

# Columbia Medicine

2016 ANNUAL REPORT

Columbia University College of Physicians & Surgeons



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## **Big Data: The New Math in Patient Care**

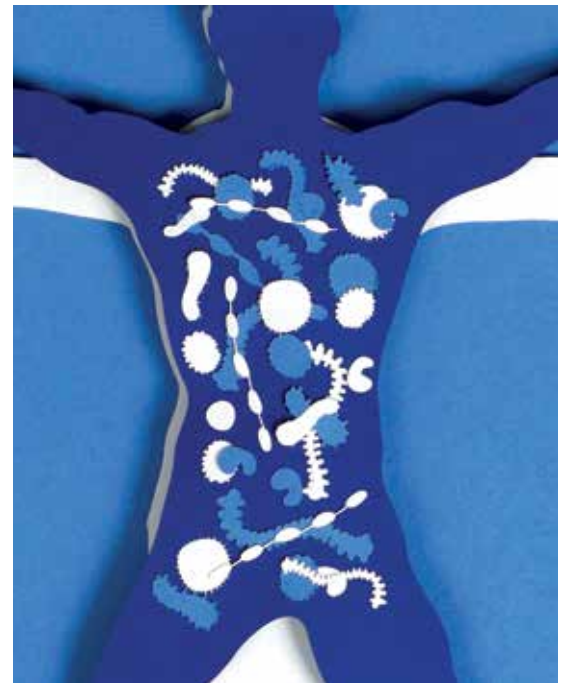
“Big data” is only as good as the computational tactics leveraged by investigators to make the information clinically relevant. Columbia researchers and clinicians are using multiple strategies to capture data to transform both research and patient care.



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## On the Cover

The opening of the Roy and Diana Vagelos Education Center is only one of the “big things” P&S celebrated in 2016. Visionary discoveries that were among the year’s accomplishments also laid the groundwork for promising future developments described in articles throughout this issue. The Next Big Things begin now.

### 2016 Annual Report

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## Closing the Books on a Great Year, Looking Ahead to an Even Better One

What can be said about the past year—Academic Year 2016—is similar to what we have said about many recent years at P&S. We are growing and thriving in so many ways:

- Our ColumbiaDoctors faculty practice organization grew by more than 8 percent last year, with an ever expanding geographic reach.
- We continue to grow our faculty at a net rate of about 6 percent per year, with outstanding faculty recruits from around the country.
- Our school's NIH grants portfolio increased by 11 percent during a year when the NIH budget increased only 1.6 percent.
- Our faculty's prolific research continues to change the face of biomedical science and medical practice, as evidenced by 74 papers in *Cell*, *Nature*, *Science*, and the *New England Journal of Medicine* alone.
- We were able to accept less than 4 percent of the nearly 8,000 students who applied to medical school this year, and year after year we have one of the country's highest yield rates on accepted students.
- We continue to have one of the most diverse student bodies, which is nearly double the national average of underrepresented minority students.
- Our commitment to our local community includes partnering in community-based participatory research, providing high-quality care to all of our neighbors, helping neighborhood children pursue their dreams of careers in medicine and science, and maintaining our campus as an open environment for our neighbors to share.

Behind those headlines are individual stories of success in all of our missions. Examples include grants large and small to study health across the lifespan, a student's scholarly project to improve a clerkship for future students, a surgeon's use of a technique that put an

11-year-old with cerebral palsy back into the basketball game she loves, and advancement of plans to close a portion of one of our streets to build a community square that will be shared with our medical center neighbors.

One annual report cannot tell all the worthy stories that illustrate a year's successes, but this report includes a selection of articles that describe some of our successes. Our ongoing work in precision medicine is exemplified in an article that shows the role and power of big data in modern patient care. An article on the microbiome shows how our researchers are going beyond just describing the microbiome to now demonstrating its influence on physiological processes. Another article takes you deep within our cells to explore the important role of noncoding RNA, previously thought to occupy only a minor role in genomic medicine. We also profile the work of four researchers involved in understanding and correcting disparities in disease and treatment among groups of patients whose health is influenced by social and environmental factors. What these varied efforts have in common is reflected in the theme of this report, "The Next Big Things," and these articles show how P&S ingenuity and perseverance generate new knowledge to advance patient care.

One of our most tangible achievements this year fits nicely into the "big things" category. As included in this report, in June we dedicated our new 14-story medical and graduate education building—the Roy and Diana Vagelos Education Center—in honor of the building's lead donors. Many other donors, including Cheryl and Philip Milstein; Kathryn and Mary Jaharis, representing the Michael Jaharis family; Roger Wu and David Wu, representing their parents, the late Helen and Clyde Wu; and Sudhir, Anita, and

Dhairya Choudhrie, representing the Choudhrie Family Foundation, were also on hand to dedicate the building. It is no exaggeration to say that we could not have built this amazing building, which was constructed entirely with private donations, without the generosity of so many philanthropists. This group of visionary supporters committed resources so that today's medical students can be trained in 21st century techniques in a learning environment that is both functional and architecturally stunning.

The futuristic theme of this report is also fitting for what we predict Academic Year 2017 has in store. As 2016 was turning over to 2017 on July 1, our faculty received major grants that will support our strategic priorities. One of the first is an NIH grant to Columbia to enroll participants in the Cohort Program of President Barack Obama's Precision Medicine Initiative. The five-year award, which has the potential to

JÖRG MEYER





total \$46.5 million, reinforces our leadership in precision medicine by extending our ongoing successes in taking an individualized approach to treating cancer and rare genetic diseases to a broader range of human illnesses. Columbia will partner with NewYork-Presbyterian, Harlem Hospital, and Weill Cornell Medicine to enroll patients as part of the national goal to enroll 1 million patient volunteers. P&S also was chosen to partner with a coalition of research organizations awarded \$13.7 million from the NIH to establish the Data and Research Support Center as part of the national Precision Medicine Initiative. Biomedical informatics experts at P&S will help curate health information being contributed to the Precision Medicine Initiative Cohort Program, including electronic health records, medical and pharmaceutical databases, and payer databases. P&S will standardize the information,

ensure the quality of the data, and convert the data into a format that is usable by researchers involved in the program. We also renewed our NIH Clinical and Translational Science Award, which funds the Irving Institute for Clinical and Translational Research at Columbia and NewYork-Presbyterian. The \$58.4 million grant will support the Irving Institute's ongoing work in translational research, speed development of new medical therapies, and align its focus on precision medicine with Columbia University's own Precision Medicine Initiative.

The end of Academic Year 2016 marks my 10-year anniversary as dean of this remarkable school. What our faculty, students, and supporters have accomplished during that decade is truly inspirational, from our phenomenal growth in research funding to our expanded clinical footprint to our impressive success in recruiting the best medical and graduate stu-

dents. As we look forward to another great year, we will have the privilege of celebrating the first 250 years of Columbia's medical school by combining historical reflections with visionary and strategic planning for the beginning of the next 250 years.

We enter this next year energized by an enthusiasm I know you—our faculty, students, alumni, generous supporters, and other readers—share. Thank you for all you contribute to our success—past, present, and future.

With best wishes,

Lee Goldman, MD, Dean  
lgoldman@columbia.edu



# BIG DATA

## THE NEW MATH IN PATIENT CARE

It was an undergrown 7-year-old boy who kindled Karina Davidson's epiphany, some 25 years ago, about the value of truly personalized medicine. The child weighed just 37 pounds, within the lowest percentile range for boys his age; he was not only failing to thrive, but also intensely violent toward himself and others. Dr. Davidson—then an intern in clinical psychology at the University of Waterloo in Canada—and the rest of the boy's clinical team struggled with how to care for him. Might megadoses of Ritalin temper his behavior? And what drove his rages? The team brainstormed hypotheses: Poor sleep? A lack of structure in his environment? Insufficient calories? His interactions with his mother?

To find out, they designed a randomized, controlled trial—a stretch of Ritalin followed by a stretch of placebo—in which the boy was the sole subject and his own time-lapsed control. Dr. Davidson asked the practice's pharmacist to formulate a Ritalin lookalike placebo. She had a statistician from the university create randomization codes to blind the clinical staff, the boy, and his family to which treatment he was receiving. The team hand-recorded endless checklists to track his acting out against sleep, diet, social interactions, and other factors, then entered the observations into a computer for analysis. It was labor-intensive,

but the approach worked. Ritalin, they learned, was not working. It suppressed his appetite and did nothing to reduce his violent and suicidal episodes. And his aggression seemed to be triggered by the dynamic with his mom. Based on these hard-won data, so specific to this one child, Dr. Davidson and her colleagues devised a treatment plan that helped him gain weight and rein in his emotional turbulence.

"The lesson that has stayed with me for a lifetime is that excellent clinical care should be informed by science, but it's best informed by the patient in front of you," says Dr. Davidson, director of Columbia's Center for Behavioral Cardiovascular Health. It is what she calls "precision therapeutics"—pinpointing the treatment that will help a specific person, rather than starting with what might benefit the average person and making guesses from there.

Her intern experience cemented Dr. Davidson's vision for excellence in the practice of medicine, but she has had to wait to see its potential begin to be realized. Only in the past few years have genome sequencing and other molecular techniques advanced enough to allow researchers to identify precise molecular differences between people and to begin to understand how those differences can be targeted therapeutically. Meanwhile, personal health tracking devices and mobile phone

Precision Medicine  
Refines its Calculus  
with Emerging  
Analytical Tools  
and Innovative  
Study Designs

By Alla Katsnelson

Photographs by Jörg Meyer



Karina Davidson, PhD

apps can now seamlessly capture and digitize blood pressure, sleep patterns, mood changes, and more in real time—the exact information Dr. Davidson and her colleagues painstakingly took down with pen and paper. By matching this phenotypic data to genomic and other types of molecular data, researchers think they can begin to figure out the underlying cause for each individual’s illness—be it acute, like a fast-moving cancer, or chronic, like high blood pressure.

