P&S 246 Years Strong

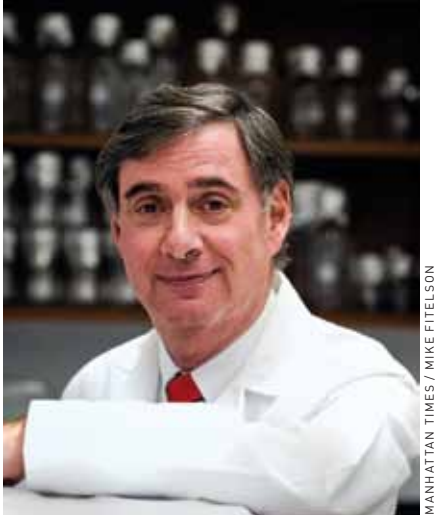
Columbia Medicine

2013 ANNUAL REPORT

Columbia University College of Physicians & Surgeons

FUSED GENES, MOUSE MODELS, EXOME SEQUENCING

Columbia Researchers Explore New Techniques to Understand Cancer



MANHATTAN TIMES / MIKE FITELSON

Toward Greater Heights at Washington Heights

This past academic year at Columbia's College of Physicians & Surgeons has been a remarkable testament to the progress that can be achieved when faculty, staff, students, and supporters work together. We are about to embark on the implementation phase of our framework for that progress, the strategic plan approved by the Columbia Trustees last year. The plan, called "2020 Vision," details ways in which we can strengthen our research, education, patient care, and community service missions.

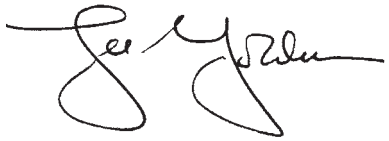
The goals, strategies, and tactics articulated in our strategic plan build on our already strong foundation and leverage the remarkable forward momentum here at P&S over the past several years. As you read more about the plan inside this 2013 annual report, you will see our strategic plan at work in some of the year's achievements and milestones:

- Tom Maniatis, PhD, the Isidore S. Edelman Professor and Chair of Biochemistry & Molecular Biophysics, was awarded the 2012 Lasker-Koshland Special Achievement Award in Medical Science. Dr. Maniatis and two other P&S department chairs—George Hripcsak, MD (Biomedical Informatics), and Steven A. Siegelbaum, PhD (Neuroscience)—were elected to the Institute of Medicine, bringing our total IOM membership to 38. Dr. Siegelbaum also was elected this year to the American Academy of Arts and Sciences. Columbia developmental neurobiologist Thomas Jessell, PhD, received the 2013 Edward M. Scolnick Prize in Neuroscience from MIT's McGovern Institute for Brain Research. Pulitzer Prize winner Siddhartha Mukherjee, MD, assistant professor of medicine, received the 2013 Memorial Sloan-Kettering Medal for Outstanding Contributions to Biomedical Research.
- ColumbiaDoctors Midtown opened in January to rave reviews from patients and physicians. The new location, at 51 W. 51st St. in Manhattan, has 25 percent more space than our prior location on the Upper East Side, with room to grow comprehensive medical services in every department. The location will be an important new portal for patients to access the network of physicians in the ColumbiaDoctors practice as it expands throughout the New York metropolitan area.
- We remain committed to programs that enhance the professional development of our students as future physicians and scientists. A centerpiece of the new P&S curriculum is a scholarly project that allows each student to pursue an area of special interest. As you will read inside this report, that pursuit also strengthened relationships between students and faculty mentors. To increase the number of academic physician-scientists, we also have begun a new program that allows scientists with PhDs to earn an MD in three years. The first four students in that program have enrolled for the 2013-14 year.

While we celebrate our achievements of 2013, we remain concerned about the federal "sequester" of research funding. The government's cuts translated into reductions of $15 million for P&S alone in the past fiscal year.

The uncertainties in federal funding make philanthropy even more important to our ability to fulfill our commitments. We are enormously grateful to our supporters and friends, who sustained our momentum by donating more than $200 million this year to our education, research, and clinical care programs. These gifts included contributions of $27 million toward our new medical and graduate education building, for which we had a groundbreaking celebration on Sept. 16. Other large gifts included $25 million for promising investigations of ALS and $7 million for the Weinberg Family Cerebral Palsy Center. Read more in this annual report about programs supported by these gifts.

Our success in the past academic year has been a true team effort. I am proud to take this opportunity to thank everyone who continues to support our progress toward our 20/20 vision.



Lee Goldman, MD

On the Cover:
A unique genetic fusion causes about 3 percent of the cases of g... fatal malignant brain tumor. The red shows the abnormal accumulati... protein in human glioblastoma stem cells isolated from a primary human g... cellular nuclei are blue. Drs. Antonio Iavarone and Anna Laso... identified t... and continue research that could result in personalized ther... tients with ... type of brain tumor. Image courtesy of Anna Lasorella and...

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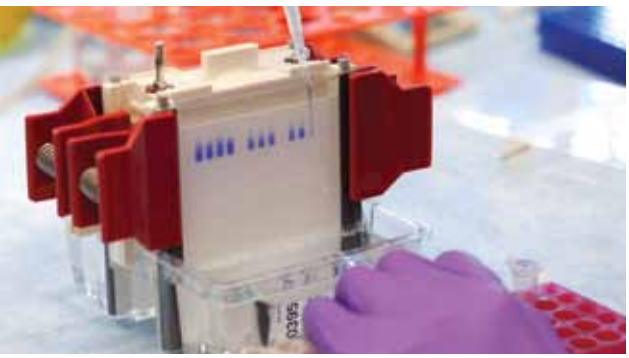
Research

on diabetes, ALS, and transplantation science



HELP FROM OUR **FRIENDS**

Real estate developer **Mortimer B. Zuckerman** has pledged $200 million to endow Columbia s interdisciplinary Mind Brain Behavior Institute, headed by P&S faculty Thomas Jessell, Richard Axel, and Eric Kandel. The institute will be housed at the 450,000 square foot Jerome L. Greene Science Center under construction on Columbia s Manhattanville campus.

"There are no quick shots on goal for translational research. You only get there with the very best biology and most rigorous testing possible."

— Christopher Henderson, PhD, co-director of the Project A.L.S./ Jenifer Estess Laboratory for Stem Cell Research

Alternative Research

A Doctor Tracks a New Approach to Diabetes

Type 2 diabetes turns each meal into a game of Russian roulette. Instead of holding blood sugar levels steady as appetite grows and then wanes through the course of a day, the insulin-producing ß cells nestled deep within the pancreas go haywire. Blood sugar spikes and plummets. By way of intervention, health care professionals champion a litany of lifestyle changes—weight loss, dietary controls, and exercise. When willpower fails, a few medications that tweak pancreatic function or increase the body's ability to respond to pancreatic hormones serve as a stopgap. When those fail, daily insulin injections supply what the pancreas no longer can.

"Existing treatments, even in the hands of the most capable physicians, are imperfect," says Domenico Accili, MD, the Russell Berrie Foundation Professor of Diabetes (in Medicine) and director of the Columbia University Diabetes Research Center. "For type 2 diabetes, it has been a mainstay of treatment to induce more insulin production by the ß cells. But it doesn't improve the course of the disease and, if anything, seems to accelerate it."

For more than 30 years, Dr. Accili—Mimmo, among friends—has combined patient care with a relentless search for a cure to restore each person's ability to regulate glucose levels without the insulin-producing drugs that may do more harm than good.

Ask Dr. Accili's colleagues about his scientific mind and words like *meticulous*, *knowledgeable*, and *pioneering* come up. *Alternative* is missing from the list, but the word fits with Dr. Accili's tendency to question dogma in diabetes research.

"As Louis Pasteur said, 'Chance favors the prepared mind,'" says Rudolph Leibel, MD, the Christopher J. Murphy Memorial Professor of Diabetes Research and co-director of the Naomi Berrie Diabetes Center. "When unexpected observations emerge, Mimmo has the intellectual horsepower to realize they shouldn't be dismissed as a mistake or artifact and proposes ways to nail down their relevance."

That quality was a big factor in leading to some of Dr. Accili's newest findings, which have overthrown popular theories about β cells in type 2 diabetes and may ultimately transform the way the disease is treated.

In the phase leading up to full-blown diabetes, ß cells go into overdrive, churning out ever more insulin in a futile attempt to redistribute the glucose flooding the bloodstream. The volume of insulin rises to a crescendo even as the cells that take up glucose become deaf to the clamor. Eventually, the ß cells just give up and insulin production plummets.

Conventional wisdom said the ß cells must be dead, but Dr. Accili was not entirely convinced. "When people with diabetes experience major weight loss, or have a regimented diet," he says, "they partly recover their ß cell function."

Unexpectedly, Dr. Accili's former graduate student and postdoc, Shivatra Chutima Talchai'10 PhD, ran into evidence that Dr. Accili was right. Her goal had been to determine if Fox01, a transcription factor Dr. Accili has studied over the past two decades, was a cause or a consequence of diabetes. "He gave me probably 95 percent intellectual freedom," says Dr. Talchai, now a lecturer on the dentistry faculty at Chulalongkorn University in her native Bangkok. "Dr. Accili knows the problem in the diabetes field very well and knows how to prove the idea in the most elegant way. I know the edge of the field, new techniques. Therefore, we make a great team."

In the course of her experiments, Dr. Talchai tagged both the β cells and the insulin they produced with fluorescent molecules to keep track of them. That's when things really got interest-

JÖRG MEYER

Domenico Accili, MD

ing. "We were expecting cell death," says Dr. Accili. Instead, the pancreatic ß cells "were still alive. But they had lost all the properties that allow us to call a ß cell a ß cell." Not only did they stop producing insulin, the cells had assumed a precursor form that could develop either into ß cells or the alpha cells that generate glucagon, insulin's antagonist that floods the bloodstream with more glucose.

"Dr. Accili was encouraging but cautious," says Dr. Talchai of the startling discovery. "We designed a series of experiments to test our ideas from different angles. It took us another two years from the discovery date to start believing in the idea." In 2012, the journal Cell published the findings.

"The observations in our Cell paper underline a potential mechanism by which some diabetic patients partially recover after lifestyle changes," says Dr. Accili. "Their ß cells have undergone de-differentiation and then the weight loss or other manipulation led to re-differentiation." To test that theory, Dr. Accili has begun analyzing data with Lloyd Ratner, MD, professor of surgery and director of renal and pancreatic transplantation, to determine whether Dr. Talchai's findings also apply to humans with diabetes.

If they do, the resulting paradigm shift could transform treatment. "We're no longer saying we should design new drugs that improve insulin production but develop drugs that prevent de-differentiation of ß cells or promote their re-differentiation," says Dr. Accili. Prescribing drugs that promote insulin production—the current standard of care—might be precisely the wrong approach. "It's like flogging a dying horse. You can push these cells only so far."

The other word colleagues use to describe Dr. Accili is *personality*, but not in a flamboyant or egotistical way. Rather, Dr. Accili is a quiet scientist, says Dr. Leibel. "I don't know anyone—and I've been at this for quite some time—who combines his gentle and knowledgeable personality, which he doesn't impose on anyone, with a real genuine desire to see his students and everyone around him succeed. He has enough faith in the people who work with and for him to let them stretch things a bit."

That same gentle personality also has a persuasive edge. "I admit I wasn't all that interested in diabetes when we first met," says Alan Tall, MD, the Tilden Weger Bieler Professor of Medicine, who was director of Columbia's Specialized Center of Research in Molecular Medicine and Atherosclerosis in 1999 when Dr. Accili was interviewing at Columbia.

During the interview process, the two began discussing the mechanisms by which diabetes and atherosclerosis create their fatal synergy. "He was asking questions and my answers were pretty fatuous," says Dr. Tall. "But our discussions about what's going on at the molecular, cellular level led to experiments, and then grants, and then more experiments and more grants."

Getting atherosclerosis researchers like Dr. Tall interested in the mechanisms of diabetes is vital for extending both lifespan and quality of life for people diagnosed with diabetes. Heart problems or stroke will kill half of the 347 million people in the world with diabetes—and control of blood sugar, alone, seems insufficient to avert such complications.

In 2007, Drs. Accili and Tall teamed up with Columbia atherosclerosis researcher Ira Tabas, MD, PhD, the Richard J. Stock Professor and vice chair of research in the Department of Medicine, to garner one of the first Program Project Grants from the National Institutes of Health to investigate the mechanisms of atherogenesis in insulin resistance. In 2012, it was renewed for another five years.

The collaboration already may have hit on a way to reduce the disproportionate impact atherosclerosis has among patients with diabetes. In an independent project, Dr. Tabas has extended findings from a joint investigation with Dr. Accili, published by the journal Cell Metabolism in 2012, that identified a novel—and extremely robust—pathway in lab animals that is associated with both diabetes and atherosclerosis. "There's evidence that it exists in humans," says Dr. Tabas, who has since developed a compound to block the pathway and launched a company to develop a drug for use in humans. "That would not have been possible without the Program Project Grant, where we would sit together month after month and teach each other about these areas. We taught him about atherosclerosis; he taught us about metabolism."

Though disparate fields are constantly melding in Dr. Accili's work, his thoughts always return to the patient. Lately Dr. Accili has had oncology on his mind, extrapolating how tactics for clinical care in diabetes could be improved by examples from other fields. "One area in which diabetes has not advanced as far as it should is the area of personalized medicine," he says. "If you're diagnosed with cancer, you undergo staging and doctors cater the treatment to your stage. We don't do that with diabetes."

Dr. Accili looks forward to the day—still several years off—when a clinical test developed in response to his work with Dr. Talchai reveals whether β cell de-differentiation has begun. "We're trying to develop biomarkers of de-differentiation," he explains. "I envision them as telltale signs that the β cell is going down this path of loss of its proper features."

