brenner, PhD, DSc

Center for the Study of Society
and Medicine and Center on
Medicine as a Profession
David J. Rothman, PhD

Center for Translational Immunology
Megan Sykes, MD

Institute for Cancer Genetics
Riccardo Dalla-Favera, MD

Institute of Comparative Medicine
Brian Karolewski, VMD, PhD

Institute of Human Nutrition
Richard J. Deckelbaum, MD

Herbert Irving Comprehensive
Cancer Center
Stephen G. Emerson, MD, PhD

Irving Institute for Clinical and
Translational Research
Henry N. Ginsberg, MD

Kavli Institute for Brain Science
Eric Kandel, MD

Gertrude H. Sergievsky Center
Richard Mayeux, MD

Taub Institute for Research
on Alzheimer's Disease and
the Aging Brain
Richard Mayeux, MD
Michael L. Shelanski, MD, PhD

Clyde and Helen Wu Center
for Molecular Cardiology
Andrew Marks, MD

P&S Hospital Affiliations

NewYork-Presbyterian Hospital,
New York, NY

New York State Psychiatric Institute,
New York, NY

Harlem Hospital,
New York, NY

James A. Peters Veterans
Administration Hospital,
Bronx, NY

Mary Imogene Bassett Hospital,
Cooperstown, NY

Stamford Hospital,
Stamford, CT

Helen Hayes Hospital,
West Haverstraw, NY

Lawrence Hospital,
Bronxville, NY

2015 Annual Report

Editor: Bonita Eaton Enochs

Principal Writer: Sharon Tregaskis

Contributing Writers: Andrea Crawford, Alla Katsnelson

Art Director: Eson Chan

**Produced by the Communications Office at Columbia
University College of Physicians & Surgeons**

Catherine Freeland, Assistant Vice Dean,
Marketing & Strategic Communications

**Office of the Chief
Executive and Dean of
the Faculties of Health
Sciences and Medicine**

Columbia University
Medical Center
630 W. 168th St.
New York, NY 10032

Communications Office

College of Physicians & Surgeons
701 W. 168th St., Box 153
New York, NY 10032
Phone: 212-305-3900
Fax: 212-305-4521

Office of Development

Columbia University
Medical Center
630 W. 168th St., P&S 2-421
New York, NY 10032
Phone: 212-342-0088

FACTS & STATISTICS, FY15

MEDICAL SCHOOL ENROLLMENT, FALL 2014

Total medical school enrollment	648
Enrollment of underrepresented minorities	142
Enrollment of minorities	246
Enrollment of international/nonresident students	16
Enrollment of in-state residents	213
Enrollment of men	317
Enrollment of women	331

ENROLLMENT BY YEAR

	MALE	FEMALE
First-Year Class	80	77
Second-Year Class	83	86
Third-Year Class	78	85
Fourth-Year Class	76	83
Total Enrollment	317	331

MEDICAL SCHOOL ETHNICITIES

Nonresident aliens	16
Hispanic/Latino	66
Black or African-American, non-Hispanic/Latino	53
White, non-Hispanic/Latino	330
American Indian or Alaskan Native, non-Hispanic/Latino	1
Asian, non-Hispanic/Latino	104
Two or more races, non-Hispanic/Latino	21
Race and/or ethnicity unknown	56

OTHER STUDENTS

MD/PhD students	120
PhD students	310
Other students (PT, OT, Nutrition, Informatics)	460

DEGREES GRANTED, JULY 2014 TO JUNE 2015

MD	153
PhD	48
Doctor of physical therapy	59
MS in nutrition	80
MS in occupational therapy	52
Certificate in psychoanalysis	3

APPLICATIONS (ENTERING CLASS 2014)

Number of applicants	7,531
Number of applications considered	7,259
Number of applicants interviewed	1,064
Number of acceptance letters issued	297
Number of new entrants	157
Bassett Program applications	688
Number of new Bassett Program entrants	10

FACULTY, 2014-2015 ACADEMIC YEAR

	FULL TIME	PART TIME
Number of clinical faculty	1,649	2,061
Number of basic sciences faculty	231	76

FACULTY HONORS

Nobel Prize in Medicine	2
National Academy of Sciences	19
National Academy of Medicine*	47
American Academy of Arts and Sciences	25
Howard Hughes Medical Institute	12

*FORMERLY THE INSTITUTE OF MEDICINE

FINANCIALS, FY15 (except where noted)

Budget	\$1.6 billion
Philanthropic support	\$269 million
Endowment	\$1.8 billion
Endowed chairs/professorships	240
NIH research support (FY 2014)	\$311.8 million



COLUMBIA UNIVERSITY
*College of Physicians
and Surgeons*

630 WEST 168TH STREET
NEW YORK, NY 10032

Non-Profit Org.
U.S. Postage
Paid
New York, NY
PERMIT NO. 3593

To Be Precise:

INVESTIGATORS TAKE A NEW TACK IN THE QUEST
FOR PERSONALIZED TREATMENTS

“

The key is to connect the genetics
of disease with the underlying
biology and use that knowledge to
develop new therapies.”

— Tom Maniatis, PhD



8



14

Learning Medicine By Reaching Around the World:

P&S STUDENTS GAIN AN INTERNATIONAL
PERSPECTIVE THROUGH LECTURES, SCHOLARLY
PROJECTS, FOREIGN EXCHANGES

“

These experiences touch very deeply
the core values that bring you into
caring for others.”

— Stephen Nicholas, MD

From Printer to Patient:

P&S CLINICIANS USE 3-D PRINTERS
TO ENHANCE PATIENT OUTCOMES

“

We see a world where, a few years from
now, when we see a patient with a
hole in his or her heart, we will be able
to visualize it and maybe even print
a device that will go into the child's
heart, sized exactly as needed.”

— Anjali Chelliah, MD



20