“We can now measure so much in exquisite detail,” says Muredach P. Reilly, MBBCh, who this year moved from the University of Pennsylvania to be director-designate of the Irving Institute for Clinical and Translational Research. “We have these incredible tools that allow us to look at each individual’s genomic and physiological profile and to map them in health and disease.”

The ability to capture this vast quantity of data is transforming both research and medical care—and Columbia researchers and clinicians are at the forefront of that transformation.

“The institutional vision for precision medicine at Columbia is very strong,” says Dr. Reilly, who will succeed Henry N. Ginsberg, MD, as director of the Irving Institute for Clinical and Translational Research next year. “There’s huge, top-down support here for developing precision medicine tools and big-data know-how for personalized care. And there’s also a vibrant feeling on the ground of a commitment to collaboration among different fields of medicine—from bioinformatics, to genomics, to cancer, to behavioral health—to make ours the leading precision medicine program in the U.S.”

The type of approach that Dr. Davidson takes is called an N of 1 study—a highly systematic and statistically rigorous examination of a single subject. Until recently, single-patient studies such as the one she ran for her young Canadian patient have been considered interesting and informative, perhaps, but anecdotal and ungeneralizable. Instead, for the past half-century, randomized controlled trials with a large N—the letter that symbolizes the number of patients—have been the gold standard in determining a treatment’s efficacy. What these studies identify is essentially the treatment that works best for the average patient.

But as researchers increasingly come to understand the extent of inter-individual variability among patients, they are realizing that what helps the average patient—whoever he or she may be—often does little for their specific patient. “For most chronic health problems—pain, obesity, sleep issues, asthma, the list goes on and on—we don’t have a single treatment that works for everybody,” Dr. Davidson explains. Because first approximations are extremely useful, and work well for many people, randomized controlled trials will probably remain the bread and butter of clinical research for the indefinite future, she says. But alongside them, more personalized approaches are sorely needed.

Take blood pressure pills. There are many kinds, and over all they have similar efficacy. But for any one person some will work while others will not. A doctor might prescribe one and then, if the desired effect isn’t achieved, add a second and even a third, never figuring out which is actually doing the job. “But if we standardly test those medications at the lowest dose in a randomized way, we might control people’s symptoms

“For most chronic health problems we don’t have a single treatment that works for everybody.”





Andrea Califano, PhD

with the fewest drugs,” she says. A clinician could identify the unique protocol that works best for one specific patient, marrying the promise of evidence-based approaches with a truly personalized touch.

Working with internist Ian Kronish, MD, Dr. Davidson is using N of 1 studies to help individuals improve their cardiovascular health. Recently she and her colleagues completed a study funded by the National Heart, Lung, and Blood Institute that explored the relationship between exercise and stress. The link, they found, was highly specific for every individual: For some, exercise seemed to drive down stress levels; for others, stress drove down exercise levels; and for others, still, there was no correlation at all. “All of those scenarios make sense, don’t they?” Dr. Davidson says. “It’s just that you have to find what’s true for *you*—not for the average person.” Unfortunately, that kind of individual variation washes out in large trials, which tend to find no association at all between stress and exercise.

Now Dr. Davidson’s team is surveying physicians, nurses, and patients nationwide to identify conditions for which N of 1 trials would most benefit patients. Hypertension is a strong candidate because it is a costly disease for which patients often take multiple drugs for life. Pain is another possibility; being able to systematically test the efficacy of multiple interventions in one person could provide life-altering relief. The team is also surveying cancer survivors about their interest in using the approach to manage their depressive and fatigue symptoms. Whichever they tackle will be a vital step toward realizing Dr. Davidson’s vision of 25 years. “It’s an exciting time,” she says, “because we could be the first in the country to offer such a service.”

**N** of 1 studies come in an array of permutations. Andrea Califano, PhD, uses the approach to find better ways to treat rare and otherwise incurable cancers. The FDA has now approved a few dozen drugs that target particular genetic mutations in tumors—but it is unclear why many patients fail to respond and, even in the best cases, initial response is followed invariably by relapse. And although genome sequencing is becoming increasingly routine in cancer care, less than 11 percent of patients who are treated with a drug based on their genomic data experience a long-term benefit.

That is because mutated genes, pinpointed through sequencing, are not always the best therapeutic targets, says Dr. Califano. In some patients, genes associated with proteins that are hyperactive in the cancer cell do not carry mutations and vice versa—some mutations do not cause proteins to misbehave because other genes can compensate for the bad code. Instead, the clinically relevant players are “master regulators,” effectively the puppeteers of the cell transcriptional state. Dr. Califano and his colleagues have used massive supercomputers to reconstruct the regulatory networks of more than 30 different cancer types. Using the RNA fingerprint of a patient’s tumor—its gene expression profile—they can use these networks to predict both the master regulator proteins and the drugs that are likely to be most effective for that person’s cancer. These drugs are then taken for a test run in mouse “avatars”—models created with the patient’s own tumor tissue. In November, Dr. Califano was named a National Cancer Institute outstanding investigator and received a seven-year, \$6.7 million grant to pursue the work. He has already piloted the approach in more than 40 patients and is testing it more widely in

# PATIENT-ORIENTED RESEARCH

It can take decades for knowledge to go from bench to bedside. To spur the momentum of early-career investigators who have promising research programs, the Irving Scholars program annually selects a cohort of P&S assistant professors to receive stipends of \$60,000 annually over three years along with a named professorship. This year's recipients:

- **Ali Jabbari, MD, PhD, Dermatology:** Patients suffer devastating psychosocial consequences of the hair loss triggered by alopecia areata, an autoimmune disease for which the FDA has yet to approve a treatment protocol. Clinical research by Dr. Jabbari and others suggests that a class of compounds known as JAK inhibitors has the potential to reverse alopecia areata symptoms. By integrating patient data with insights from mouse models of the disease, Dr. Jabbari seeks to identify the mechanisms by which JAK inhibitors spur hair regrowth.
- **Fay Kastrinos, MD, Medicine:** As a gastroenterologist with Columbia's Pancreas Center, Dr. Kastrinos oversees the clinical practice for the Muzzi Mirza Pancreatic Cancer Prevention and Genetics Program. By integrating data from the center's pancreatic cancer family registry with patient imaging and other clinical information, Dr. Kastrinos and her collaborators are developing a clinical prediction model to identify people at greatest risk for hereditary susceptibility to pancreatic cancer, the fourth leading cause of death for American men and women.
- **Krzysztof Kiryluk, MD, Medicine:** Dr. Kiryluk investigates IgA nephropathy, the most common form of primary glomerulonephritis worldwide. While up to 40 percent of patients with IgA nephropathy develop end-stage kidney failure within two decades of the diagnosis, the variable course of the disease has prevented doctors from offering patients a clear prognosis. Dr. Kiryluk and his team seek to home in on the genetic mechanisms of IgA nephropathy, enable noninvasive diagnosis, improve personalized prognostication, predict relapse and recurrence, and, ultimately, develop novel targeted therapeutics.
- **Joanna E. Steinglass, MD, Psychiatry:** Now an associate professor, Dr. Steinglass investigates the cognitive neuroscience of anorexia nervosa, a debilitating illness for which clinical interventions are only modestly effective. Her analyses combine clinical data with brain imaging to reveal the link between neural mechanisms that drive food choice and the behavioral disturbances manifested by people with the illness. She aims to leverage those insights to develop treatments to prevent relapse.
- **Nicholas Tatonetti, PhD, Biomedical Informatics:** Every day, electronic health records capture billions of clinical data points around the world. Dr. Tatonetti and his team use rigorous computational and mathematical methods to advance data science in the realm of "systems pharmacology." By integrating medical observations with systems and chemical biology models, they intend to pursue understanding of basic biology and human disease, explain drug effects, and predict adverse drug reactions.

several follow-up clinical trials. "The fact that you can computationally predict the most effective drugs and test them in a mouse model of the patient's tumor to find the ones that effectively kill it," he says, "is unprecedented."

Master regulator networks play a role, too, in alopecia areata, a genetically inherited condition in which deranged immune cells attack hair follicles. Associated with severe hair loss and currently very difficult to treat, the disease has been the primary topic of study by genetics and dermatology researcher Angela M. Christiano, PhD, since she was diagnosed with the condition more than 15 years ago.

In November 2015, Cell Systems published work by post-doc James C. Chen, PhD, with Dr. Christiano and her team to untangle how master regulator networks influence the pathology of alopecia areata. "We wanted to track the process of immune cells infiltrating an organ," says Dr. Christiano, who notes that unlike cancer, which typically involves a single cell type, a technical challenge associated with autoimmune disease is the interaction among tissue types—in this case, hair follicles and T cells.

Beyond insights into the mechanisms of pathology in autoimmunity, Dr. Christiano's work offers a through-the-looking-glass perspective on the quest for better ways to fight cancer. In alopecia areata, overzealous T cells destroy otherwise healthy hair follicles. In their quest for immunotherapy treatments, oncologists seek a tactic to spur T-cell function to boost patients' capacity to blast their own tumors. "Our hypothesis was that if we could do it in autoimmunity, we could find the drivers and extend it back to cancer," says Dr. Christiano. "For autoimmunity, we'd like to down-regulate or dampen the process of T cells attacking an organ, but for cancer you would try to find ways to enhance it."

Dr. Christiano credits Dr. Chen—a recipient of one of four precision medicine fellowships announced by the Irving Institute for Clinical and Translational Research in January 2016—for spurring the new line of inquiry for her group, which has used genome-wide association studies to identify pathways that could be targeted by a class of compounds known as JAK inhibitors to spur complete hair regrowth for 75 percent of clinical trial participants with alopecia areata. As a doctoral student with Dr. Califano, Dr. Chen investigated the role of master regulator networks in a particularly vicious form of brain tumor known as glioblastoma. Now he works with Dr. Christiano to extend those techniques to autoimmunity and understand what is going on at a molecular level for patients who do or do not respond to treatment with JAK inhibitors. "When a patient comes in with a new spot of hair loss from alopecia areata, it's not clear just by looking at them whether they'll get better, get worse, or stay the same," says Dr. Christiano. "For us, precision medicine means better diagnosis and being able to direct them toward or away from a JAK inhibitor or other new therapies on the horizon."