Knowing how far the cascade has progressed would allow physicians to tailor patient treatment to each individual's metabolic status, perhaps treating aggressively with insulin to give over-tired ß cells a much-deserved break, before they de-differentiate, or prescribing a drug to promote re-differentiation of pancreatic cells that have already reverted to a progenitor state.

"Diabetes is a disease with a complex physiology, a complex cause," says Dr. Accili.

"It's unlikely that a single medication acting on a single cause is going to be able to reverse or stop it. We have to address the underlying physiology, which means each patient should be treated with drugs that improve insulin sensitivity and β cell function." ❖

HELP FROM OUR **FRIENDS**

When Barbara Picower read a New York Times article about Domenico Accili's work on what happens to beta cells in diabetes, she was intrigued and reached out to Dr. Accili to discuss funding his research. The result was a three-year, $1.6 million grant from the **JPB Foundation,** part of the philanthropic legacy of Mrs. Picower and the late Jeffry M. Picower. The foundation's mission is "to enhance the quality of life in the United States through transformational initiatives that promote the health of our communities by creating opportunities for those living in poverty, enabling pioneering medical research, and enriching and sustaining our environment."

Of Mice and Men

Megan Sykes was a third-year medical student in January 1981 when the New England Journal of Medicine reported that the immunosuppressant drug cyclosporine had been successfully deployed to stave off organ rejection in liver transplant patients. Her mentors were abuzz. "Transplantation," she says, "was undergoing a revolution."

Now the director of Columbia's Center for Translational Immunology, Dr. Sykes is at the forefront of the next revolution in transplantation: tactics to make drugs, such as cyclosporine, which come with a raft of nasty side effects including predisposition to infection and the threat of organ failure and cancer, obsolete.

"I began my career fascinated by the ability of the immune system to distinguish self and nonself," says Dr. Sykes, the Michael J. Friedlander Professor of Medicine and a professor of microbiology & immunology and of surgical sciences. Now she uses what she has learned over three decades of research to develop alternatives to immune-suppressing drugs among people receiving donor organs and cells. "My goal is to develop clinically relevant protocols to induce tolerance of transplants without immunosuppression," she says. "The big challenge has been to develop methods to overcome the immune barrier without too much toxic treatment or allowing host vs. graft disease."

In the process, Dr. Sykes' lab has delved into everything from skin grafts, to multiple myeloma (treated with bone marrow transplants), to kidney and heart transplants, even type 1 diabetes, in which islet cell transplantation can allow a person's pancreas to resume insulin production. "What I've learned in each area has fed the other," she says. "That's helped to develop my vision for a translational immunology center. There's vertical translation—between lab and clinic—and then there's horizontal translation, among autoimmune diseases, tumor immunology, and transplantation medicine. Yes, you have to take into account different conditions—treating a tumor compared with inducing tolerance to a new organ—but nevertheless it's the same immune system."

> The goal is to make immunosuppression drugs used after organ transplantation obsolete.

JÖRG MEYER

Megan Sykes, MD

In September 2012, Dr. Sykes attracted attention for developing a mouse with an immune system modeled on her own. Today, her team is using the same technique to develop mice whose immune systems mirror those of people with diabetes, in hopes of fine-tuning personalized treatments in the lab, instead of wasting precious time in the clinic. She hopes to do the same with cancer. "We want to make mice with immune systems of people with tumors, put the patient's tumor into the mouse, and ask how the bone marrow transplant and immunotherapy will affect that specific patient," she says.

In some situations, however, mice just are not a close enough fit for translation from lab to clinic. In those cases, Dr. Sykes turns to larger animal models. "There are things that can't be translated from the mouse into patients," she says. "You need a species closer to humans in order to be sure it's going to work and it's going to be safe." That is especially true if human trials for alternatives to drugs like cyclosporine risk deadly organ rejection. "You have to have really good evidence that what you're going to do will be successful, so when you stop the patient's immunosuppression treatment, the graft will survive." ❖

HELP FROM OUR **FRIENDS**

Joseph M. and JoAnn M. Murphy have made a substantial impact on diabetes research and care as lead supporters of the Naomi Berrie Diabetes Center. They are also past co-chairs of the Diabetes Advisory Committee, and they endowed the Christopher J. Murphy Memorial Professorship of Diabetes Research, named for the Murphys' son, who died in 2001 from complications of type 1 diabetes. The Murphys have extended their support to translational research, particularly the type 1 diabetes research conducted by Megan Sykes, MD, director of the Columbia Center for Translational Immunology. To further Dr. Sykes' work, the Murphys made a gift that allowed P&S to recruit Xiaojuan Chen, MD, PhD, from Northwestern University, where she directed the Human Islet Isolation and Transplantation Laboratory. Her expertise in islet cell transplantation will contribute to the team's efforts to cure type 1 diabetes.

Baseball legend Lou Gehrig died at age 37 from amyotrophic lateral sclerosis, a disease now commonly called Lou Gehrig's disease.

PHOTO COURTESY OF COLUMBIA UNIVERSITY ARCHIVES

When Good Neurons Go Wrong

"Columbia Lou" was just 19 years old in April 1923 when he took to the Columbia South Field pitcher's mound and proceeded to strike out 17 Williams College sluggers for a team record. The Lions lost the game, but Lou Gehrig was just getting started. He signed with the Yankees that spring and went on to play 2,130 consecutive games, batting more home runs with the bases loaded than any player before or since and earning a new nickname: "The Iron Horse."

Then something changed. Gehrig had a dismal season in 1938. In April 1939, he fell while running the bases during spring training, he couldn't tie his shoes, he stumbled over curbs when crossing the street. By 1941, he was dead.

Seventy-five years after Gehrig developed the first symptoms of amyotrophic lateral sclerosis, a progressive and fatal condition now popularly known as Lou Gehrig's disease, scientists still do not understand precisely what launches the cascade of motor neuron death that characterizes ALS.

Early in 2013, a trio of Manhattan philanthropists launched Target ALS, a three-year, $25 million initiative to fuel the search for a rational treatment; the effort is the second phase of a project initiated by Project A.L.S., a New York-based foundation, and the Packard Institute at Johns Hopkins. Funded by Bloomberg LP CEO and president Daniel L. Doctoroff with David M. Rubinstein, co-CEO of the Carlyle Group, and Bloomberg Philanthropies, Target ALS will fund the development of core facilities and fund new research consortia, thereby promoting collaboration among ALS investigators around the nation and beyond.

The effort takes its name from its top priority—identification of likely therapeutic targets. "Currently, there are no validated targets—a gene or enzyme where we can say, 'If we block this, we can slow or prevent the disease,'" says Target ALS scientific director Christopher Henderson, PhD, co-director of the Project A.L.S./Jenifer Estess Laboratory for Stem Cell Research at Columbia. "Targets are a common language between basic researchers like myself and people in industry."

For more than 30 years, Dr. Henderson, the Gurewitsch/Vidda Professor of Rehabilitation & Regenerative Medicine, Pathology, Neurology, and Neuroscience, has researched the growth, survival, and death of motor neurons. Much of his work has focused on what happens when that process goes wrong, as in ALS and spinal muscular atrophy, a genetic neuromuscular condition that strikes infants and children. "Our focus remains resolutely on helping to find a treatment for ALS and SMA," says Dr. Henderson, who co-founded the Center for Motor Neuron Biology and Disease, a collective of 40 Columbia scientists who share that goal. "There's currently no successful, effective treatment for either disease."

Dr. Henderson made his first foray into translation from research to treatment in 1999, when he co-founded a small biotech firm called Trophos in France, where he worked at INSERM, the French analog to the National Institutes of Health. High-throughput screening by the company using motor neurons in the petri dish led them to discover a cholesterol-like compound that promotes motor neuron survival. This compound, olesoxime, also looked promising in mouse models. While it was safe in humans, phase 3 clinical trials that ended in 2011 revealed that the drug had no effect in halting Lou Gehrig's disease. However, it is still being tested in SMA.

When the ALS clinical trial ended in France, scientists speculated that olesoxime was ineffective because of the advanced state of disease progression in the people with ALS who were included in the trial. Dr. Henderson thinks scientists have more work to do to improve the process that precedes clinical trials, especially in development of better tools for preliminary identification of promising molecules. "Any drug for ALS or SMA is only going to be as good as the system used to discover and test it. One can only get clean results from clean experimental systems," says Dr. Henderson, noting that back in the early 1990s when he helped identify the first neurotrophic factors for motor neurons, state-of-the-art assays relied on cells harvested from rat embryos.

Dr. Henderson, who is also director of the Columbia Stem Cell Initiative, has since worked on defining more predictive systems than rat embryos. In 2008, with Hynek Wichterle, PhD, co-director of the Project A.L.S. laboratory, and Kevin Eggan, PhD, a collaborator at Harvard, he designed a protocol for transforming the skin cells of people with ALS into stem cells and from there to motor neurons to evaluate prospective treatments. Yet actually growing enough cells to test large numbers of target compounds was agonizingly slow. In January 2013, the Wichterle/Henderson team published a technique for generating motor neurons from human stem cells with greater speed and greater yields. Another project continues to test 50,000 compounds for their ability to stimulate nerve growth, as a potential way to repair the damage caused by ALS in the peripheral nerve. "There are no quick shots on goal for translational research," Dr. Henderson says. "You only get there with the very best biology and most rigorous testing possible. This is exactly the type of project that will benefit from the multidisciplinary environment provided by the emerging Columbia Translational Neuroscience Initiative." ❖

HELP FROM OUR **FRIENDS**

P&S honored some of its most valued philanthropic partners at the third annual Crown Awards in December 2012, held at New York City's Plaza Hotel. Nearly 400 friends and supporters of P&S attended the event, where honorees included **Claire and Leonard Tow,** recognized for their instrumental support for CUMC's motor neuron disease research; **Meredith, Valerie, and Jenifer Estess,** who created Project A.L.S. to find a cure for amyotrophic lateral sclerosis; and **Loren Eng and Dinakar Singh,** founders of the SMA Foundation, which supports research to cure spinal muscular atrophy. Pictured, from left, are CUMC Board of Advisors Chair P. Roy Vagelos, Valerie Estess, and Leonard Tow.

Research Highlights

"Organ on a Chip"

In a quest to streamline drug development and testing, the NIH and the Defense Advanced Research Projects Agency awarded $132 million to seven scientists to develop 3-D "organ-on-a-chip" systems to simulate the human body. Angela M. Christiano, PhD, the Richard and Mildred Rhodebeck Professor of Dermatology and Genetics & Development and an expert in the genetic basis of inherited skin and hair disorders, will use adult induced pluripotent stem cells to create an unlimited supply of disease-specific donor cells to model complex skin conditions. The project promises to reduce the number of compounds abandoned in late-stage human clinical trials due to adverse effects. Support leading up to this work was provided to Dr. Christiano and her research team by NYSTEM, the NIH/NIAMS Skin Disease Research Center in the Department of Dermatology, and internal funds from the Mandl Connective Tissue Research Fellowship and a Helmsley Stem Cell Starter Grant from the Columbia Stem Cell Initiative.

Clues to PTSD Treatment

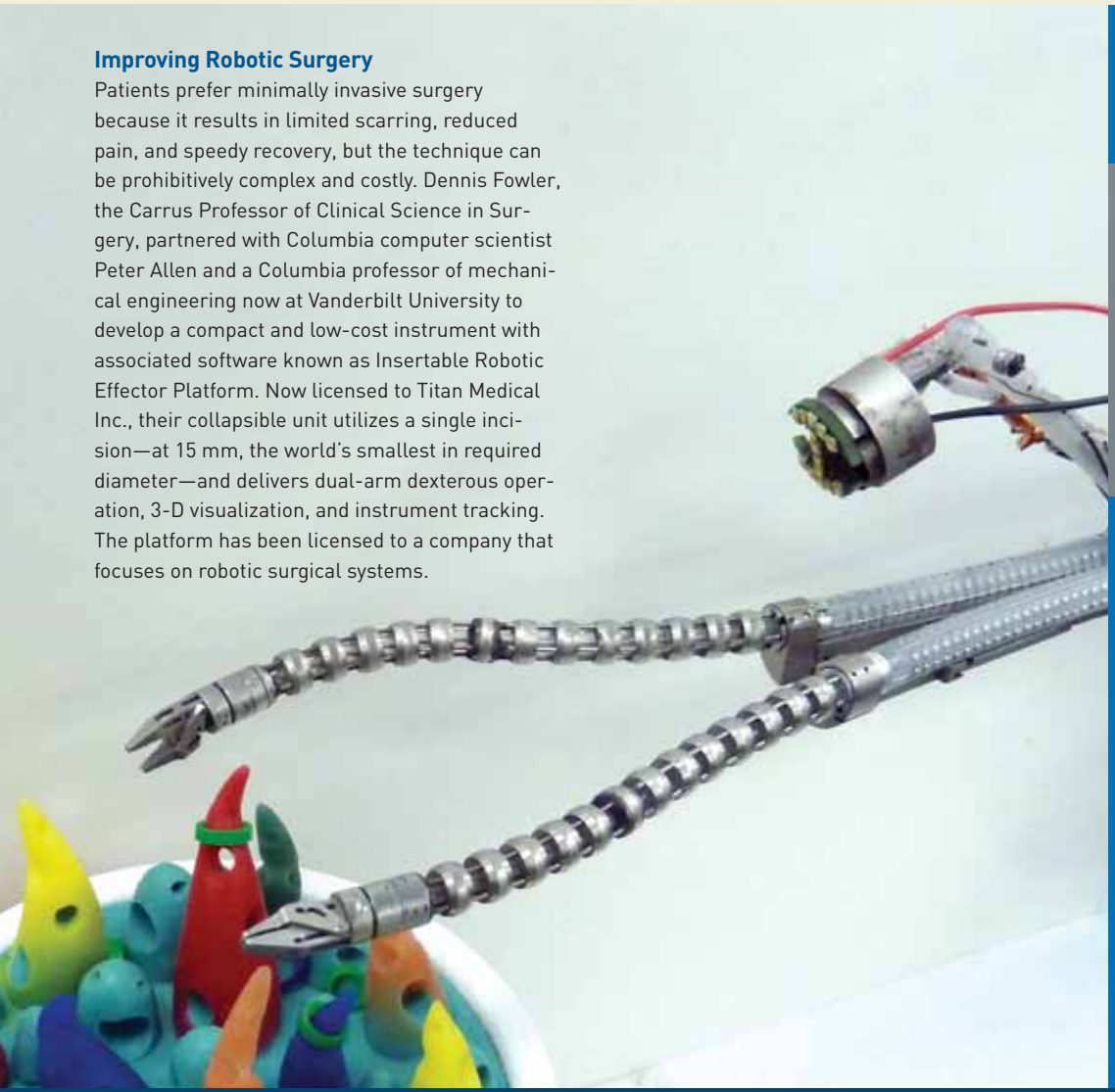
More than 5 million Americans suffer from PTSD, an anxiety disorder whose symptoms include cognitive dysfunction. Using a mouse model, Andrew Marks, MD, chair and professor of physiology & cellular biophysics and director of the Wu Center for Molecular Cardiology, has demonstrated how chronic stress affects memory and learning through the destabilization of a hippocampus calcium channel known as RyR2. "With the dramatic rise in cases of PTSD among our combat veterans and following common afflictions such as heart attacks, there is a pressing need for new and better therapies," says Dr. Marks, whose lab has developed Rycal S107, a small molecule that stabilizes RyR2.

A Mouse to Study Typhoid

The bacterium *Salmonella typhi* sickens more than 2 million people every year. Mice and rats—the species on which scientists rely for vaccine development—are lucky; they are immune to typhoid. Sankar Ghosh, PhD, the Silverstein and Hutt Family Professor and chair of microbiology & immunology, and Matthew S. Hayden, MD, PhD, assistant professor of dermatology and of microbiology & immu-

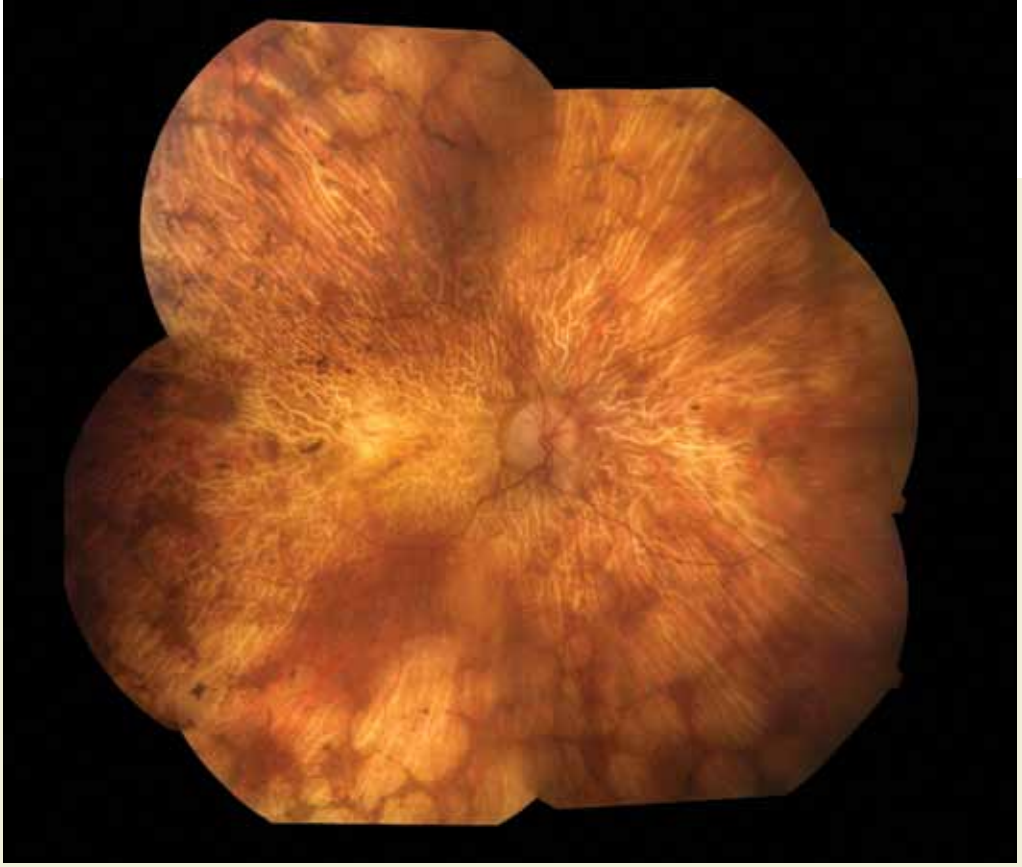
Improving Robotic Surgery

Patients prefer minimally invasive surgery because it results in limited scarring, reduced pain, and speedy recovery, but the technique can be prohibitively complex and costly. Dennis Fowler, the Carrus Professor of Clinical Science in Surgery, partnered with Columbia computer scientist Peter Allen and a Columbia professor of mechanical engineering now at Vanderbilt University to develop a compact and low-cost instrument with associated software known as Insertable Robotic Effector Platform. Now licensed to Titan Medical Inc., their collapsible unit utilizes a single incision—at 15 mm, the world's smallest in required diameter—and delivers dual-arm dexterous operation, 3-D visualization, and instrument tracking. The platform has been licensed to a company that focuses on robotic surgical systems.



HELP FROM OUR **FRIENDS**

Janet Carrus and the Carrus Foundation established the Gerald and Janet Carrus Professorship of Surgical Sciences in 1998. In September 2012, a dinner in New York City celebrated the appointment of robotic surgeon Dennis Fowler, MD, to the professorship and acknowledged the philanthropy of the Carrus family and foundation. Dr. Fowler, a pioneer in endoscopic surgery, is medical director of CUMC's Simulation Center, director of the Reemtsma Center for Innovation and Outcomes Research, and professor of clinical surgery. During the 2012 dinner, Dr. Fowler and Mrs. Carrus, pictured here, received medallions to commemorate their contributions to the medical center's mission.



Hope for Common Form of Inherited Blindness

Retinitis pigmentosa is the most common form of inherited blindness, and doctors have no cure. Stephen H. Tsang, MD, PhD, associate professor of pathology & cell biology and of ophthalmology, has developed two treatments—gene therapy and stem cell transplants—tested in young mice whose progressive loss of photoreceptor cells mimics the disease course in humans. "While these therapies still need to be refined, the results are highly encouraging," says Dr. Tsang, who is pursuing FDA approval for clinical trials. "We hope we may finally have something to offer patients with this form of vision loss."

nology, have cracked the code that yields murine immunity; they genetically engineered a knockout mouse susceptible to typhoid. "With our new mouse model," says Dr. Ghosh, "we have a powerful tool for investigating the disease and devising better vaccine strategies."

Genetics and Schizophrenia

Nature Genetics has published an analysis of the genomes of 231 patient trios—a person with schizophrenia and both biological parents without the disease—that implicates dozens of novel mutations plus four potentially key genes in the disease. The project, led by Maria Karayiorgou, MD, professor of psychiatry, suggests how prenatal environmental insults—such as malnutrition or infections during the second and third trimester—lead to symptoms that typically emerge during the teen or early adult years.

Race and Alzheimer's

A study led by Columbia that involved nearly 6,000 African-American participants implicates a variant of the gene ABCA7 in the risk of African-Americans developing late-onset Alzheimer's. Involved in the production of cholesterol and lipids, the gene has an effect on disease risk comparable to that of APOE-e4, which has been known for two decades to be a major genetic risk factor in whites. "Until now," says senior author Richard Mayeux, MD, professor and chair of neurology, "data on the genetics of Alzheimer's in this patient population have been extremely limited." The study was published by the Journal of the American Medical Association.

PTSD and Stroke

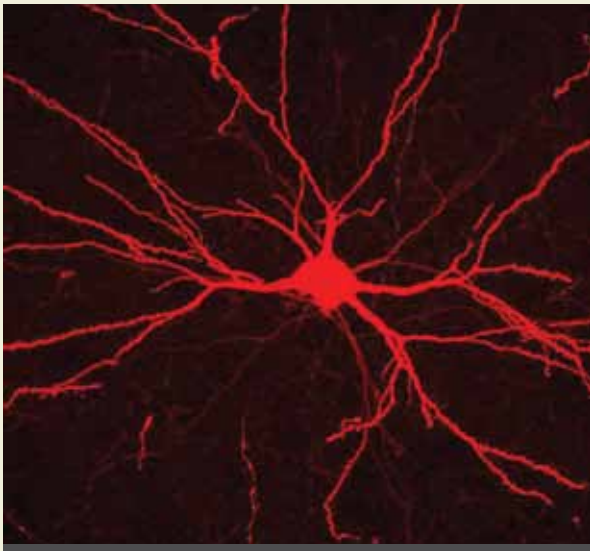
A quarter of survivors of a stroke or transient ischemic attack develop PTSD, which has symptoms that endanger people with compromised cardiovascular health. "PTSD in stroke and TIA survivors may increase their risk for recurrent stroke and other cardiovascular events," says Donald Edmondson, PhD, assistant professor of behavioral medicine, first author on the published study. "Health care providers should make it a priority to screen for symptoms of depression, anxiety, and PTSD among these patient populations," says Ian M. Kronish, MD, assistant professor of medicine and the study's senior author.

Clues to Origin of OCD

Obsessive compulsive disorder—an anxiety disorder characterized by recurrent, intrusive thoughts and behaviors—implicates both the orbital frontal cortex, which governs decision making and volitional activity, and the ventromedial striatum, which mediates the experience of fear and risk. In a study published in Science, Susanne Ahmari, MD, PhD, assistant professor of clinical psychiatry, used optogenetics, in which neural cells could be turned on and off using pulses of light, to create a mouse model revealing how repeated stimulation of certain neural pathways linking the orbital frontal cortex and the ventromedial striatum can induce the condition.

New Thoughts on Brain's Wiring

Tech geeks have long known that dividing a task and assigning components to multiple processors speeds execution. It turns out our brains do the same thing. "Our findings challenge dogma," says Randy Bruno, PhD, assistant professor of neuroscience and a member of the Zuckerman Mind Brain Behavior Institute and the Kavli Institute for Brain Science, who conducted research on the rat whisker sensory system with Christine Constantinople, who received her PhD this year. Their findings were published in Science. The discovery, says Dr. Bruno, "opens up a different way of thinking about how the cerebral cortex does what it does."



Research led by Randy Bruno on how rats process information coming from their whiskers has changed the way neuroscientists think of the entire cerebral cortex. Instead of processing information sequentially, the brain divides a task into components that are sent to different parts of the cortex for simultaneous processing. Here, a neuron from the rat cortex is labeled red.

Education

Revised curriculum transforms the student experience

"If you are able to tap into the notion of medicine as a calling, you will be fortunate indeed. It holds the key to a career characterized by fulfillment, contentment, and a sense of accomplishment. The simple secret is, you just have to believe in it."

— Robert Lefkowitz, MD, 2013 graduation speaker, 2012 Nobel Laureate, and 1966 graduate of P&S

Rebecca Eskin Berger'13

In New Curriculum, Students Explore Passions, Sometimes Finding New Ones

On the cusp of her fourth year of medical school, Rebecca Eskin Berger'13 got serious about her interest in promoting quality improvement of the health care system. Her goal: facilitating clear conversations about advanced health planning between physicians at NewYork-Presbyterian/Columbia's Allen Hospital and their elderly, chronically ill patients. While a student, Dr. Berger worked with Beth Barron, MD, assistant clinical professor of medicine, to design a training module for the doctors, then surveyed both the health care providers and their patients to assess the extent to which the program addressed their needs and concerns. During the spring, she presented her findings—her P&S scholarly project—at two national conferences.

"I came into medical school not expecting to do research," says Dr. Berger, who now plans to pursue a career in academic medicine, where she will be able to integrate her longstanding commitment to patient care with her newfound interest in data-based quality improvement. "It's been an eye opener learning how diverse research can be and how directly it can relate to patient care in a way that makes you a better doctor."

Dr. Berger and her P&S classmates were the first to study for medical careers using a transformed curriculum that integrates classroom and clinical training, tailors learning to students' unique interests, and requires that each candidate for an MD degree complete a scholarly project of his or her own design that yields a publication-quality paper or poster. "The whole idea is to provide our students with a first-rate education and give them time for a one-on-one mentored experience that emphasizes each student's passion," says Vice Dean for Education Ronald Drusin, MD, who oversaw the team of 125 faculty, staff, and medical students responsible for the first re-design of the P&S curriculum since 1991.

The new curriculum bears little semblance to its precursor. Preclinical classroom instruction—classically spread over the course of two years—was reorganized and condensed into 18 months. As a result, P&S students begin their clinical clerkships six months earlier than their peers at other schools, before taking the U.S. Medical Licensing Exam Step 1. The Class of 2013 had mean scores for the exam higher than any prior P&S class. "You sit in a classroom getting theoretical concepts, but they don't make sense until you're in the role of a health care provider with real patients with real needs," says Stephen Nicholas, MD, professor of clinical pediatrics who oversees the scholarly project global health track. "Having the boards after they come back from

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the wards gives them a chance to review that theoretical information and flesh it out with their experiential knowledge—they have a depth of understanding that lasts a lot longer."