Data scientist Raul Rabadan, PhD, takes an *in silico* approach to patient-specific data. A theoretical physicist by training who turned his attention to biology about a decade ago, Dr. Rabadan



Angela M. Christiano, PhD



Raul Rabadan, PhD

uses genomics and a branch of mathematics called topology to map large genomic datasets. He is the director of an NCI center, the Center for Topology of Cancer Evolution and Heterogeneity, that connects mathematicians, physicists, biologists, and clinicians to study cancer using large-scale genomic data.

Dr. Rabadan is leveraging genomic and mathematical approaches to gain greater insight into the mechanisms by which tumor cells evolve in response to cancer-killing drugs. Mutations accrue over time, as well as in response to the therapies that a patient receives. No two patients will develop the

same set of mutations, but a tumor's evolution may well affect the cancer's response to subsequent therapies. Some mutations will affect the tumor's growth, or its resistance to a particular drug protocol, while some will not have any effect at all. Last year, by using a mathematical approach to probe the genomes of patients with a particularly aggressive form of lymphoma, Dr. Rabadan's team was able to identify a novel pathway that drives the cancer in many cases. Because drugs targeting this pathway have already been approved by the FDA to treat other conditions, the study identified a new tactic available to oncologists treating patients in whom that target is mutated. Now Dr. Rabadan has focused his efforts on understanding how brain tumors evolve under therapy. A recent analysis reported in *Nature Genetics* in June was the largest ever study of brain tumors, conducted through an international collaboration led by his group. The group identified several genetic mechanisms of resistance that drive evolution of these tumors under standard therapy, providing important clues for novel treatments and showing how genomics can be used for precision medicine approaches to cancer.

Dr. Rabadan is also working with the group led by Tom Maniatis, PhD, director of Columbia's Precision Medicine Initiative, to refine and apply these computational tools to the study of stem cell differentiation at the single cell level. By following the trajectories of single cells—and the 20,000 or so genes they express—through space and time, his group seeks to capture the biological phenom-

By following the trajectories of single cells, researchers seek to capture the biological phenomena that would otherwise be lost in the shuffle of complexity.



Tom Maniatis, PhD

ena that would otherwise be lost in the shuffle of complexity. This collaborative study has identified new genes involved in the differentiation of embryonic stem cells to produce motor neurons and made it possible to identify all of the genes expressed in individual cells at multiple stages of differentiation, a “systems” approach to understand complex cellular differentiation. In addition, this method should make it possible to identify neurodegenerative disease mechanisms using cells obtained from neurodegenerative disease patients, such as those with amyotrophic lateral sclerosis, known as Lou Gehrig’s disease. In this case, patient fibroblasts are converted to induced pluripotent stem cells—iPS cells—which in turn are differentiated to produce motor neurons. Comparison with motor neurons produced from control cells may provide important insight into ALS disease mechanisms.

**R**esearch and interventions focused on individual patients have an unprecedented ability to pinpoint biological disease mechanisms and identify therapies that traditional clinical trials will miss. But scientists do not have to work at the individual level to contribute to the endeavor of precision medicine, says George Hripcsak, MD, a clinical informatics pioneer. His research gleans information about widely used treatments by examining select groups of patients with similar characteristics—an approach known as “stratified medicine.”

Dr. Hripcsak is the co-PI of an international program called Observational Health Data Sciences and Informatics, or OHDSI, a voluntary network of 60 patient databases in 14 countries that so far total about 600 million patient records. Network investigators aim to enroll 1 billion patients by 2023.

Using those records, any network participant can set up quick observational studies that analyze the patient data to address an important question about health care. “Observational studies don’t prove causality, but randomized clinical trials often can’t be generalized to *my* patient,” says Dr. Hripcsak. By analyzing subsets of patients matched for shared features—response to a particular sequence of drugs, for example—clinicians may be able to tailor treatment more narrowly within large populations, such as people with diabetes, hypertension, heart disease, and other chronic conditions.

In the network’s first major paper, published in June in the Proceedings of the National Academy of Sciences USA, Dr. Hripcsak and his colleagues provided proof of concept of that strategy with an analysis of the treatments received by patients with diabetes, hypertension, and depression around the world. The team set narrow parameters for which patients to include, whittling down the study sample to fewer than 1.8 million records. Then they queried the database for the sequence of treatments these select patients had received. Generally, patients with diabetes received the same first treatment around the world, but the researchers found huge variability for the other conditions.

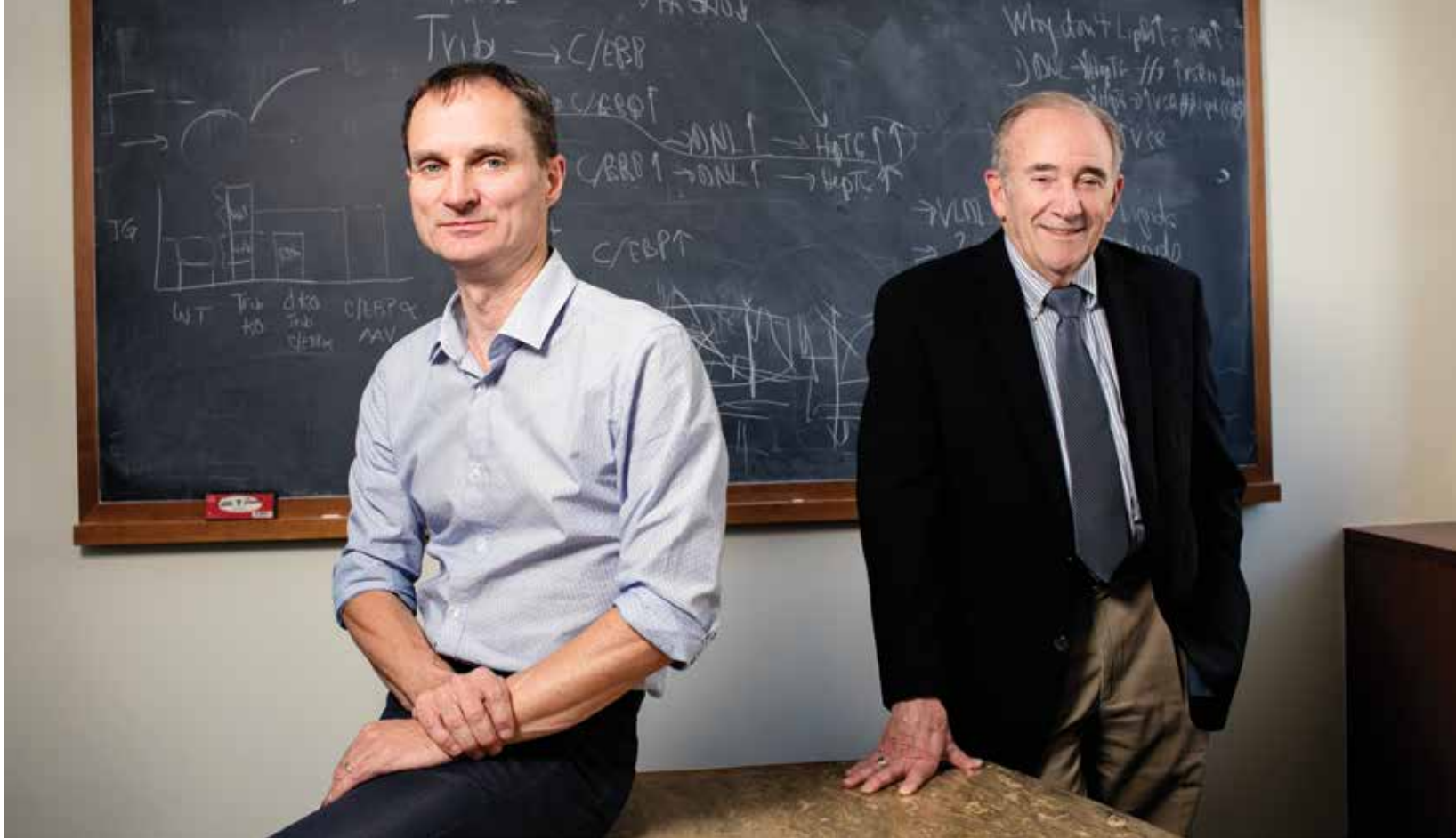
Knowing which therapies are actually used is crucial in conducting randomized trials for new therapies, says Dr. Hripcsak, and for integrating evidence-based approaches gleaned from randomized trials with a more personal approach. “It’s hard to learn what’s good treatment, or compare a prospective therapy to some standard care, when clinicians worldwide are all doing something different. If it turns out nobody uses the recommended therapy, then you end up doing very expensive randomized trials to prove that one unused drug should be replaced with another unused drug.”

That study was something of a trial run for the network, but Dr. Hripcsak looks forward to addressing other questions using the network. His team’s next study will examine side effects for all marketed medications. Of course, the massive analysis will not show whether any particular drugs cause the side effects, but the analysis will be able to flag the high and low fliers, he says. Meanwhile, independent of the OHDSI project, Dr. Hripcsak and colleagues are beginning to design patient-specific computational models for people with type 2 diabetes that predict in real time how their bodies will respond to certain food intake or activity levels. When programmed into a wearable device, these programs, tuned to the specifics of the wearers’ bodies, will help diabetics know when and what to eat and when and how much to exercise to achieve their goals for disease management. “The availability of all these data—and also new algorithms and computing techniques—allows us to calculate things that even a few years ago just weren’t feasible,” he says.