For students and faculty alike, Match Day proved an even stronger endorsement of the new curriculum, particularly the scholarly project—a four-month foray into one of six tracks: basic science research, clinical research, global health, community health, narrative and social medicine, or medical education. "It was something residency interviewers were very interested in and that students enjoyed talking about," says Senior Associate Dean for Student Affairs Lisa Mellman, MD. Dr. Berger, who matched to Massachusetts General Hospital in internal medicine—her top choice—says her work at the Allen Hospital was a centerpiece of each of her residency interviews.

In the new curriculum, each MD candidate completes a scholarly project of his or her own design.

Relationships forged during the scholarly project were central to the compelling letters of recommendation penned by the faculty, says Jonathan Amiel, MD, associate dean for curricular affairs, who oversees the scholarly projects program. Perhaps even more important, the sustained interaction among faculty and students has triggered a new paradigm for student evaluation. "We've always looked at grades and academic achievement in a pretty traditional way," he says. "Now, through the scholarly projects, we can see students excelling according to their own interests. It's made us think differently about who are our strongest students. I think we're going to learn from that again and again as we re-conceptualize what makes a successful medical school experience."

Dr. Nicholas, also associate dean for admissions, chooses from the best and brightest applicants to each P&S class, with nearly 8,000 applications this past year for about 170 spaces. These days, he sees many more self-motivated, passionate students rising to the top of the recruitment process. "In the old days, you'd get a generic question about strengths and weaknesses of the medical school curriculum, but no one came in asking detailed questions," he says. "Now it's very much part of the discussion during interviews. We're putting pedagogy up front: We want to equip you to be a lifelong learner and we're going to give you tools to do that." ❖

HELP FROM OUR **FRIENDS**

The planned new Medical and Graduate Education Building has several major benefactors. The latest are **Philip and Cheryl Milstein,** who made a $20 million pledge to campus revitalization. Mr. Milstein is a Columbia University trustee emeritus, a member of the CUMC Board of Advisors, and a trustee of NewYork-Presbyterian Hospital. As chair of the Capital Planning Committee of the CUMC Board of Advisors, Mr. Milstein has played a crucial leadership role in ushering in a new age of medical and graduate education at Columbia. This latest gift continues the Milstein family's ongoing commitment to the advancement of medicine at the medical center. His parents, Vivian and Seymour Milstein, began their association with Columbia and the hospital in the 1950s.

Education Highlights

Columbia-Bassett Program

Now in their fourth year of medical school, the 10 students in the inaugural class of the Columbia-Bassett program have declared their scholarly project plans. Three of the 10 will remain in Cooperstown for their projects: Two will investigate clinical questions (efficacy of the topical analgesic capsaicin as an indicator of whether patients will experience chest pain associated with recurrent heart conditions; whether bruising patterns can predict the location of ACL tears), and the third student will quantify student competency in communicating with patients before and after a module on patient communication taught in conjunction with guest faculty.

Columbia-Bassett students

From PhD to MD in 3 Years

Four PhD-trained biological scientists are part of the inaugural class of a 36-month PhD-to-MD degree program designed by the Department of Medicine. "We conceived this as a way to attract a highly select group of people committed to careers as physician-scientists," says program co-director Nicholas Fiebach, MD, vice chair for graduate and continuing medical education in the Department of Medicine. "We thought there might be PhDs who want to round out their education in medical school on the way to careers as physician-scientists. We were amazed to find that a substantial number of highly qualified applicants are committed to this career track."

Apgar Academy

Twelve members of the P&S faculty were elected this year to the prestigious Virginia Apgar Academy of Medical Educators, a recognition of their excel-

lence in five categories: teaching, instructional development and curriculum design, mentorship and advising, administration and leadership, and publications. The academy honors the medical school's best teachers and engages them to promote pedagogical excellence through faculty workshops on such topics as teaching in acute care settings, giving feedback, and team-based learning. Deborah Cabaniss, MD, clinical professor of psychiatry and director of psychotherapy training, directs the academy, which was founded in 2011 as one of four components of the Glenda Garvey Teaching Academy. The Apgar Academy now has 42 members. The 12 newest members are Anne Armstrong-Coben, MD (Pediatrics); Beth Sharon Brodsky, PhD (Psychiatry); Mitchell Elkind, MD (Neurology); Dennis Fowler, MD (Surgery); Rachel Gordon, MD (Medicine); M. Christine Krause, MD (Pediatrics); Danielle Ludwin, MD (Anesthesiology); John Markowitz, MD (Psychiatry); Lisa Mellman, MD (Psychiatry); Sumit Mohan, MD, (Medicine); James Noble, MD (Neurology); and Donald Quest, MD (Neurological Surgery).

Gross Anatomy Modernized

When members of the Class of 2017 receive their gross anatomy dissection manuals in the fall of 2013, it will be in the form of a URL. Working with a dozen medical students every summer since 2011, course director Paulette Bernd, PhD, professor of clinical pathology & cell biology, and medical student Dustin Tetzl'14 have overhauled the classic print manual with digital photos and video, line drawings, and a hyperlinked glossary in a format compatible with desktop, tablet, and mobile phone platforms. Compared with earlier classes relying on the print textbook, P&S students using the new manual have seen a significant boost in quiz scores early in the course. In April, Mr. Tetzl's presentation on the group's work won an "Excellence in Medical Education Award" at the AAMC Northeast Group for Educational Affairs conference.

Education Building

Preparation is under way for construction of the Medical and Graduate Education Building on Haven Avenue between West 171st and West 172nd streets, after a Sept. 16 groundbreaking. The 14-story tower, designed by Diller Scofidio + Renfro, will have 100,000 square feet of classroom facilities, including 13,000 square feet dedicated to simulation training. The building has received extensive press coverage by several New York newspapers and more than 30 architecture, design, real estate, and trade publications. The New York Times noted "the design … is unorthodox for a medical school not only in its verticality and sculptural treatment of exposed interiors but also, according to the architects, in its reflection of a new more collaborative, team-based mode of teaching."

Brain Expo

In March, CUMC hosted a Community Brain Expo organized by Kelley Remole'12 PhD, founder of Columbia University Neuroscience Outreach and director of neuroscience outreach for the Zuckerman Mind Brain Behavior Institute. The event drew 140 visitors, including families and a Harlem Children's Zone group. Alexis Hill, a PhD student in neurobiology and behavior, recruited 15 volunteer graduate students and faculty members to staff exhibits of human and animal brains and led activities featuring visual illusions and eye-hand coordination challenges. "Our objective was to make available to the public some of the great scientists and research available at the university," says Dr. Remole, "and help the scientists convey their enthusiasm to a wide audience."

TEDMED Day

Ten students in the Class of 2016—all members of the P&S Innovative Medicine Interest Group—organized the first TEDMED Day at CUMC. The six-hour event in mid-April featured live video from the national TEDMed conference in Washington, D.C., plus discussion led by eight CUMC experts. The short lectures were on such topics as paradigms for palliative care gleaned from Zen Buddhism, the integration of artificial intelligence into electronic medical records, and popular culture's dystopian anxiety about clinical genetics gone wrong.

Clinical Care

A new clinical presence in Midtown Manhattan

"There are people out there who need the best care, and we at Columbia are committed to improving the lives of their patients by providing that care and by conducting the research that will improve that care."

— Stephen Emerson, MD, PhD, director of the Herbert Irving Comprehensive Cancer Center and the Clyde and Helen Wu Professor of Immunology & Medicine

51 | 51:

Patient Care at the Center of the Universe

Columbia Medical Expertise Moves Downtown in Expansion of Faculty Practice

At ColumbiaDoctors Midtown, every hallway ends in a vast window framing a unique view of the location's Manhattan neighborhood—Rockefeller Center, Radio City Music Hall, Sixth Avenue, Central Park. Even on cloudy days, the natural light that streams through those windows promotes the well-being of patients and staff as they move through clinical and administrative spaces.

"We wanted to be able to orient people to the outside, using daylight," says Amy Mays, a senior interior project designer for Perkins+Will, the firm that designed the 125,000-square-foot ColumbiaDoctors Midtown facility, which occupies three floors at 51 W. 51st St. "We Americans spend 90 percent of our time indoors; we wanted to provide a setting that promotes health, where the attention to the individual visitor or patient could be intimate, personalized."

The 225 physicians, dentists, and nurse practitioners of ColumbiaDoctors Midtown—formerly ColumbiaDoctors Eastside on East 60th Street—offer comprehensive medical services, including cardiology, executive health, pre- and postsurgical care, psychiatry, radiology, dermatology, travel medicine, and women's health plus laboratory services and same-day urgent care. With evening and weekend hours, as well as the capacity to accommodate a 40 percent increase in patient visits each year, the location symbolizes a significant shift in the breadth of ColumbiaDoctors, whose 1,200 members also see patients in other New York City neighborhoods, surrounding counties, and other locations throughout the tri-state area.

"We're delighted to serve our patients with this far more convenient, elegant, and spacious new facility," says Robyn Gmyrek, MD, chair of the Board of Directors for ColumbiaDoctors Midtown. "For patients in my dermatology practice, the abundant natural light has been an especially welcome feature."

Like patients who visit other ColumbiaDoctors locations, patients at ColumbiaDoctors Midtown will continue to have access to the entire ColumbiaDoctors multispecialty practice network. Shuttle service is available between ColumbiaDoctors Midtown and the flagship ColumbiaDoctors practice in Washington Heights.

The new ColumbiaDoctors Midtown facility also re-connects the University to its midtown legacy. Until 1985, Columbia owned 11.7 acres of land, including Rockefeller Center, which was donated to the University by New York state in 1814. Comprised of faculty from P&S, the College of Dental Medicine, and the School of Nursing, the practice is just blocks from the Madison Avenue campus that Columbia University occupied from 1857 until its 1897 move to Morningside Heights.

Already, the new facility is making its mark on the architecture and design world. The International Interior Design Association honored the project as best in category for an ambulatory care facility in its annual healthcare interior design competition. Also, the U.S. Green Building Council awarded the building gold LEED (Leadership in Energy and Environmental Design) certification as part of its program recognizing the design, construction, and operation of high performance green buildings. The new facility offers many health-conscious features, with daylight flooding through those enormous windows, vinyl-free flooring, and low-mercury lighting—and a host of environmentally friendly considerations,

PHOTOS BY JÖRG MEYER


ColumbiaDoctors


ORTHOPEDICS
NEUROLOGY
NEUROSURGERY
SURGERY
REHABILITATION
UROLOGY
OTOLARYNGOLOGY
DERMATOLOGY & SKIN/
Robyn Gmyrek, MD

including use of materials manufactured on Long Island and the facility's ease of access by mass transit. "There are ways to do good for patient care and do good for the environment at the same time," says architect Robin Guenther, author of the "Green Guide for Health Care" and leader of the Perkins+Will team. "The more we learn about the connection between the built environment and human health, the more the imperative and understanding of health care's mission to first do no harm come forward."

Creating a calm, soothing interior environment was a top priority for practice members, says Louis Bigliani, MD, president and chair of the board of ColumbiaDoctors and chair of orthopedic surgery at P&S. "The whole experience gives people a sense of comfort, a sense that we're organized and caring," he says, noting the concierge parking service and central welcome desk. Staff wear coordinated button-down shirts, cardigans, and blazers in Columbia blue, embroidered with the ColumbiaDoctors logo. Clinicians have similarly embellished white coats. "The staff is attentive and geared to patient satisfaction," says Dr. Bigliani, who credits the move to the new location with a culture shift among staff. "There's a new sense of unity and collegiality."

To help visitors find their way among the 14 specialties represented at 51 W. 51st St., designers used an accent wall in each waiting room, painted in earth tones—mustard yellow for otolaryngology, smokey turquoise for dermatology and psychiatry, lakewater blue for cardiology—with hallway signs to match. "It's a very large footprint and we knew there would be a wide range of users who would need to get from point A to point B," says Ms. Mays. "Tying the color palette into wayfinding was something we focused on early on." Individual doctors at the facility keep unique schedules, so easy-to-update electronic signs at each practice that list the clinicians present each day ease navigation for patients.

Thoughtful adjacencies among practices promote patient service, with pediatrics adjoining obstetrics & gynecology on the south hallway, while orthopedics and the 1,800-square-foot rehabilitation facility occupy neighboring spaces on the north hallway. Behind the scenes, service corridors parallel to the public passages connect the practices and administrative staff. The radiology and interventional radiology practices even chose to share a waiting room and reception staff. "The whole floor is extremely well organized for physicians to collaborate and work together," says Dr. Bigliani. "In our former location, radiology was a slow elevator ride away. Now radiology is just down the hall. If something comes up, we can walk right over and speak to them."

'The whole experience gives people a sense of comfort, a sense that we're organized and caring.'

Almost 30 percent of the office furniture was moved from the Eastside practice to conserve materials and reduce waste, but many practices acquired new, advanced clinical equipment—including two MRIs, a PET CT scanner, and mammography, bone density, and ultrasound equipment. "Now we have the capacity to do many more studies, so we can make diagnoses on the same day," says Dr. Bigliani. "It saves time and allows us to accurately diagnose complex problems."

Other construction projects, such as the prospective residential Hudson Yards development project, will likely transform the neighborhood in coming years, making flexible design a top priority in planning the ColumbiaDoctors Midtown facility. The 25-year lease includes an option to expand to additional floors at the same address. "In our previous location, practices had isolated spaces with separated waiting and clinical areas, so shrinking or growing was a major construction project," says Robin Worley, director of operations for ColumbiaDoctors.

"We've made a statement," says Dr. Bigliani, "in creating an exceptional facility in midtown that is patient- and physician-friendly, from the quality of care to amenities that support a stress-free environment." ❖

Louis Bigliani, MD

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ColumbiaDoctors: www.columbiadoctors.org

ColumbiaDoctors Midtown:
51 W. 51st St. (between Fifth and Sixth avenues), New York, NY 10019
Monday-Saturday hours
www.columbiadoctors.org/midtown
212-326-8500

Ronald Wapner, MD

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A Clearer View Inside the Womb

A rich trove of information lies embedded within our DNA—from the color of our eyes to our predisposition for a variety of medical conditions. For more than 30 years, pregnant women have had a window on prenatal development through karyotyping—a microscopic technique used to reveal chromosomal anomalies in amniotic fluid or, more recently, placental samples. The results are a little like looking through a dirty window to read a newspaper inside; it is easier than peering through a brick wall, but reading the full story is challenging.

Over the past five years, increasing numbers of women and their doctors have turned to chromosomal microarray, a computerized analysis of fetal DNA that yields far greater genomic detail. In December 2012, the New England Journal of Medicine published results of a 4,406-patient study led by Ronald Wapner, MD, professor of obstetrics & gynecology and vice chair for research in the Department of Obstetrics & Gynecology, that compared chromosomal microarray analysis and karyotyping for prenatal diagnosis. The prospective, blinded trial spanned four years and included women from 29 medical centers nationwide, making it the largest study of its kind. Dr. Wapner and his colleagues found that microarray boasts both greater precision and greater clinical relevance, the medical equivalent to cleaning the grime from that dirty window.

Study investigators recruited women based on advanced age or abnormal results from a screening test or ultrasound. Among the women who received abnormal ultrasound results but had normal karyotyping, microarray detected chromosomal deletions or duplications in 6 percent of cases. Among women of advanced maternal age, the technique revealed genetic abnormalities in about 2 percent of cases missed by karyotyping. "This technique has the capability to provide a better picture for future parents," says Dr. Wapner. With its higher resolution and sensitivity, chromosomal microarray can detect even copy number variants and other gene-level permutations. "With that level of detail, we can tailor postnatal care to a child's needs, combining personalized diagnosis with the kinds of early intervention that yield the best outcomes."

Like karyotyping, chromosomal microarray requires a small amount of amniotic fluid or placental tissue, and—due to the invasive nature of sample collection—poses a slight hazard of miscarriage. "We hope that in the future—when microarray can be done noninvasively—every woman who wishes will be offered microarray," says Dr. Wapner, "so that she can have as much information as possible about her pregnancy."

Microarray, which currently costs about twice as much as karyotyping, can reveal rare conditions that might not otherwise be detected until long after birth, as well as conditions influenced as much by elements of the postnatal environment as by underlying genes. And while most conditions associated with copy number variants have known outcomes, some do not. Thus, all of that data embedded within a microarray analysis also comes with a caveat. "Although 98 percent of the women in this study received reassurance that their pregnancies were normal and healthy or received well-defined abnormal results," says Dr. Wapner, "we need to continue our work to better interpret results for the other 2 percent." Dr. Wapner has already launched follow-up studies to track how variations detected by microarray play out in real time, after babies depart the delivery room. "With more information comes the imperative for a lot more discussion—among physicians and patients and within society about how we use that knowledge." ❖

Clinical Highlights

Hip Hop and Stroke Awareness

Associate Professor of Clinical Neurology Olajide "Jide" Williams has partnered with rapper Doug E. Fresh, a "Sesame Street" writer, and a team of fifth-graders to found the Hip Hop Public Health Center. The nonprofit's multimedia program includes an album, music videos, and video games

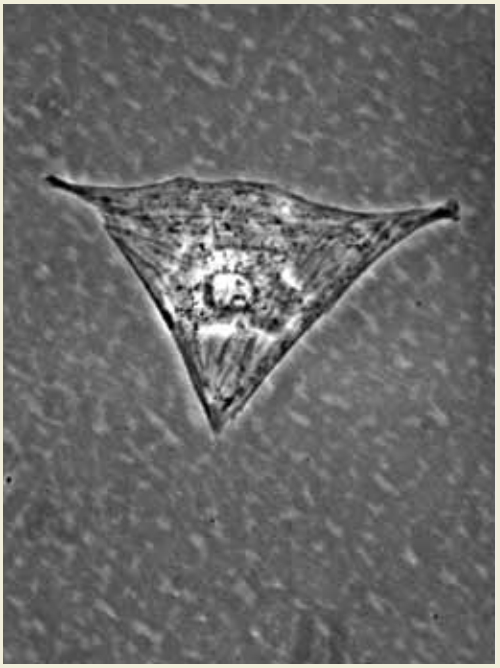
to raise awareness of stroke and other chronic diseases among school-age African-American and Latino children. Neurology published an analysis by Dr. Williams showing that the children's ability to recognize and react to strokes persisted for 15 months. The NIH awarded Dr. Williams and collaborators a $12 million grant to establish a Center for Stroke Disparities Solutions.

Improved Arthritis Diagnosis

Experts at Columbia launched a new clinic to speed evaluation and diagnosis of arthritis. The FAST clinic—named for fast arthritis sonographic evaluation and therapy—offers a pledge that every patient will be evaluated within 72 hours. The clinic also promotes the use of musculoskeletal ultrasound over X-rays or MRI, which can be expensive and delay diagnosis and therapy. Used during an initial exam, ultrasound allows rheumatologists to visualize inflammation or fluid in the joints, speeding treatment of such painful conditions as rheumatoid arthritis, gout, and osteoarthritis. Ultrasound also allows the doctors to assess treatment response and place needles more accurately.

The Long Road

Work begun six years ago could offer a roadmap for the development of patient-specific treatment. In 2007, Wendy Chung, MD, PhD, associate professor of pediatrics, diagnosed a newborn boy with long QT syndrome, a rare genetic disorder of the cardiac electrical system that causes the heart to beat irregularly in a manner that could prove fatal. Dr. Chung collaborated with Robert S. Kass, PhD, chair of the Department of Pharmacology and vice dean for research at P&S, and used a sample of the child's skin to generate induced pluripotent stem cells which in turn were transformed into beating heart cells (see figure) that reproduced the child's disease in a dish. These cells were then used to test which medications and clinical regimens would best control his heart rhythm. The work was detailed in the January 2013 Journal of General Physiology.



A Place for Adult CP Patients to Go

The Weinberg Family Cerebral Palsy Center opened at Columbia last fall to help adults with cerebral palsy get the medical care they need. People think of children when they think of cerebral palsy, but half of all people living with CP are now adults who get lost in the medical system. Patients have difficulty finding physicians willing to see them because their stiff and rigid muscles make physical exams difficult and slow. Special training is required for physicians, and the new Weinberg Center has 40 physicians from 20 specialties. The center also counters the notion that nothing can be done for an adult patient's cerebral palsy. Early joint degeneration is one common problem for middle-aged CP patients, because high tension in patients' muscles places excess stress on the joint. The center recognizes that the problem can be delayed with Botox, physical therapy, and sometimes surgery, but most adult providers do not know the options. As one patient says, "When you have CP, everything is connected and you need someone to look at the big picture. I'm so happy that I found a place where the doctors have experience with CP and are willing to provide the care. I feel like all of my health care needs are being taken care of now."

HELP FROM OUR **FRIENDS**

Debby and Peter A. Weinberg and several of their family members and friends donated $7 million to found the Weinberg Family Cerebral Palsy Center at Columbia. The gift recognizes the support and care Columbia has given to the Weinbergs' youngest son, who was diagnosed with a rare form of cerebral palsy at age 3 months. New York City Mayor Michael Bloomberg joined Mr. and Mrs. Weinberg and Columbia leaders at a celebration of the new center.

Improved Hearing

A Long Island woman got her hearing back when Anil Lalwani, MD, professor of otolaryngology/head & neck surgery, implanted a thumb-sized aid worn behind her ear and anchored by a small magnet inserted under her skin. Dr. Lalwani, director of Columbia's Cochlear Implantation Program, is the first physician in metro New York to offer the device, called the Sophono Alpha 2. "The system functions much like a 'work around' in people with conductive hearing loss, which occurs when there is a blockage between the outer and inner ear," says Dr. Lalwani.

Surgery vs. Medical Management for Diabetes

Research continues to show the benefits of metabolic surgery in controlling diabetes. The latest study published in JAMA compared gastric bypass with medical management in controlling diabetes risk factors. Judith Korner, MD, PhD, associate professor of medicine and director of CUMC's Weight Control Center, was part of an international team that assigned 120 obese people with diabetes to treatment either with gastric bypass or intensive medical management, including nutritional counseling and medication. After 12 months, 49 percent of those treated surgically had blood sugar, cholesterol, and blood pressure measurements that met American Diabetes Association targets, compared with 19 percent of the medical management group. "The big question now," says Dr. Korner, "is how long the improvements will last."

Diagnosis by the Book

The fifth edition of the Diagnostic and Statistical Manual (DSM-5)—the handbook of clinical psychiatry—was released in May, at the annual meeting of the American Psychiatric Association. Several P&S psychiatry faculty were involved in the process: David Shaffer, B. Timothy Walsh, Heino Meyer-Bahlburg, Helen Blair Simpson, Evelyn Attia, Roberto Lewis-Fernandez, and Deborah Hasin. Also at the May APA meeting, Jeffrey Lieberman, MD, chair of psychiatry at P&S, assumed the presidency of the APA.

Testing for Some Inherited Conditions

Mitochondrial DNA—mtDNA—comprises only two-tenths of a percent of our cellular DNA, yet its mutation can lead to such symptoms as stunted growth, kidney disease, muscle weakness, and myriad fatal syndromes. Work published in Nature by Michio Hirano, MD, professor of neurology and co-director of Columbia's Muscular Dystrophy Association Clinic, and Mark Sauer, MD, may limit mtDNA inheritance through transfer of the nucleus from a human egg. "This technique may allow us to provide women with a therapeutic option that will prevent these disorders," says Dr. Sauer, vice chairman of obstetrics & gynecology and chief of reproductive endocrinology. "Women who carry mutant mitochondrial DNA may no longer have to worry that their children will become sick."

Focusing on Blood Cancers

Five experts in blood cancers joined the Herbert Irving Comprehensive Cancer Center in January 2013 after they were recruited from Memorial Sloan-Kettering Cancer Center. The five have a combined 60 years of experience with both acute and chronic leukemia in adults and children. Their recruitment was made possible through a $40 million donation to the cancer center from benefactors Herbert and Florence Irving.

Blood cancer doctors, from left: Mark L. Heaney, MD, PhD; Mark G. Frattini, MD, PhD; Todd Rosenblat, MD; Joseph G. Juric, MD; and Nicole Lamanna, MD

Fighting Cancer to Give Patients

Researchers Find Creative Ways to Improve the Odds Against Brain Tumors, Leukemia, Other Cancers

Less to Fight

Cancer. Perhaps the word draws its ominous power from the vast array of diagnoses that fall within the umbrella of unconstrained cell growth, from aggressive brain tumors to slow-growing prostate cancer. Or perhaps its heft owes to the sheer numbers of Americans affected: More than 1.5 million individuals every year hear the words, "You have cancer," and more than 13 million men and women have a cancer diagnosis in their medical history.

In 1971, when President Nixon signed the National Cancer Act and launched a new era of federal funding for research, the disease was something of a black box. While clinician-scientists have made vast strides toward revealing cancer's mechanisms at the molecular level and developing new cures, the disease remains the second most common cause of death in the United States.

Throughout Columbia University Medical Center, clinicians, lab scientists, statisticians, postdocs, residents, and students are contributing to the ongoing effort to make a dent in cancer's toll. This past fiscal year, clinicians and scientists at the Herbert Irving Comprehensive Cancer Center of Columbia University have led this effort by diagnosing and treating more than 3,500 new cancer cases. The HICCC's 200 members, from the medical center's four schools and Columbia schools beyond the medical campus, also conduct basic, clinical, and population-based cancer research under the leadership of Stephen Emerson, MD, PhD, the Clyde Wu Professor of Immunology and Medicine, who became director in April 2012.

HICCC investigators delve into cancer's molecular and cellular mechanisms; investigate its unique behavior in breast, brain, bladder, and other sites; and analyze statistical aspects of its occurrence and treatment in large populations.

Cancer patients at Columbia have access to 200 ongoing clinical trials that delve into the promise of new therapeutic regimens, investigations to reveal the incidence and progression of cancer, and interventions to improve quality of life for people with cancer.

The articles on these pages highlight the work of a small group of cancer researchers whose investigations over the past year inspire hope among patients and doctors alike and have inspired clinical trials which may yet make their hopes comes true. The work of these few is but a small representation of an effort being replicated in labs and offices across the medical center, each effort in its own way contributing to progress toward chipping away at a disease that affects 1 in 25 Americans directly and countless more indirectly. ❖

HELP FROM OUR **FRIENDS**

Columbia's Herbert Irving Comprehensive Cancer Center bears the Irving name, thanks to its endowment and many years of support by **Herbert and Florence Irving.** The Irvings, married for 71 years, have been indispensable benefactors of Columbia, with support extending far beyond the cancer center. For their sustained generosity and vision, Columbia University awarded the Brooklyn natives honorary Doctor of Laws degrees at this year's commencement. Their funding of the cancer center and other cancer-related programs reaches back 26 years and has totaled millions of dollars. Other support includes the 108 Irving Scholars trained since 1987, a group of young physician-scientists who are now defining the future of medicine as deans of medical schools, national leaders in clinical research, and directors of departments, divisions, centers, and programs, both at P&S and other academic medical centers. The Irving Institute for Clinical and Translational Research, founded to fast-track delivery of new treatments to the patients who need them, is also part of the Irvings' legacy of generosity. The Irvings started from modest means but have given so much. Their personal commitment to Columbia and enduring marriage have taught us all about the value of helping others—and about lives well lived. More information about the Herbert Irving Comprehensive Cancer Center is available at www.hiccc.columbia.edu.