Dr. Reilly, too, studies subsets of human subjects, but his goal is to hand-select subjects with specific genetic mutations in order to conduct deep-dive research into how genes function in health and disease. Genomic analysis has linked a multitude of genes to specific conditions, but of some 18,000 protein-coding genes in

## Who’s Who

- **Andrea Califano, PhD**, the Clyde ’56 and Helen Wu Professor of Chemical Biology (in Biomedical Informatics and the Institute for Cancer Genetics), professor of biochemistry & molecular biophysics, and chair of the Department of Systems Biology
- **George Hripcsak, MD**, the Vivian Beaumont Allen Professor of Biomedical Informatics and chair of the Department of Biomedical Informatics
- **Angela M. Christiano, PhD**, the Richard and Mildred Rhodebeck Professor of Dermatology and professor of genetics & development
- **Ian Kronish, MD**, Florence Irving Assistant Professor of Medicine
- **Karina Davidson, PhD**, professor of behavioral medicine in medicine and psychiatry, director of Columbia’s Center for Behavioral Cardiovascular Health, and vice dean for organizational effectiveness
- **Tom Maniatis, PhD**, the Isidore S. Edelman Professor of Biochemistry & Molecular Biophysics, chair of the Department of Biochemistry & Molecular Biophysics, and director of the Columbia University Precision Medicine Initiative
- **Henry Ginsberg, MD**, the Herbert and Florence Irving Professor of Medicine and director of the Irving Institute for Clinical and Translational Research
- **Raul Rabadan, PhD**, associate professor of systems biology and of biomedical informatics
- **Muredach P. Reilly, MBCh**, director-designate of the Irving Institute for Clinical and Translational Research and the Florence and Herbert Irving Professor of Medicine



the human genome, the effect of about 15,000 is unknown. Dr. Reilly studies the genomics of cardiovascular disease, and you might call one focus of his studies “natural mutants,” people who have been found, through gene sequencing, to have a mutation in a gene that has been implicated but not proved in a condition.

Dr. Reilly riffs that he works not on N of 1 studies, but on N of 10, or 20, or 30. “These are really intense studies of very selected people,” he says, “to understand what a particular gene does.” In many cases these people appear healthy and “normal,” he explains, but subtle changes in factors like response to stressors or immune or metabolic changes can be uncovered by probing widely into their physiology. “If we think a gene alters the course of heart disease, it may affect multiple things, like exercise capacity, metabolic rates, or energy consumption.” Maybe it affects a person’s heart rate and blood pressure during exercise, but not at rest, for example. “We need to study the human very carefully to gain these insights into personal health and the role of specific genes in the human setting.”

In genetic studies of people with coronary artery disease, for example, Dr. Reilly’s group explored one gene, ADAMTS7, which codes for an enzyme that modulates matrix proteins in the blood vessel walls. The group is now looking for loss-of-function mutations of this gene in humans to understand specifically how that gene function contributes to cardiovascular effects. Following the trail of genes by characterizing them from the molecular to functional level can create possibilities for therapeutic targets, he says.

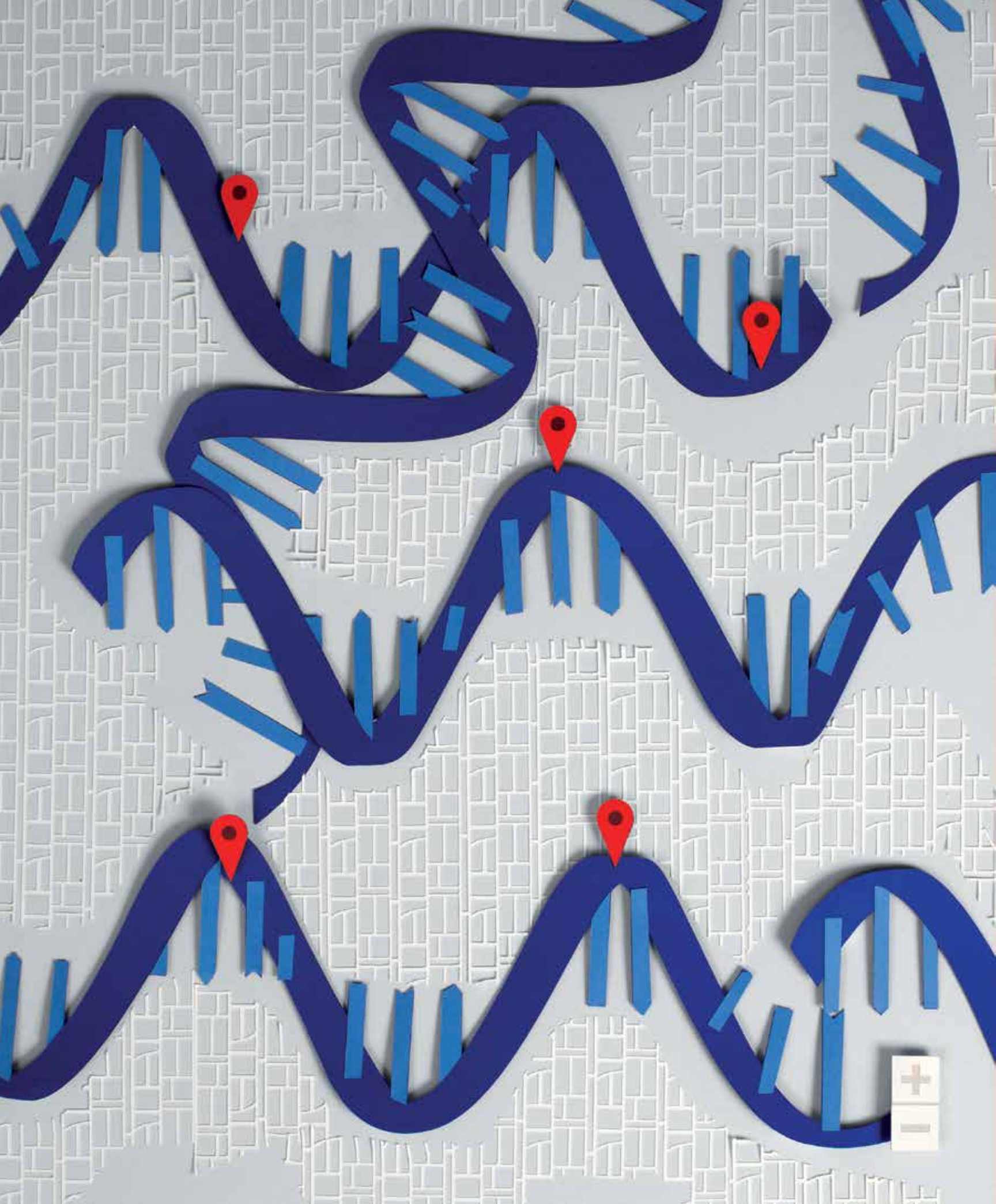
Another focus of Dr. Reilly’s inquiry is immune response to stress, which can change in response to high-fat food and exercise

and which in turn can alter the risk for other deleterious conditions, such as diabetes, stroke, and cancer. He and his colleagues set up a paradigm to inject tiny levels of inflammatory toxin into 300 healthy people, then intensely studied their subjects’ responses, following their innate immune responses as well as gene transcription changes in multiple cell types like blood and adipose tissue. That work, published in March, led them to discover a new part of the genome that regulates whether a person develops a high or a low fever in response to an immune system stressor. “The area of the genome associated with the fever was not associated at all with a person’s resting temperature,” says Dr. Reilly. That finding points to a separate genetic dial controlling how a person regulates his or her response to infection and trauma. Understanding that is important because both high- and low-temperature response to infection and trauma predicts death.

Ultimately, the next frontier in medicine will involve analyzing multiple layers of data on sick and healthy people, to tie molecular differences within and among people to differences in physiology, behavior, and environment, says Dr. Reilly. “We spend a lot of time knocking out genes in mice, zebrafish, or *Drosophila* to create models of disease and those are incredibly important for understanding molecular, biochemical, and physiological mechanisms,” he says. “But when it comes to understanding molecular mechanisms of the genome of a human, the human is the best model.” ❖

Muredach P. Reilly, MBBCh, left, joined P&S as director-designate of the Irving Institute for Clinical and Translational Research and will become director next year when he succeeds Henry N. Ginsberg, MD, who has been director since 1995.

“When it comes to understanding molecular mechanisms of the genome of a human, the human is the best model.”



## New Techniques Reveal How the Immune System Stays Nimble

# Map Quest

By Nancy Averett

Denis Burkitt, an Irish surgeon with a glass eye and a missionary's zeal, traveled 10,000 dusty miles in a cantankerous Ford station wagon across equatorial Africa in the 1950s. His aim was to map the boundaries of an aggressive cancer that caused grapefruit-sized facial tumors forcing children's eyes to protrude, their cheeks to bulge, and their teeth to fall out.

Through his travels, Dr. Burkitt discovered that the fatal malady was common in lush, forested regions and rolling savannas where mosquitoes and the malarial parasite they spread are endemic. During the next decade, he integrated his observations with those of others to realize that where DDT-spraying programs controlled mosquito populations—as on the island of Zanzibar, off the Tanzanian coast—both malaria and the cancer were almost nonexistent.

Sixty years later, African children are still dying from what's now known as Burkitt lymphoma—the cause of death for 3,000 children each year and the most common pediatric cancer in sub-Saharan Africa—and investigators are still trying to piece together its relationship to malaria.

Scientists are not without clues: Among Burkitt lymphoma patients, a particular chromosomal mutation—known for its potential to promote unregulated cell growth—is common. And that genetic glitch nestles within the immune system's B cells—the same cells that produce the antibodies needed to fight off pathogens, the same cells that malaria kicks into overdrive.

Many investigators suspect the malaria pathogen reprograms the immune system's antibody manufacturing process to produce the precancerous mutation. The details, though, remain a mystery. “The correlation has been reported for many years,” says Columbia malaria expert David Fidock, PhD. “But no one had the faintest idea what connected the two.”