Anna Lasorella, MD

BY THE NUMBERS

Analysis of the Genome Reveals Culprit in One Form of Deadly Cancer

"When she was good, she was very, very good," wrote poet Henry Wadsworth Longfellow of his girl with the curl in the middle of her forehead. "But when she was bad, she was horrid." Much the same could be said of glial cells, the "glue" of the human brain.

Glial cells handle the behind-the-scenes chores that keep the neural system humming. A living scaffold that envelops the neurons, they insulate the synapses. Glial cells also regulate metabolic activity in the brain, provide quick bursts of fuel for hard-firing neurons, regulate neurotransmitter and ion levels, and maintain the blood-brain barrier, which protects against pathogens.

Fully half of the volume of the human brain consists of glial cells (the other half is made up of neurons) and they grow fast, supported by a rich network of blood vessels. Gone haywire, as in the malignant tumors known as glioblastomas, they can wreak havoc. The most common and aggressive form of brain cancer, glioblastoma has a dismal prognosis. Doctors measure a patient's prospects in months rather than years and offer surgery—if possible—to buy a little time. Median survival for people with a glioblastoma diagnosis is just 14 months; few survive more than two years, and the five-year survival rate is only 4 percent (compared with 97 percent for some forms of prostate cancer).

Antonio Iavarone, MD

PHOTOS BY JÖRG MEYER

Stark brain tumor survival statistics were a given when Anna Lasorella, MD, was a medical student and later a pediatric oncologist at the Catholic University School of Medicine in Rome. "It was terrible," says Dr. Lasorella, now associate professor of pathology & cell biology and of pediatrics at P&S. "All of the children were dying. The treatment was having no effect."

"We knew the type of drugs we gave to these children probably wouldn't work," says Antonio Iavarone, MD, Dr. Lasorella's husband and collaborator and now professor of neurology and of pathology at P&S. His investigations of the cellular biology of brain tumors date back to the late '80s when he was a trainee in pediatric oncology at the Catholic University School of Medicine. "That was the main reason I chose to do research on brain tumors. If you don't do research at a high level, it's basically impossible to expect a change in the likelihood of a cure."

Today, Drs. Lasorella and Iavarone are optimistic that prospects will improve for people diagnosed with glioblastoma. In September 2012, the journal Science published their finding that a small subset—3 percent—of glioblastoma cases are caused by a unique genetic fusion, essentially a splicing error introduced during stem cell division. When the fused gene was transplanted into the brains of mice, 90 percent developed glioblastoma. Within eight months, the mice had died from the tumor. Testing a variety of pharmaceutical compounds, the team found one that targets the protein produced by the rogue gene. Mice treated with the compound survived twice as long as their counterparts, whose untreated tumors grew exponentially. "From the moment the paper was published, we could easily have found patients to test a drug that targets this gene," says Dr. Iavarone, who regularly receives calls and e-mails from desperate patients and their families. He has begun negotiations with drug companies to develop treatments based on the findings. "We have the immediate possibility of having a real impact in the clinical setting."

Scientists were just beginning to delve into the genetic underpinnings of breast and colon cancer in the late '80s, when Dr. Iavarone's zeal for the promise of basic research caught Dr. Lasorella's imagination. At the time, most medical investigators considered brain tumors a lost cause. "The brain is very difficult to study and it's difficult to get tissue," she says. "It was kind of a neglected area and Antonio passionately believed that research was the only way we could change the fate of these patients."

Their first papers—a series investigating the mechanisms by which a radiopharmaceutical compound used to treat neuroblastoma disrupts the cancer—were published in 1991. They married in 1999, soon after they accepted research posts in the United States. "At some point," says Dr. Lasorella, "our personal and scientific lives kind of merged."

As with any good marriage of the minds, the intellectual partnership the two have forged—much of it focused on the role of ID2, a protein implicated in brain cancer that inhibits stem cell differentiation—relies heavily on the synergy of their scientific sensibilities. Dr. Lasorella takes a developmental approach, toggling between the deranged trajectory of cancer growth and the arc of a healthy cell's growth and differentiation. "I try to translate what we learn from normal development of the brain to this process that has been perturbed," she says, "and look at whether there's a way to re-establish a normal situation, reverse the tumor." Dr. Iavarone's approach is infused by an interest in genetic aberrations. "He tries to understand whether those cells can be fixed genetically," she says. "In that way we complement each other."

In Italy, Dr. Iavarone ran the lab associated with the pediatric oncology clinic overseen by Dr. Lasorella, who still keeps in touch with the families of some of those early patients. "I have very wonderful memories," she says, "even of children who weren't doing well. They teach you a lot."

At Columbia, Drs. Iavarone and Lasorella head independent lab groups that frequently join forces. Neither physician pursued clinical licensure in the United States. "I felt that when you treat patients with a very terrible disease, they deserve 100 percent of your attention," says Dr. Lasorella. "When you work on the science that might transform their prognosis, you have to devote yourself 100 percent. For me, 50-50 wouldn't work. I knew that I get involved very heavily and the patients are my priority. If I were working for them, I wouldn't be able to carry my scientific responsibility."

Despite Dr. Lasorella's full-time research appointment, her strong clinical perspective persists and infuses their partnership, Dr. Iavarone says. "I am convinced that research and clinical work should always go together," he says. "To find a cure, you need people who have different visions."

Among the visionaries with whom they collaborate is Andrea Califano, PhD, chair of the new Columbia Department of Systems Biology and associate director of the Herbert Irving Comprehensive Cancer Center, who trained first as a physicist and later became a systems biologist. "Anna and Antonio combine rigor and scientific insight of the highest caliber with a sincere desire to complement their approach with computational methods to elucidate mechanisms that drive brain tumorigenesis," says Dr. Califano.

The trio's first effort revealed the role of C/EBPβ and STAT3 as synergistic master regulators of the mesenchymal subtype of human high-grade glioma, a particularly aggressive form of brain cancer. "That work was seminal in developing the master regulator analysis approach, which allows us to first assemble regulatory models for a cancer of interest and then use them to identify genes that represent the elusive masterminds of cancer," says Dr. Califano. The trick, he explains, is using regulatory networks to discern the drivers from the passengers in the cancer genome. "This technique goes from the full genetic signature of the tumor to the handful of genes that regulate a particular tumor, allowing it to survive and progress."

Each cancer is different, says Dr. Califano, making regulatory models all the more important for scientists intent on developing personalized treatments. "If I give you a box with all of the parts of a 747, you'll have a box with 6 million pieces," he says. "But you still won't be able to assemble the plane, because you don't have an assembly manual, a blueprint. Every kind of cancer has its own assembly manual—each is very different in the way it's built. In that original glioblastoma study and now with our current collaboration on neuroblastoma, we have been working with Anna and Antonio to write and analyze the assembly manuals of these tumors."

In the case of their 2012 Science paper on the glioblastoma fusion gene, Drs. Iavarone and Lasorella assembled a dream team of two dozen scientists, a mix of MDs and PhDs with training in neuropathology, neuro-oncology, biomedical computation, algorithm optimization, and computer science working at academic medical centers throughout the United States and in Canada, China, Italy, and Taiwan. "Science is a global enterprise," says co-author Raul Rabadan, PhD, assistant professor of biomedical informatics, who has collaborated with Drs. Iavarone and Lasorella to craft multiple algorithms—including those used in the Science paper—to interrogate the cancer genome.

Beyond giving hope to people with glioblastoma, Drs. Rabadan, Iavarone, and Lasorella created a new technique to help scientists analyze the deluge of data associated with the cancer genome. Known as TX-Fuse, the algorithm hunts for unique fusion genes within the RNA of a tumor sample. In addition to revealing the glioblastoma fusion gene detailed in their Science paper, TX-Fuse has been used to interrogate more than 200 tumor samples. "It's unlikely that we will find a single gene fusion responsible for most glioblastomas," says Dr. Lasorella, "but we may be able to discover a number of other gene fusions, each accounting for a small percentage of tumors and each with its own specific therapy."

Dr. Iavarone traces the project's intellectual legacy to the development of Gleevec, now the standard of care for chronic myelogenous leukemia. In 1960, a pair of scientists discovered that people with CML share a common anomaly, dubbed the Philadelphia chromosome. As technology improved over the next three decades, CML researchers used emerging sequencing techniques to identify the anom-

'We have the immediate possibility of having a real impact in the clinical setting.'

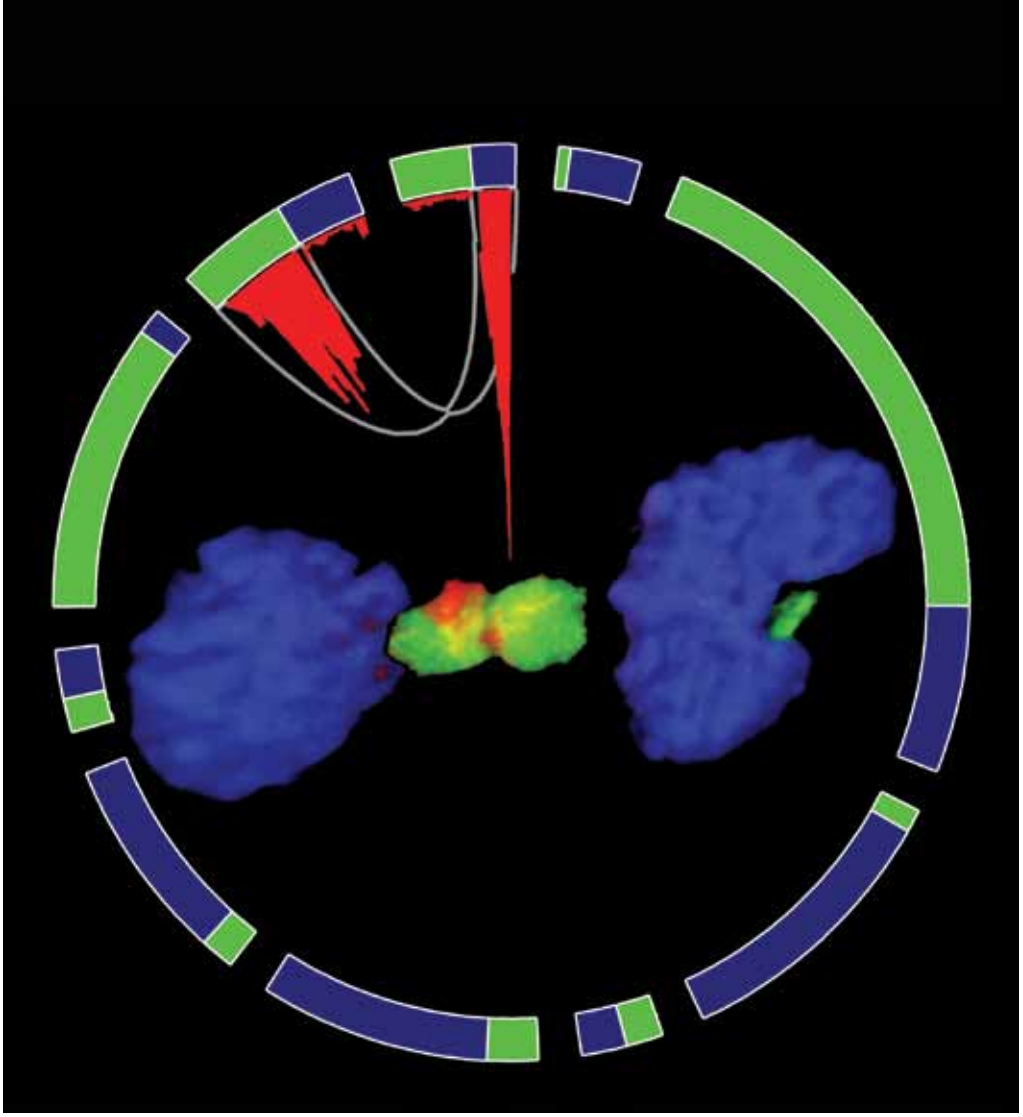


IMAGE COURTESY OF ANTONIO IAVARONE, JOSEPH CHAN, OLIVER ELLIOTT, AND RAUL RABADAN

Graphic representation of the collaboration between experimental and computational biology. The outer ring represents results of next-generation genetic sequencing of the glioblastoma genome, showing expression of the FGFR-TACC fusion gene (red peaks). In the center, FGFR-TACC fusion protein (red) can be seen disrupting tubulin bundles (green), structures that support cell division, or mitosis, at the point connecting the two daughter cells (whose nuclei are colored blue).

aly as the unique fusion of two genes, which produced a novel protein, BCR-Abl tyrosine kinase enzyme. In 1990, a Los Angeles-based team showed how the enzyme affects white blood cell production. Over the next 20 years, scientists honed in on the design of a tailored compound to derail that novel protein. "Fusion genes result in the production of proteins that don't exist in normal cells," says Dr. Iavarone. "A drug that targets the fusion protein has the chance of being incredibly selective."

In the case of CML, it took four decades for the relevant drug to reach patients. In 2001, the FDA fast-tracked approval of imatinib, marketed as Gleevec, which nearly tripled the five-year survival rate for CML, from 30 percent to 89 percent. "Gleevec has resulted in a major beneficial effect in terms of prognosis and survival for these patients," says Dr. Iavarone, who notes that the identification of gene fusions in other cancers has led to the development of additional therapeutic compounds. "In the case of glioblastoma, there had never been evidence of gene fusion. That's why we started to look for it."

The science behind Gleevec spanned 40 years, lurching forward as the tools for genetic and computational analysis became available. The groundwork laid by Drs. Iavarone and Lasorella with their collaborators—hastened by supercomputers and advanced sequencing—took 20 months. After identifying promising RNA sequences from the glioma stem cells of nine tumors and refining their approach, the team sequenced another 97 samples from the NIH Cancer Genome Atlas. Then the algorithm TX-Fuse churned through the resulting flood of sequencing data seeking novel replication errors among adjacent genes.

What they found was FGFR-TACC, a fusion of fibroblast growth factor receptor and transforming acidic coiled-coil, genes vital to late-stage cell division. "It's clear that the development of sequencing and computational techniques is becoming more and more important to teams trying to understand the complexity of data," says Dr. Rabadan, a theoretical physicist. "I see my work as a translator—taking a problem in biology and making it intelligible to a computer, something that can be coded and solved. Anna and Antonio move the information from a line in the computer code to something that can make a drug, can make a difference."

When cell division stays on course, identical daughter cells result. When the process goes awry, as when FGFR-TACC interrupts late-stage mitosis, chromosomally unstable aberrants result. To reveal the clinical implications of that particular mitotic meltdown, the team conducted experiments in mice to confirm the gene's effect and identified a compound that inhibits FGFR kinase, an enzyme central to the fusion gene's action. "If you block the function of the gene fusion, you can have a very strong anti-tumor effect," says Dr. Iavarone. "That's why we're very excited about the therapeutic opportunities."

After Science published the team's findings, Drs. Iavarone and Lasorella started hearing from patients and their families hoping to enroll in a clinical trial. Sadly, for patients who already have been diagnosed with the rapidly growing cancer, science will not be fast enough to change their prognosis. "We feel intense pressure," says Dr. Iavarone. "Strong, basic research should be immediately followed by therapeutic intervention—especially for patients like these, who have a particularly dismal prognosis."

Dr. Iavarone and Dr. Lasorella have begun developing a screen compatible with clinical pathology protocols to identify the FGFR-TACC gene in glioblastoma biopsies. "Ninety percent of patients have surgery," he says. "After the tumor has been removed, it can be analyzed for the presence of fusion genes and any other genetic alterations. Identifying this fusion is great for this particular subgroup of patients. That doesn't mean that the remaining 97 percent should receive no treatment. They should receive a targeted treatment for their genetic situation. The goal is personalized therapy." ❖

Studying Cancer Using Mouse Models

Most men survive decades after being diagnosed with prostate cancer. It usually grows so slowly, many never have to consider treatment: They are old enough at the time of diagnosis that other diseases are a greater threat than the cancer. Yet among a small subset, the disease spreads fast and furiously, metastasizing to the bones. For clinicians, the challenge is determining who has the aggressive form of the disease and who will benefit from a wait-and-see approach.

The imperative to discern a patient's particular form of cancer and treat it accordingly is not unique to prostate cancer. Doctors have long known that if they identify the type of cell from which breast cancer originates, they can confidently forecast a woman's prognosis and tailor her treatment. In February 2013, the journal Nature Cell Biology published findings revealing that prostate cancer, too, varies predictably based on the cell type—in this case, basal, or luminal epithelial—from which it originated. The research, by a team at the Herbert Irving Comprehensive Cancer Center, was led by Michael Shen, PhD, professor of medicine and of genetics & development. The findings offer a vital clue toward optimizing treatment of the 2.5 million Americans who have been diagnosed with the disease.

One of Dr. Shen's collaborators on the paper was Cory Abate-Shen, PhD, associate director of the Herbert Irving Comprehensive Cancer Center who oversees translation from bench to bedside. The Shens began their collaboration in the early '90s and have since published more than 36 articles together. "I started working with Michael to expand into *in vivo* work," says Dr. Abate-Shen. "I married him to make sure it was a full collaboration.

"We have a wonderful synergy," says Dr. Abate-Shen, professor of urology and of pathology & cell biology. "I'm always the one revving the engine, he's the one putting on the brakes. I'm a hard-core molecular biologist, always reducing things to the mechanism. He thinks about how the whole organism works."

Together, they have elucidated the role of Nkx3.1, a gene responsible for formation of the prostate early in embryonic development and whose mutation is implicated in prostate cancer late in life. In 1999, Drs. Shen and Abate-Shen began developing a series of genetically engineered mice featuring a mutated form of Nkx3.1 to further their studies of the gene's role in carcinogenesis and metastasis. "We have some beautiful models of metastatic prostate cancer," she says, noting that their work in that realm is far from complete. "Men who die of prostate cancer die of bone metastases. To really recapitulate the disease, we need a mouse model that metastasizes to the bone and that has been very difficult to get."

Already, Dr. Abate-Shen has begun using her mouse models to evaluate new therapeutic approaches to treating cancer. "We do pre-clinical studies to test new drugs, new treatments, and new combinations of treatments," she explains. The team assesses whether a given compound works, documents treatment schemes involving multiple compounds in varying doses, and investigates the molecular mechanisms by which such compounds work their magic. Dr. Abate-Shen also has a strict lab policy that once a given genetically engineered mouse model has been published in a peer-reviewed journal, her team will provide it to the National Cancer Institute's Mouse Repository, which makes mice available to scientists around the world. "They're freely available to the community. We have a very strong commitment to that policy."

In 2009, Dr. Abate-Shen began investigating bladder cancer, a disease about which far less is known. In the process, her team developed one of the only mouse models of invasive bladder cancer available. Two recent studies used it to evaluate preclinical treatments. "Cancer is a deeply complicated biological problem," she says. "As PhDs, we can learn about the problem in a way that most readily helps patients. You don't have to be an MD to want to help patients and have that as your end goal." ❖

JÖRG MEYER

Cory Abate-Shen, PhD
Michael Shen, PhD

Adolfo Ferrando, MD, PhD

JÖRG MEYER

Relapse Specific Mutations Drive Chemotherapy Resistance in Human Leukemia

Imagine a game of poker in which the dealer refuses to reveal whether the house rules are Texas hold 'em or seven-card stud. For decades, it was a similar story for molecular biologists investigating the mechanisms of leukemia. "What we were doing before, it's as if we were playing a game without knowing the rules," says Adolfo Ferrando, MD, PhD, professor of pediatrics and of pathology & cell biology in Columbia's Institute for Cancer Genetics and director of the Lymphoid Malignancies and Development Program at the Herbert Irving Comprehensive Cancer Center.

"Not so long ago, when we had a patient with leukemia coming through the door, the pathologist could tell you what the leukemia cells looked like, but we didn't know what was driving the disease, why one patient would be different from another, and why one would be cured and another wouldn't be."

Dr. Ferrando has dedicated his research to unlocking the genetic secrets of T-cell acute lymphoblastic leukemia (T-ALL), an aggressive hematologic tumor that strikes predominantly in young people, hijacking the precursors that generate T-cells. Current cure rates hover at 75 percent for children and 50 percent for adults. Clinicians have long known that patients whose leukemias do not respond promptly to chemotherapeutic treatment have a worse prognosis than those for whom the treatment starts working immediately, but they did not know how to detect who would fall into each group or understand the mechanisms of resistance and relapse.

In February 2013, Nature Medicine published findings of a team led by Dr. Ferrando that implicated mutations to a gene known as *NTC52* in resistance to two nucleoside analogs, drugs at the core of conventional chemotherapy treatment for T-ALL. "We hope that this might translate into new therapies that will convert people from poor prognosis into a more favorable outcome," says Dr. Ferrando, who collected blood samples from children at diagnosis, treatment, and relapse stages, then used high-throughput parallel exome sequencing to identify mutations common to those who relapsed. "Now we can start, in a rational way, to intervene in the pathways that are most clinically relevant."

By deploying the same genomic techniques that revealed the role of *NTC52* mutations in some cases of relapse, Dr. Ferrando hopes to identify additional mutations at play in adults with T-ALL. Beyond the immediate therapeutic value of such studies for people with T-ALL, the scientific techniques his lab develops might be applied to other forms of cancer. "The study of leukemia is a step ahead of the broader field of cancer research, because getting relapse samples from a leukemia patient is much easier than biopsying a solid tumor," says Dr. Ferrando, whose early work on the role of the *NOTCH1* gene in T-ALL has since become pertinent in the development of new drugs to treat more common forms of leukemia. ❖

JÖRG MEYER

From Bench to Bedside

The Herbert Irving Comprehensive Cancer Center, one of 41 National Cancer Institute-designated comprehensive cancer centers, must excel at clinical research to qualify as a comprehensive cancer center. The 200 clinical trials run by the center give patients access to emerging treatments and are important in the quest to improve patient survival.

"The rich connection between basic science and clinical care at the HICCC allows us to provide cutting-edge care for people with cancer today," says Andrew Kung, MD, PhD, chief of pediatric hematology, oncology, and stem cell transplantation in the Department of Pediatrics, "and at the same time accelerates the types of discoveries that will make a difference in terms of outcomes for tomorrow's patients."

Dr. Kung was recruited to Columbia and HICCC in 2012 to develop a program to tailor treatments to individual patients and speed development of new pediatric therapies. "With emerging insights into genetics and disease biology, participants in cancer trials have a unique influence on the course of research, and patients are increasingly important in terms of teaching us what we should be studying in the lab," says Dr. Kung, who notes that 90 percent of the HICCC's pediatric oncology patients are enrolled in clinical trials. "It's not just basic researchers coming up with ideas and going to their clinical partners. It's becoming a bidirectional process."

Andrew Lassman, MD, chief of neuro-oncology, oversees several trials at the forefront of personalized medicine. In each, participation is limited to the small subset of individuals whose brain tumors share a particular genetic signature, which may function as a "driver mutation." "A single mutation in a cancer cell may drive the entirety of a tumor to grow," Dr. Lassman says. "By inhibiting that driver, we can melt away the tumor."

For scientists, success at the interface of clinical and basic research demands a capacity for cross-cultural communication, says Cory Abate-Shen, PhD, HICCC associate director for translation from bench to bedside. "Respect and ability to communicate with people who have different expertise is critical. Often clinicians and basic scientists don't speak the same language and may not even work the same hours."

To promote stronger teamwork, Dr. Abate-Shen brings trainees together, building relationships among them and urging them to ask—and answer—tough questions about their research. "We get people together in a room and ask: Why is that a relevant experiment? Why are you using this drug and not that drug? Why are you using this model instead of that model? A lot of it is about teaching communication, teaching respect, teaching each group to understand what the other needs to do effective translational research."

The HICCC also offers services to facilitate the administration of clinical trials, including Community & Ambulatory Research & Enrollment, directed by pediatric oncologist Manuela Orjuela-Grimm, MD, and the Clinical Research Management Office, headed by Dr. Lassman. "At HICCC, we want to be a place that not only has outstanding basic research and outstanding clinical care," says Dr. Lassman, "but also excels in connecting those two spheres." ❖

News from around the College of Physicians & Surgeons

P&S news

Discover. Educate. Care. **Lead.**

New Initiative in LGBT Health

A program has been created by the Department of Psychiatry to address the health needs and improve the overall well-being of lesbian, gay, bisexual, and transgender individuals. The vision guiding the new LGBT Health Initiative is to draw upon the world-class clinical, research, and educational resources of Columbia University Medical Center to support the needs of the LGBT community and their loved ones by fostering research, creating innovative medical and mental health services, and promoting the development of outreach strategies specific to the LGBT community's needs. LGBT Health is co-directed by Walter Bockting, PhD, one of the world's premier scholars of transgender health, who joined Columbia this year as professor of medical psychology in P&S and the School of Nursing. LGBT Health is based in the Department of Psychiatry's Division of Gender, Sexuality, and Health. Dr. Bockting is editor-in-chief of the International Journal of Transgenderism.

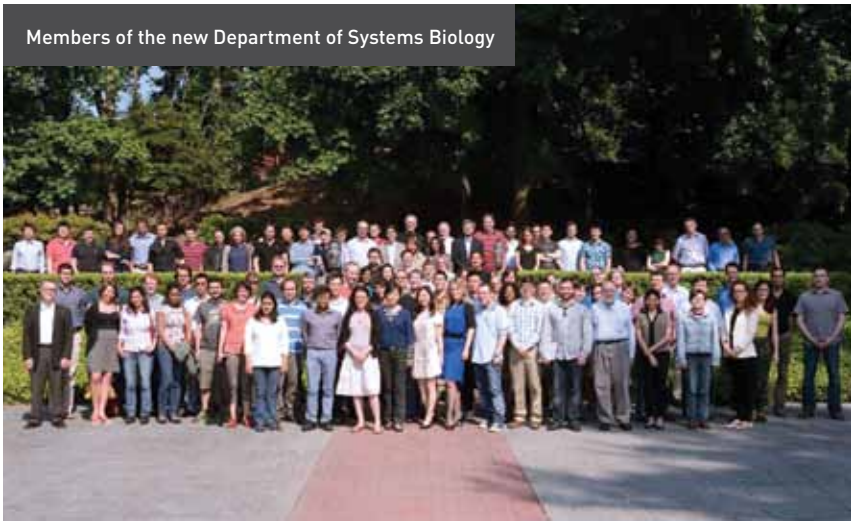
New Dean for Graduate Affairs

Arthur G. Palmer III, PhD, the Robert Wood Johnson Jr. Professor of Biochemistry & Molecular Biophysics, was appointed associate dean for graduate affairs last fall. An authority on the molecular dynamics of proteins, Dr. Palmer joined the P&S faculty in 1992 and has served as vice chair of the Department of Biochemistry & Molecular Biophysics since 2009.

Bard Athletic Center Facelift

A significantly improved Bard Athletic Center was unveiled in January, boasting a renovated squash court, additional cardio equipment, a new heating and air conditioning system, and modifications to make the facility more handicap-accessible. Housed in Bard Hall—an 11-story Art Deco building that opened in 1931—the athletic center is among the most extensive gym facilities offered in any medical school. The project was paid for by the "four deans fund," which pools resources of the four CUMC schools to improve the quality of life for students, faculty, and staff.