This fall, Uttiya Basu, PhD, will embark on an investigation that might finally reveal the missing link. Like Dr. Burkitt, Dr. Basu boasts a detective's meticulous attention to detail. And like Dr. Burkitt, the microbiologist builds maps related to disease. But unlike Dr. Burkitt, whose maps spanned vast geographical regions, Dr. Basu will focus on microscopic areas deep within our cells, inhabited by long-ignored actors in the human genome known as noncoding RNA—the foremen of

the manufacturing sites—where he suspects antibody production sometimes goes bad. “If we can understand how malaria and Burkitt lymphoma are related,” Dr. Basu says, “we could attack them simultaneously.”

**D**r. Burkitt moved to Africa in 1946. His dream of becoming a surgeon had been cut short by the loss of his right eye during a childhood scuffle, but he harbored another passion—missionary work. So he took a post at Uganda’s Mulago Hospital. It was there in 1958 that he encountered a 5-year-old boy with a jaw tumor and extensive facial disfigurements. A few days later, while visiting a hospital in a nearby town, Dr. Burkitt saw another child with a similar tumor. When he returned to Mulago, he began digging through records; 29 other children had been admitted with comparable tumors.



Uttiya Basu, PhD

JÖRG MEYER

A few years later, Dr. Burkitt sent tumor samples to Michael Anthony Epstein, who thought a virus might be causing the children’s jaw cancers. Dr. Epstein found virus particles for what is now known as Epstein-Barr virus (EBV) in some of the tumor cells, providing the first evidence that endemic Burkitt lymphoma cells are often infected by EBV. Nevertheless the role of this virus in the pathogenesis of Burkitt lymphoma remains controversial.

Whether from Epstein-Barr or malaria, pathogens only make us sick if they dupe our immune system. To detect such hazards, the immune system conducts constant surveillance—and it only works if we have the right antibodies. While genetic mutation can quickly go off the rails, the process serves a vital, adaptive function within the immune system. “We encounter more pathogens in our lifetime than the number of stars we can count,” says Dr. Basu. “Each requires a perfect fit with an antibody to neutralize it, but we only have so many genes that can make antibodies.”

To surmount that constraint, the immune system leverages a kind of guided mutation to shift DNA sequences within each antibody gene to create a rich diversity of antibodies.

Dr. Basu began studying those processes at Harvard in 2004 as a postdoc in the lab of immunologist Frederick Alt, PhD, a former member of the Columbia faculty. In Dr. Alt’s lab, Dr. Basu homed in on activation-induced cytidine deaminase (AID), an enzyme whose presence during transcription seemed central to those guided mutation processes. “When I started working in Fred’s lab, antibody diversity was new to me and it was very exciting,” says Dr. Basu. “But in the last six to eight years, things have changed and how antibodies generate this diversity by genome rearrangement and mutagenesis has taken a new twist.”

### SENSE VS. ANTISENSE

For decades, biology’s central dogma has been that DNA makes coding or messenger RNA (mRNA), mRNA makes proteins, and proteins drive our cellular functions. Since nonprotein coding RNA (ncRNA) does not appear in that litany, it has received relatively short shrift in the genomic medicine revolution. The disregard was once so pervasive, it even informs the molecule’s alternative eponym—“antisense” RNA (sense RNA being, of course, mRNA).

With limited computational and analytical tools and a dominant paradigm intent on DNA and mRNA, scientists ignored ncRNA. Instead, they focused on transcription, the production line on which our genes make proteins. The manufacturing process begins when an enzyme attaches to a gene and uncouples the gene’s DNA from its double helix shape—imagine opening a zipper. Next, the enzyme slides along one strand of the zipper, adding complementary nucleotides to create a strand of mRNA (a process termed “transcription”). Finally, when the enzyme reaches the gene’s end, transcription stops and the freshly manufactured mRNA detaches and floats away to be translated on the ribosome and form a protein.

Think of AID, the enzyme Dr. Basu was investigating at Harvard, as a special foreman who only intermittently visits





the transcription factory floor. In its absence, DNA and RNA nucleotides match cytosine to guanine and adenine to thymine. But in its presence, the pairing process “deaminates,” linking cytosine to uracil and creating a U:G mismatch.

At Harvard, Dr. Basu discovered the “switch” that activates AID in the immune system. Nature published the finding in October 2005. Little did Dr. Basu realize, when that highly acclaimed paper was released, just how much more there was to learn. AID creates the good mutations needed for antibody diversification but also introduces genomic alterations that can lead to chromosomal translocations including those found in people with Burkitt lymphoma.

The key genetic lesion detectable in 100 percent of Burkitt lymphoma cells, the chromosomal translocation involving the *c-MYC* oncogene, was identified in 1982 by Riccardo Dalla-Favera, MD, then an investigator at the National Cancer Institute. Now director of Columbia’s Institute for Cancer Genetics, Dr. Dalla-Favera has published dozens of papers on the oncogene and its role in Burkitt and other forms of non-Hodgkin’s lymphoma. His work has yielded new insights into the pathogenesis of human B-cell lymphomas and, in particular, the genetic lesions and biological mechanisms responsible for the development of these diseases.

Since joining the Columbia faculty in 2009, Dr. Basu has focused on how the immune system’s B cells regulate AID—what is the quality control mechanism that allows most of us to benefit from AID-activated antibody diversification, and

P&S researchers use an array of options—biomolecular assays, whole exome sequencing, whole transcriptome sequencing, and genetically engineered mouse models—to disclose the cellular pathways disrupted by the genetic mutations common to lymphoma.

how does the process go wrong to create mutations and translocations like those seen in *c-MYC*? As would be expected, Dr. Basu was motivated and influenced by Dr. Dalla-Favera’s earlier studies. In a 2011 *Cell* paper, Dr. Basu and his lab showed that a large cellular complex called the RNA exosome recruits AID to modify DNA during transcription.

Until Dr. Basu’s discovery of the RNA exosome’s role in guided mutation, scientists thought of the exosome’s primary job as degrading ncRNA. Combined with his new insight into the role of the RNA exosome in antibody diversification, Dr. Basu and his team turned their attention to a new question: What is the relationship between noncoding RNA and AID?

The RNA exosome works so fast to degrade ncRNA that scientists cannot even see it happen. To investigate its role, Dr. Basu and his students engineered a knockout mouse with a nonfunctioning exosome. The knockout lets noncoding RNA pile up in the murine B cells, giving Dr. Basu and his team enough time to collect data on them. Data in hand, they

turned to quantitative computational scientist Raul Rabadan, PhD, and his postdoc, Jiguang Wang, PhD, to build a tool that would analyze those accumulated ncRNA.

To help the investigators visualize their data, Dr. Wang wrote algorithms to sort the various ncRNA and create a Google Maps-like browser. Users type in a gene name and the program spits back any ncRNA in that region. Color coding highlights ncRNA expression in both exosome-deficient mice and normal mice; by zooming in and out, scientists can get a local or global view of the genome. “Because we can actually map the ncRNA and study it globally, we can learn much more about it,” says Dr. Basu. “There are long ncRNA, micro ncRNA, enhancer ncRNA, and promoter ncRNA—they come in many flavors.”

### LIKE SPACE EXPLORATION

The flavors Dr. Basu’s lab was most interested in were those controlled by the exosome. But first they had to build their exosome-deficient knockout mouse, sequence its ncRNA, and hand off that information to Dr. Wang, a process that took nearly 12 months. In 2012, the data were finally ready. Now a research scientist at Regeneron Pharmaceuticals, Evangelos Pefanis’14 PhD, was a graduate student at the time. On one fateful February morning, Dr. Pefanis got to the lab early, opened his laptop, and began typing gene names into Dr. Wang’s browser. Right away, he says, “I could see something interesting was going on.” Moments later, when Dr. Basu walked in, Dr. Pefanis waved him over. “Hey, take a look at this gene,” he said. “And take a look at this one and this one.”

Dr. Basu stared at the screen as the graduate student clicked through the data. There they were, plain as day: strands of ncRNA spread across the genome, clustering around genes known to undergo bidirectional transcription, a unique regulatory mechanism that may play a role in switching genes on and off. There also

were large quantities of ncRNA on the parts of antibody genes where DNA double-strand breaks happen to create the “good” mutations that diversify our antibody inventory. But there were also large quantities of ncRNA near five precancerous genes known to be erroneous targets of AID, including c-MYC, the proto-oncogene common among people with Burkitt lymphoma. The results, which were published in *Nature* in October 2014, were strong evidence: Antisense RNA plays a leading role in guiding mutations. The implications of the results were further discussed in a review article in *Advances in Immunology* published in May 2015.

“When you make a discovery like that,” says Dr. Basu, “it’s a bit like being the first to go to the moon, or Mars, or some other crazy planet.”

Perhaps even more important than revealing the existence of that crazy planet, his team had assembled the tools to explore it. Now that they could poke around within the immune system’s ncRNA, Dr. Basu’s team created additional exosome-deficient mouse models to extend their reach.

In the new knockout mice, they found additional types of antisense RNA, including genetic sequences that activate gene transcription (called enhancers). These antisense RNA also tended to be adjacent to genes susceptible to both good and bad AID-induced mutations. They also found that without a functioning exosome quickly degrading the ncRNA as soon as its job was done, the presence of ncRNA set the stage for yet another type of mutation. When functioning optimally, Dr. Basu and his team concluded, the antisense RNA works like a matchmaker: It steps in to attract AID to various genes but then it better get lost; its mere presence can lead to inappropriate attraction of AID to genes, which will cause unwanted mutations.

Finally, because DNA exists in tertiary structures called chromosomes that are bunched and looped, Dr. Basu and his

## New Celiac Risk Factor Identified

**FOR PEOPLE WITH CELIAC DISEASE**, ingesting gluten—proteins found in wheat, rye, and barley—triggers an autoimmune reaction characterized by severe gastrointestinal symptoms. An estimated 40 percent of the population has the gene variants associated with celiac disease, but only 1 percent of people with these genes will develop intestinal inflammation and damage after ingesting gluten.

Researchers from Columbia’s Celiac Disease Center and the Department of Microbiology & Immunology—including Peter Green, MD, director of the Celiac Disease Center, and Sankar Ghosh, PhD, chair of microbiology & immunology—have identified a segment of RNA that, when suppressed, may contribute to celiac-associated intestinal inflammation. The findings point to a possible new risk factor for the disease.

In a series of experiments reported in *Science*, the team demonstrated that a long non-coding chain of RNA dampens the expression of celiac-associated genes. They then discovered that people with celiac disease had unusually low levels of this RNA in their intestines, suggesting that the reduced levels may contribute to the inflammation seen in celiac disease by turning off the normal regulatory pathway.



students wondered if some antisense RNA might influence that three-dimensional topography. The investigators knew that sometimes DNA loops shift and when they touch one another, the adjacency can alter gene expression. Might antisense RNA serve not only as a matchmaker among enzymes and genes, but also as a facilitator to the unique bunching and looping of DNA strands within a chromosome?

Indeed, when Dr. Basu's team started removing strands of antisense RNA depending on their location within the genome, they found that they could impede the capacity of a regulatory component of antibody genes to initiate guided mutation some 2.6 million nucleotides away from the material they had removed.

As they pondered these discoveries, which *Cell* published in May 2015, Dr. Basu and his students began to wonder: Could something other than a scientist—a pathogen or a virus, perhaps—also disrupt all of that carefully calibrated ncRNA machinery?

### STUDYING MICE WITH MALARIA TO HELP BURKITT LYMPHOMA PATIENTS

This fall, Dr. Basu and his students will begin infecting mice with the malaria parasite—the first step in generating a new map to show how the mosquito-borne pathogen affects the ncRNA landscape. Based on earlier work from their team and other groups, the researchers have a hunch about the location within the genetic code where the mutation common to Burkitt lymphoma patients originates. To test their hypothesis, they are zeroing in on differences in that region between normal mice and infected mice. They expect that the pathogen will cause increases in ncRNA—as well as the increased potential for structural mutations—near a genetic component common among people with Burkitt lymphoma. Finally, they will experiment with methods to prevent the mutation by injecting mice with antibodies that inhibit AID expression. Eventually, they hope to develop drugs to cause that suppression.

Even as they dig deeper into the mechanisms at play in Burkitt lymphoma, Dr. Basu and his collaborators continue to refine their understanding of the various mechanisms by which lymphocytes operate within the immune system to monitor progression of cancer and onset of many other diseases. In November 2015, *Cell Reports* published Dr. Basu's paper, co-authored with Jianbo Sun, PhD, Dr. Rabadan, Dr. Pefanis, Dr. Wang, and other scientists, on the use of transcription analyses to identify a biomarker for B cells with immune suppression functions. Unpublished studies from Dr. Basu's laboratory done in collaboration with Columbia neurosurgeon Adam Sonabend, MD, have yielded identification of a novel mechanism of immune system-mediated clearance of cancer of the human brain.

Meanwhile, Dr. Rabadan and his systems biology colleagues have delved deeper into the association of Epstein-Barr virus with some cases of Burkitt lymphoma. By using next-generation sequencing, they were able to classify the RNA mutations associated with each of the three clinical forms of Burkitt lymphoma—endemic, sporadic, and immunodeficiency-related. In October,

### Who's Who

- Uttiya Basu, PhD, associate professor of microbiology & immunology
- Riccardo Dalla-Favera, MD, the Percy & Joanne Uris Professor of Clinical Medicine, professor of microbiology & immunology, pathology & cell biology, and genetics & development, and director of the Institute for Cancer Genetics
- David Fidock, PhD, professor of microbiology & immunology and of medical sciences (in medicine/division of infectious diseases)
- Laura Pasqualucci, MD, associate professor of pathology & cell biology (in the Institute for Cancer Genetics) at CUMC
- Evangelos Pefanis, PhD, scientist, Regeneron Pharmaceuticals
- Raul Rabadan, PhD, associate professor of systems biology and of biomedical informatics and director of the Center for Topology of Cancer Evolution and Heterogeneity
- Adam Sonabend, MD, assistant professor of neurological surgery
- Jianbo Sun, PhD, former associate research scientist in microbiology & immunology
- Jiguang Wang, PhD, associate research scientist in biomedical informatics

the journal *PLOS Pathogens* published their analysis. “When studying the mutational profile of endemic Burkitt tumors,” wrote Dr. Rabadan and his co-authors, “we find recurrent alterations in genes rarely mutated in sporadic Burkitt lymphomas.”

As technology has advanced, P&S investigators, including Dr. Dalla-Favera, Dr. Rabadan, and Laura Pasqualucci, MD, have leveraged an array of options including biomolecular assays, whole exome sequencing, whole transcriptome sequencing, and genetically engineered mouse models to disclose the cellular pathways disrupted by the genetic mutations common to lymphoma and Burkitt lymphoma in particular. That work promises to reveal new therapeutic targets to boost treatment options for the condition, which remains incurable in approximately 30 percent of patients.

Such endeavors would have been hard for Dr. Burkitt to imagine. When the missionary doctor encountered the disfiguring lymphoma that now bears his name, cancer treatments were in their infancy and nothing could be done for his young patients. “This is the gloomy part of medicine,” he told a colleague. Little did he know that his own persistence in describing the disease—one that took him around the edges of his adopted land—might culminate decades later in another epic journey, only this time in the tiniest of landscapes.

Dr. Basu believes the work has implications far beyond Burkitt lymphoma, with the potential to help clinicians fight a wide variety of diseases at the molecular level. He looks forward to growth in the field as fellow investigators map ncRNA in cell types throughout the body, including neuronal cells and cardiac muscle cells, and continue to innovate and refine techniques for investigating how ncRNA operates. Says Dr. Basu: “There's all kinds of different noncoding RNA species just waiting to be discovered.” ❖

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## Microbes Within Us

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Scientists  
Investigate  
How the  
Microbiome  
Influences  
Human Health

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By Sharon Tregaskis

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Photographs by Jörg Meyer

Anyone who has ever announced a pregnancy knows how freely others offer advice on sleeping habits, feeding, and other challenges that follow birth. But P&S bacteria researcher Yiping Han, PhD, offers a tip rarely included in the free-flowing advice: See a dentist and get serious about brushing, flossing, and rinsing with an alcohol-free mouthwash.

Her advice goes further: Optimize dental health in the months before you start trying to conceive to boost the baby's prospects for a healthy birth weight and full gestational age. Should an infection and swollen, bleeding gums simultaneously strike during pregnancy, says Dr. Han, see a doctor.

The advice emerges from more than 15 years in which Dr. Han's research has investigated the role of the oral microbiome in adverse pregnancy outcomes—miscarriage, preterm labor, low birth weight, and neonatal sepsis. Much of that work has focused on *Fusobacterium nucleatum*, a tubular bacterium implicated in periodontal disease and also associated with appendicitis, rheumatoid arthritis, Alzheimer's disease, and other maladies.

"There's a saying in the dental field that the mouth is the gateway to your health," says Dr. Han, also a faculty member in Columbia's College of Dental Medicine. "I think there's some justification to that."

Trillions of bacteria, fungi, and viruses populate our skin, sinuses, lungs, guts, and urinary and reproductive tracts. The oral cavity alone is home to between 700 and 1,000 species of microorganisms, which occupy such distinct habitats as the teeth, tongue, hard palate, soft palate, tonsils, and the "gingival sulcus," where teeth meet gum tissue. So many billions of beings comprise the human microbiome that scientists now estimate that their genes outnumber our own by a factor of 100 to 1. "If you add up all of the microbes in the gut, they weigh more than the brain in terms of physical mass," says biologist Harris Wang, PhD, assistant professor of systems biology. "They outnumber human cells 10 to 1. They constitute a very important area of the normal human physiology."

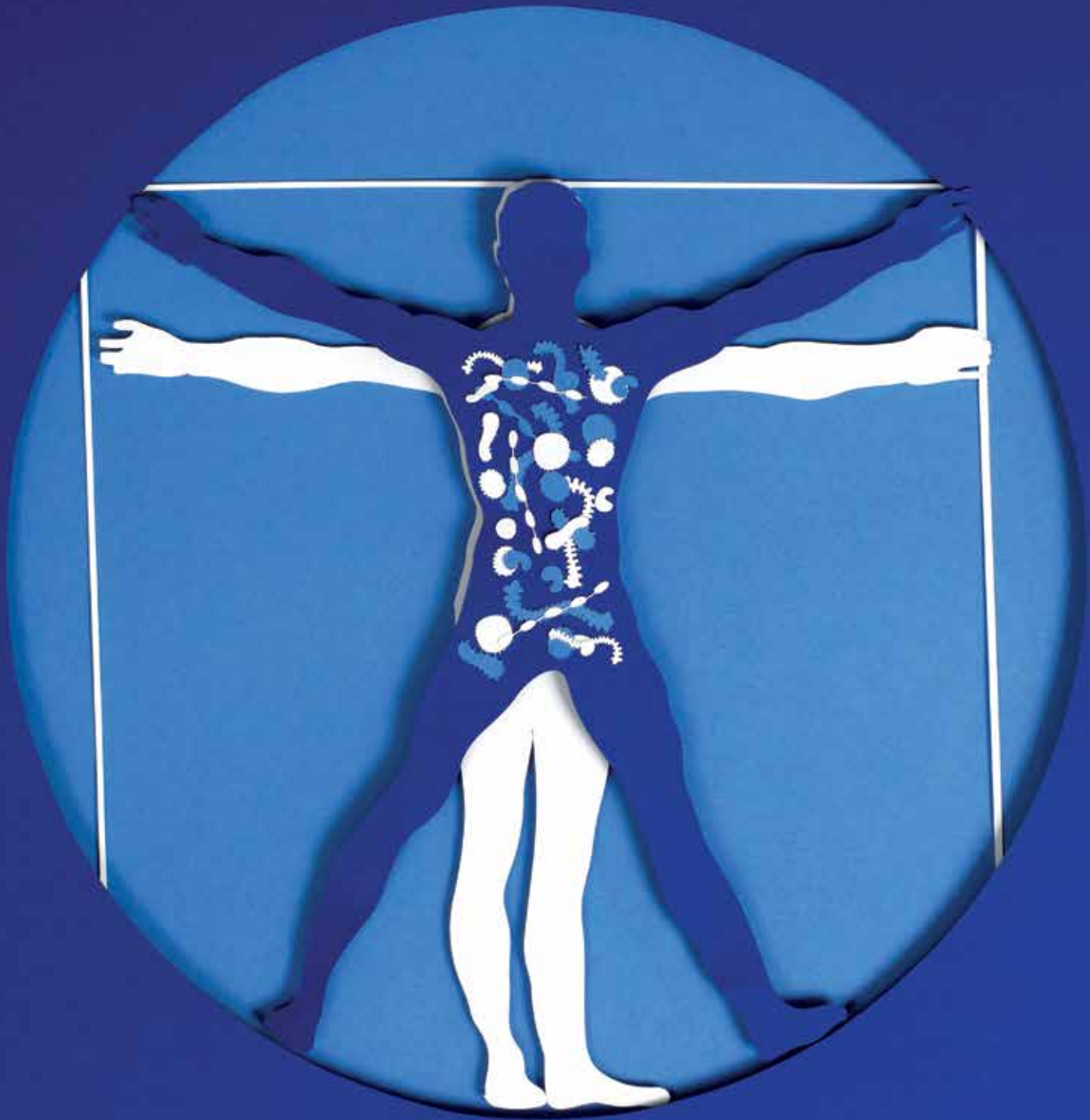
Don't make the mistake of imagining those microbes as mere bit players, says internationally renowned virus hunter W. Ian Lipkin, MD, who has joint appointments in P&S and the