Members of the new Department of Systems Biology



Systems Biology: Medical School's 25th Department

Columbia Trustees in June approved the expansion of the Columbia Initiative in Systems Biology into a full-fledged department, the Department of Systems Biology. Created in 2010, the Initiative coordinated the work of the JP Sulzberger Columbia Genome Center and the Center for Computational Biology and Bioinformatics. The new department will continue this endeavor, seeking to use quantitative analysis and experimental technologies to understand complex biological systems. "Systems biology is paving the way toward new, more rational approaches in basic and translational research," says department chair Andrea Califano, PhD, the Clyde and Helen Wu Professor of Chemical Systems Biology. "It is very exciting to see Columbia take this step."

Two New University Professors

Two long-time Columbia faculty members, Wafaa El-Sadr, MD, and Martin Chalfie, PhD, were recognized for their exceptional scholarly merit and distinguished service by being appointed University Professors, Columbia's highest academic honor. Dr. El-Sadr, professor of medicine at P&S and of epidemiology at the Mailman School of Public Health, is an authority on the prevention and management of HIV/AIDS, tuberculosis and other diseases. A MacArthur Fellow, she directs the internationally renowned ICAP at the Mailman School. She joined the Columbia faculty in 1988. Dr. Chalfie, the William R. Kenan Jr. Professor of Biological Sciences at Morningside, received the Nobel Prize in Chemistry in 2008 for his use of green fluorescent protein as a biological marker, an innovation that has since become a fundamental tool for studying disease processes in model organisms. Dr. Chalfie, who works closely with many P&S faculty on the interdepartmental and intercampus neurobiology and behavior PhD program, joined Columbia in 1982. Other University Professors at P&S are Richard Axel, Wayne Hendrickson, and Eric Kandel.

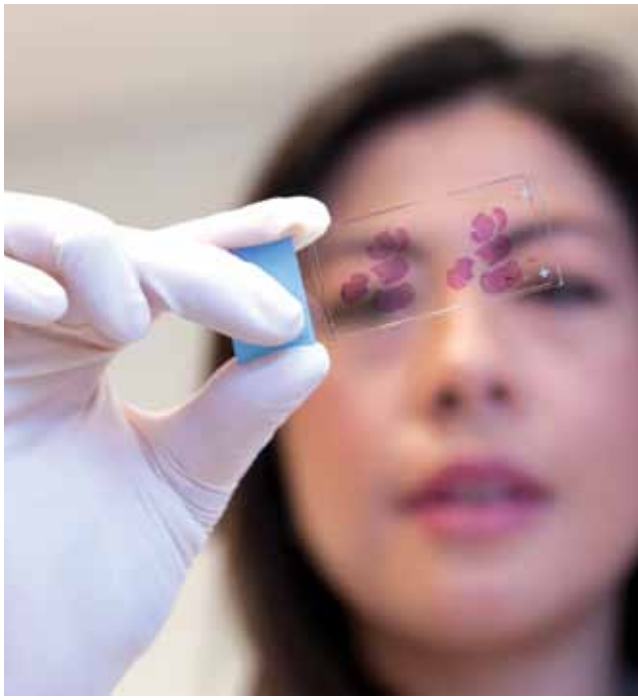
P&S Strategic Plan: A Vision for the Future

P&S has entered the third phase—the implementation—of its strategic plan, "2020 Vision." After more than 100 individuals were involved in discussing and crafting the plan during the initial phase and more than 350 individuals formed committees during phase two to review priorities, implementation of the plan will involve even more individuals who will work to bring to fruition the priorities set by the plan.

The process, begun in October 2011, resulted in a vision to guide P&S for the next five to 10 years. A common vision articulated throughout the process: "to be indisputably in the top five schools of medicine and arguably the best."

Personalized medicine, care, and education are priorities during this first year of the plan's implementation. The plan defines personalized medicine as prevention, diagnosis, and treatment targeted to the unique risks of patients and increasingly based on their genetic and genomic makeup. Personalized care is accessible, friendly, comprehensive, and expert attention to an individual's preferences and medical needs. Personalized education means students have options tailored to their needs, allowing them to design their own curriculum and experiences with faculty supervision and within frameworks established by the faculty.

The strategic plan outlines four major goals and multiple strategies and tactics for achieving the goals.



JÖRG MEYER

Goal 1: *Be a research pioneer and innovation engine.*

- P&S plans to expand its research portfolio by focusing on scientific priorities that define the future of health and biomedical science.
- Being a leader in cross-cutting scientific methods means focusing on systems biology and genomics, genetics, stem cell biology, and health practice research.
- State-of-the-art core resources, such as imaging facilities, biobanking, and animal facilities, will be strengthened.
- Key research partnerships will be facilitated, including the Zuckerman Mind Brain Behavior Institute, Morningside disciplines such as biomedical engineering, and the New York Genome Center.
- P&S will work to increase the number of principal investigators by 20 percent (100 new PIs) as a way to elevate the quantity and quality of P&S research.
- New research space that will become available (space vacated by researchers who will move to the Columbia Manhattanville building and the new education building on Haven Avenue) will help with recruitment. P&S should be able to capitalize on more than 100,000 net area square feet expected to become available.
- Under the umbrella of personalized medicine, new research initiatives in translational neuroscience, human genetics, and "I-4" (the Initiative in Immunity, Infection, and Inflammation) will join existing interdepartmental initiatives in cancer, transplantation medicine, cardiovascular research, systems biology, and stem cells.

Goal 2: *Be the dominant tertiary/quarternary medical center in the tri-state area.*

- Recruiting and retaining top faculty, strengthening the ColumbiaDoctors faculty practice organization, and establishing a ColumbiaDoctors standard of superior personal care will help P&S achieve dominance in patient care. The parameters of the ColumbiaDoctors standard of care are easy and rapid access for appointments in multidisciplinary practices, seamless internal referrals, quality service in pleasant environments, and continued commitment to vulnerable populations in Northern Manhattan.
- Implementation of multidisciplinary clinical care includes reconfiguring the floors in the Herbert Irving Pavilion (the primary outpatient care building at the Washington Heights campus) by discipline to help patients find care they need in one location and to facilitate clinician-to-clinician dialogue.
- The new practice site for ColumbiaDoctors Midtown and a growth in key suburban areas will expand the school's geographic reach for ambulatory care. Recently assimilated practices in Westchester, Orange, and Rockland counties have added physicians to the practice. The plan also recommends consolidation and expansion of practices in northern New Jersey and an increase in ColumbiaDoctors' presence on Manhattan's west side.
- In addition to the ongoing upgrade in the Herbert Irving Pavilion, construction of a new ambulatory building will be pursued for the CUMC campus.

- P&S will grow primary care medicine by increasing capacity at 168th Street and including primary care at ColumbiaDoctors Midtown and west side practices. P&S will strengthen links with affiliated physicians in Washington Heights/Inwood to offer more primary care.
- A priority of the plan is to be where the patients are. Columbia doctors will become "go-to" doctors because of their recognition as top doctors (New York magazine's top doctors list has more Columbia doctors than any other New York City medical campus), the full spectrum of illnesses treated (1,450 doctors in 65 locations and 1.2 million annual office visits), and clinicians' access to unique medical discoveries that can be translated to care that improves and saves lives.

Goal 3: *Be the leading research-based medical educational center.*

- Improving the research base starts with attracting trainees with the best academic potential and improving the curricula for academic leadership, recognizing that trainees are the pipeline for future faculty talent at P&S.
- Starting with the Class of 2015, most medical students will be in the 3 Plus 1 Curriculum in which they can devote a full year to their scholarly projects.
- P&S is seeking University approval for the Class of 2017 (starting in August 2013) to have the option to obtain an MSc degree for qualifying coursework and research during four years or an optional fifth year. The strategic plan also calls for increasing dual-degree options and re-energizing master's and doctoral degrees in medical science.

"Strategic planning builds on our already strong foundation and leverages the positive momentum that P&S has enjoyed over the past few years. These goals, strategies, and tactics will ensure that we maintain our position among the top medical schools," says Lee Goldman, dean. "Just as important as plans for new buildings, additional recruits, more research dollars, and curricular improvements are the core values our strategic process identified: excellence, collaboration/teamwork/diversity, innovation/discovery/scholarship, integrity, respect, and social responsibility. If we adhere to these core values, our efforts to achieve our goals become as important as meeting them and will signify resounding success."

- A program for scientists with PhDs to earn an MD degree in three years begins in Fall 2013. This new program will better integrate PhD programs into P&S life and allow scientists to expand their commitment to becoming physician-scientists.
- The medical school will explore creation of a new major in human biology at Columbia College as another pipeline for research-oriented medical and PhD students.

Goal 4: *Make CUMC a destination campus for work, education, and patient care.*

- Providing facilities, programs, and infrastructure commensurate with the stature of Columbia will make CUMC the destination of choice for faculty, staff, students, and patients.
- Implementation includes 525,000 net area square feet already renovated in existing buildings since 2006. Construction will begin in Fall 2013 on the new medical and graduate education building on Haven Avenue. A Facilities SWAT team will continue to ensure that campus buildings, some of which are 80 years old, remain clean and in good repair.
- Plans for further campus revitalization include new entrances for P&S and Black buildings and a renovated P&S auditorium with food court.
- Efforts for faculty and staff will focus on making CUMC a collaborative, respectful, and satisfying place to work. More housing options on and near campus and more environmentally green spaces and common areas are of particular importance to students and employees.
- Community partnerships will be strengthened through the new education building and improved car and taxi access and convenience.
- Columbia and NewYork-Presbyterian are working with the Metropolitan Transportation Authority to upgrade the 168th Street subway station through better lighting, new flooring, enhanced safety measures, and improved access to cellular phone service. Preparations for that upgrade began in Summer 2013.

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Office of the Executive Vice President for Health and Biomedical Sciences
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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
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Principal Writer: Sharon Tregaskis
Art Director: Eson Chan

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FACTS & STATISTICS, FY 13

MEDICAL SCHOOL ENROLLMENT, FALL 2012

Total medical school enrollment	662
Total enrollment of underrepresented minorities	137
Total enrollment of minorities	242
Total enrollment of international/nonresident students	23
Total enrollment of in-state residents	231
Total enrollment of men	332
Total enrollment of women	330

ETHNIC BREAKDOWN

Nonresident aliens	23
Hispanic/Latino	57
Black or African-American, non-Hispanic/Latino	58
White, non-Hispanic/Latino	359
American Indian or Alaskan Native, non-Hispanic/Latino	2
Asian, non-Hispanic/Latino	105
Two or more races, non-Hispanic/Latino	20
Race and/or ethnicity unknown	38

ENROLLMENT BY YEAR

	MALE	FEMALE
First-Year Class	83	84
Second-Year Class	83	84
Third-Year Class	87	84
Fourth-Year Class	79	78
Total Enrollment	332	330

DEGREES GRANTED, JULY 2012 TO JUNE 2013

MD	162
PhD	70
Doctor of physical therapy	60
MS in nutrition	78
MS in occupational therapy	59
Certificate in psychoanalysis	6

APPLICATIONS (ENTERING CLASS 2012)

Number of applicants	7,466
Number of applications considered	6,801
Number of applicants interviewed	1,042
Number of acceptance letters issued	309
Number of new entrants	167
Bassett Program applications	971
Number of new Bassett Program entrants	10

FACULTY DURING 2012-2013 ACADEMIC YEAR

	FULL TIME	PART TIME
Number of basic sciences faculty	230	70
Number of clinical faculty	1,676	2,588
Total medical school faculty	1,906	2,658

FACULTY HONORS

Nobel Prize in Medicine	2
National Academy of Sciences	15
Institute of Medicine of the National Academy of Sciences	38
Howard Hughes Medical Institute	14

FINANCIALS, FY 13 (except where noted)

Budget	$1.46 billion
Philanthropic support	$202 million
Endowment	$1.6 billion
Endowed chairs/professorships	228
Research support (FY 2012)	$403 million
NIH research support (FY 2012)	$253 million

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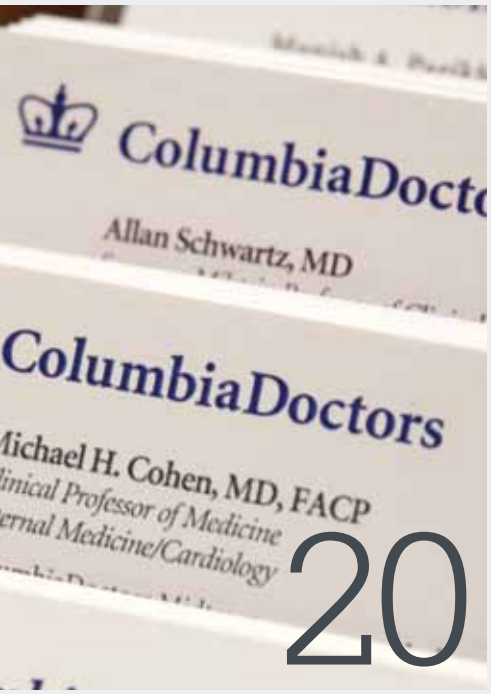

51 | 51: Patient Care at the Center of the Universe

From 1814 to 1985, Columbia owned land at Rockefeller Center in midtown New York City. Now Columbia has returned to the neighborhood with the opening of ColumbiaDoctors Midtown, a faculty practice located at 51 W. 51st Street, in the heart of New York City. Patients who visit physicians, nurses, and dentists there have a new gateway to the full spectrum of the ColumbiaDoctors multispecialty practice network.

In New Curriculum, Students Explore Passions, Sometimes Finding New Ones

The medical school curriculum that greeted members of the Class of 2013 when they enrolled in 2009 proved to be beneficial for students and faculty alike by creating a sustained interaction between student and mentor that resulted in a new paradigm for student evaluation.

Alternative Research: A New Approach to Diabetes

Calling existing treatments—"even in the hands of the most capable physicians"—imperfect, diabetes researcher Domenico Accili, MD, combines patient care with an ongoing search for ways to restore a person's ability to regulate glucose levels without insulin-producing drugs.