Mailman School of Public Health. "We interact with them continuously and they mold who we are and what we will become. They've played important roles in evolution and they play important roles in everyday life—from how the immune system is tuned to how we respond to our environment and how we digest food."

Early research in the field—including the NIH's Human Microbiome Project, which launched in 2007—focused on naming and describing the species common to the human body. Dr. Lipkin, featured in a video as part of the American Museum of Natural History exhibition "The Secret World Inside of You," has been a leader in such efforts for more than three decades. "We have a symbiotic, or at least mutually respectful, relationship with our microbiome," he says. "It's when things get out of balance that we have difficulties—the *dis-ease* we perceive as disease."

Dr. Lipkin and Dr. Han are among a growing cadre of P&S investigators exploring what constitutes balance within the microbiome and how the many species involved maintain homeostasis with us, their human hosts. By getting a better handle on how the whole system functions, they hope to identify interventions that can promote health and prevent disease. "What I have been pushing for the last few years is for us to create an effort that moves beyond description," says Microbiology & Immunology Chair Sankar Ghosh, PhD, "to start exploring the mechanisms by which the microbiome influences physiological processes."

That effort extends from basic science to clinical applications, from new methods for microbial analysis to classic culturing. In Dr. Ghosh's lab, a team seeks to reveal how receptors within the immune system monitor the microbiome and the mechanisms by which our bodies respond briskly and aggressively to potentially dangerous species while giving beneficial species a pass. This year, Harris Wang received more than \$4 million in awards from the NIH, the Defense Advanced Research Projects Agency, and the Office of Naval Research to develop computational techniques to speed microbial discovery and genomic engineering strategies to unlock the secrets of microbes that scientists have not yet been able to culture in the lab. The projects include collaboration with



Ivaylo Ivanov, PhD, assistant professor of microbiology & immunology, on engineering commensals involved in inflammation.

In a project funded by the NIH with a five-year, \$2 million award, Dr. Han has partnered with Timothy Wang, MD, chief of digestive and liver diseases, to explore the role of *F. nucleatum* in colorectal cancer. Dr. Lipkin combines novel molecular diagnostic innovations with epidemiology and conventional clinical data to investigate the microbial hit-and-run events that seem to trigger such conditions as autism and chronic fatigue. Hepatologist Elizabeth C. Verna, MD, has begun monitoring the gut microbiome of people with liver disease, looking for clues to optimize post-transplant recovery.

#### An Ecological Mindset

When it comes to interactions between microbes and their human hosts, researchers sound rather like park rangers discussing how fire, drought, and myriad other environmental conditions can weight the scales in favor of one species or another. It's all about the web that holds the species together, their fates inextricably linked. "It's important to think

about bacteria, fungi, viruses, and human cells as existing in equilibrium," says Dr. Lipkin. "If equilibrium is maintained, we have health."

Like the keystone at the crown of a Roman arch, commensal species serve as vital placeholders. Take, for example, the commensal oral microbe *F. nucleatum*, the subject of Dr. Han's research and a building block of dental plaque. "Oral plaque consists of many, many bacteria—hundreds of species," she says. "They don't all just pile up randomly; they're very organized." Early colonizers bind to the protein layer that coats the tooth surface, creating crags and crevices for the secondary colonizers—*F. nucleatum* and its ilk. Late colonizers bind to the *Fusobacterium*. Without the bacteria, we would be spared tooth decay triggered by the acidic byproduct of bacterial metabolism but would be at risk of attack from more dangerous microbes. "The commensal bacteria occupy the sites in the host so that foreign pathogens—the exogenous pathogens—cannot colonize," says Dr. Han. "They build colonization resistance."

Imagine the give and take among microbes as something akin to international commerce, suggests Harris Wang, whose paper, "An Economic

Framework of Microbial Trade," appeared in PLOS One in July 2015. "A large fraction of microbial life on Earth exists in complex communities where metabolic exchange is vital," he and his co-authors wrote. "Microbes trade essential resources to promote their own growth in an analogous way to countries that exchange goods in modern economic markets." Extending the metaphor, the collaborators developed a model of microbial population dynamics based on the economic theory of general equilibrium. "Our model suggests that microbial communities can grow faster when species are unable to produce essential resources that are obtained through trade," they wrote, "thereby promoting metabolic specialization and increased intercellular exchange. Furthermore, we find that species engaged in trade exhibit a fundamental trade-off between growth rate and relative population abundance, and that different environments that put greater pressure on group selection versus individual selection will promote varying strategies along this growth-abundance spectrum."

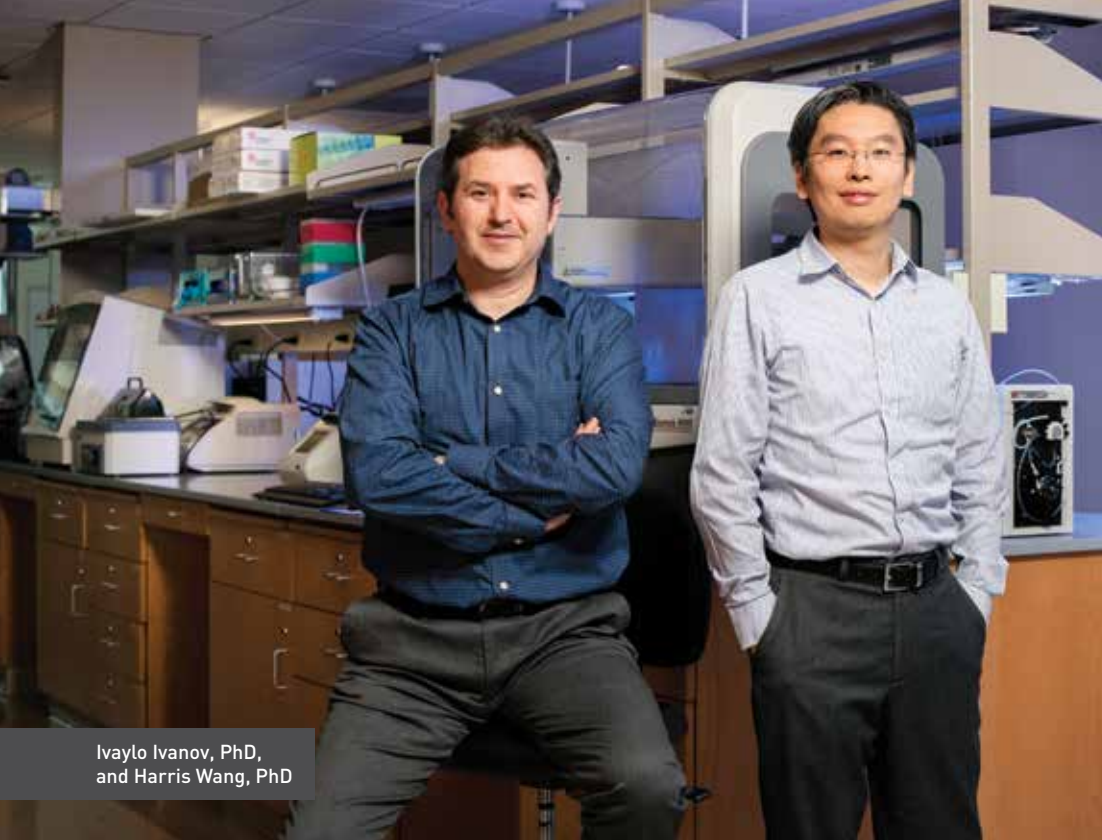
Imagine, then, how easily a commensal within the human habitat can become a pathogen. Take, for example, the fungus *Candida*, a standard fea-



W. Ian Lipkin, MD



Sankar Ghosh, PhD



Ivaylo Ivanov, PhD,  
and Harris Wang, PhD

ture of the human microbiome. Typically, our immune system keeps its population in check. But when the system gets disrupted—as with AIDS or in the aftermath of intensive antibiotic treatment—oral thrush or a yeast infection emerges. Likewise, *E. nucleatum* is ubiquitous within the oral cavity but typically held in check by a robust immune system abetted by regular brushing and flossing. “Everybody has *Fusobacterium*, but not everybody has periodontal disease,” says Dr. Han. “Under normal, healthy conditions, this bacterium can exist in our oral cavity without causing much harm. What kind of role the bacterium plays depends on the host ecological environment.”

The human immune system factors heavily among the environmental influences on the microbiome, and vice versa. Over the past five years, Dr. Ivanov has investigated how relationships between commensal microbes and their host regulate and modulate the immune system. Using a combination of genomic techniques and studies conducted in a germ-free facility with specially engineered mice, his team has elucidated the molecular communion between segmented filamentous bacteria, an intestinal commensal, and the leukocytes known as Th17 cells. Known to contribute to host defense against extracellular pathogens, Th17 cells also have been implicated in the pathogenesis of multiple inflammatory and autoimmune disorders. In 2009, Cell published Dr. Ivanov’s discovery that colonization with segmented filamentous bacteria spurs Th17

cell induction, one of the first direct examples of a specific commensal modulating intestinal immune function. “It was a huge advance,” says Dr. Ghosh. “It took the microbiome down from trillions of bacteria and thousands of different species to one bacteria and from many physiological processes to the production of one cell.”

In 2012, Dr. Ivanov was named a Pew Scholar in the Biomedical Sciences and in 2013 he received a senior research award from the Crohn’s and Colitis Foundation of America to investigate how commensal microbes battle inflammatory bowel diseases. In March his project, “Keeping a Healthy Gut: Commensal Bacteria Know-Hows,” earned Dr. Ivanov a 2016 Schaefer Research Scholar award—\$50,000 in discretionary funds and \$200,000 in direct costs. Such investigations of the mechanisms by which key commensal species regulate host immunity are sure to reveal new ways of treating immune diseases, says the scientist.

#### Good Bug, Bad Bug

Healthy and unhealthy guts alike feature *Helicobacter pylori*, a common stomach bacterium whose population takes its cues from conditions within each individual’s digestive tract. Once vilified as a pathogen for its role in stomach ulcers, the helical microbe gets more complicated with each clue investigators eke from their studies. Timothy Wang’s research, for example, has revealed that long-term exposure to *H. pylori* triggers atrophy

of the stomach’s acid-secreting cells, with a concomitant rise in pH, which ultimately makes the stomach inhospitable to *H. pylori*. At the same time, other species thrive in the less acidic environment. “There are two microbiomes of the stomach, one with *H. pylori* and one without,” says Timothy Wang.

Perhaps, he says, *H. pylori* should be reconceived as a commensal—basically neutral, providing that it stays where it belongs and remains in balance with the other species in its web of life, host included. For evidence, he turns to ancient history. Stomach ulcers are a 20th century affliction, but DNA evidence suggests that *H. pylori* has been present in the human gut for more than 200,000 years—long before our population outgrew the cradle of civilization. “In the vast majority of people—85 to 90 percent of people—they experience no harm from the bacteria and there may be some protective effects,” he says. “Maybe in the past, we never survived long enough to get ulcers.”

The same might be said of gastric cancer, another hazard of long-term exposure to *H. pylori*. Among people whose gut hosts the bacterium, between 1 percent and 2 percent develop malignancies in

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“We have a symbiotic, or at least mutually respectful, relationship with our microbiome. It’s when things get out of balance that we have difficulties.”

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the lining of their stomachs. Early in his career, Timothy Wang leveraged that statistic to develop the first rodent model of gastric cancer, by exposing mice to *Helicobacter felis*, a close relative of *H. pylori*. Since then, he has devoted much of his research portfolio to uncovering the mechanisms by which the bacterium induces malignancy. “It turned out, in our animal models—and we found this was also true in human patients—that when the cancer actually develops it’s in the setting of severe inflammation,” he says. “It was our hypothesis that the bacteria were modulating the host immune response leading to the cancer. This is the view of many people in the microbiome field—that

it's through the modulation of inflammation that a lot of the effects occur."

In particular, Timothy Wang and his collaborators have homed in on a curious detail: While the presence of *H. pylori* is predictive of future cancer risk, the bacterium seems to disappear around the same time malignancies actually take root. In a series of experiments with knockout mice in a germ-free facility, Timothy Wang and collaborators have shown a role for the additional bacte-

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“Right now a lot of microbiome research is correlative. Actually showing causality is difficult.”

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ria whose populations thrive as *H. pylori* pushes the stomach pH ever higher. “We demonstrated unequivocally that late-stage progression of gastric cancer is inhibited in a germ-free facility,” says Dr. Wang. “It’s really the bacterial overgrowth that is responsible for the progression of gastric cancer.”

Stomach acidity is not the only host environmental condition that constrains *H. pylori*. It turns out that modern living itself—our penchant for antibiotics and a class of antacids known as proton pump inhibitors—has precipitated a dramatic decrease in the number of people whose gut microbiome even contains *H. pylori*. Meanwhile, esophageal cancer seems to have reached epidemic proportions in developed countries. The divergent trends have led some scientists to speculate that perhaps *H. pylori* actually protects against esophageal cancer.

To test the association, Timothy Wang has partnered with Julian Abrams, MD, an expert in esophageal cancer. “We think that the upper GI tract microbiome plays a big role in the development of gastric cancer,” says Dr. Wang. “We’re starting to see that at the junction of the esophagus and stomach, the microbiome probably changes based on whether or not *H. pylori* is present in the stomach.” To reveal the mechanisms by which the bacterium exerts its influence, Dr. Wang is running a new series of experiments in a germ-free facility, this time with mice susceptible to esophageal cancer. “Perhaps *H. pylori* alters the stomach microbiome, thereby altering the esophageal microbiome, and that somehow affects the

development of esophageal adenocarcinoma,” he says. “At least, that’s the hypothesis.”

Another possible explanation for the negative association of *H. pylori* with esophageal cancer is that *H. pylori* is our microbial canary in the coal mine—just one among many gut microbes whose populations are failing under the onslaught of antibiotics and the rise of modern living. “There are thousands of species and there’s a dynamic balance,” says Dr. Lipkin. “We know that bacteriophages control levels of bacterial populations, but we don’t yet know the details.” The hazard is a slow, steady constriction of the microbial populations that hold our immune system in balance—and potentially the rise of far more vicious pathogens. As Dr. Lipkin notes, “Nature abhors a vacuum.” Perhaps, says Timothy Wang, *H. pylori* actually has nothing to do with esophageal cancer and some other microbe—not yet detected or named—is the real protector of esophageal health. “It’s like frogs disappearing in the swamps,” he says. “We’re not really that concerned about the frogs; it’s what the frogs represent, which is the disappearance of a lot of other species.”

#### Exploring Mechanisms of Inflammation

A growing body of research—including work by Timothy Wang—delves into the mechanisms by which inflammation mediates the microbial ecology and its association with malignancy. “When you get inflammation, even if that inflammation is not due to the bacteria, it changes the bacteria around that tissue,” says Dr. Wang. “It’s dysbiosis—abnormal bacterial colonization.” While the association is robust, scientists have struggled to demonstrate how A leads to B leads to C—or whether, perhaps, C initiates A. “The chicken or the egg is complicated. Does the inflammation come first or the change in the bacteria? Do they occur simultaneously? It’s hard to say. Right now a lot of microbiome research is correlative. Actually showing causality is difficult.”

Hepatologist Elizabeth C. Verna, MD, has turned her attention to the mechanisms by which the ecology of the digestive tract affects inflammation of the liver, that rubbery, three-pound organ tucked under the rib cage to filter and detoxify our blood. “The gut in a normal person is filled with millions of microbes, but for the most part the intestine creates a barrier to contain those microbes,” she explains. “And that barrier is tightly regulated.” Chronic liver disease, including

hepatitis C, the focus of Dr. Verna’s prior research, turns the gut barrier into a leaky sieve. It also triggers shifts in gut ecology to favor more pathogenic organisms, which can throw blood chemistry for a loop. The combination puts a dual strain on the liver, tasked with cleaning every ounce of blood that filters from the digestive tract before it moves on through the rest of the body. Says Dr. Verna: “Bacterial particles that leak across the gut and changes in metabolism both have a very strong impact on inflammation and scarring in the liver.”

As a clinician with Columbia’s Center for Liver Disease and Transplantation, Dr. Verna sees the aftermath of inflammation and scarring, the hallmarks of chronic liver disease. Each year, she and her colleagues manage postoperative care for 140 patients recuperating from a liver transplant, a major abdominal surgery followed by a lifelong protocol of immune-suppressing medications. In December, the National Institute of Diabetes and Digestive and Kidney Diseases awarded her a \$607,941 grant for a four-year project to investigate the role of the intestinal microbiome in recurrent disease following liver transplantation. “I’m interested in mechanisms of liver injury and scarring in general and in particular among liver transplant patients,” she says, “because they



Anne-Catrin Uhlemann, MD, PhD



have an abnormal intestinal microbiome at the time of transplant, which puts them at high risk of having this mechanism of liver injury. Transplant recipients can have very severe outcomes, including mortality.”

Over the past three years, Dr. Verna has enrolled individuals willing to provide serial blood and stool samples as they prepare to undergo a liver transplant and in the months and years following the procedure. To track participants’ digestive microbes, Dr. Verna and her collaborators, including bacteriologist and infectious diseases specialist Anne-Catrin Uhlemann, MD, PhD, perform 16S rRNA sequencing of the stool samples. To approximate the burden of digestive microbes within the blood, the scientists have homed in on endotoxins, bacterial cell wall components the liver has failed to filter, and immune markers associated with intestinal permeability. Over time, they plan to collect additional samples from the digestive tract to expand their data set. It is a particularly exciting project, says Dr. Verna. “This work is at the interface between big data—large bodies of information about large numbers of people, each of whom has a large population of digestive microbes—and the specificity of personalized medicine to assess an individual patient’s risk and how we might modulate that risk.”

Such efforts got a technical boost this year when the Department of Medicine committed funds to launch a Microbiome Core Facility for researchers across campus. Services include guidance on various elements of study design; protocols for collecting, storing, and shipping sensitive samples for genetic sequencing; and analyses. In addition, the facility provides assistance with DNA extraction and batch samples from multiple labs to make sequencing more cost-effective across the institution. Dr. Uhlemann leads the facility. “Our idea,” says Dr. Uhlemann, “is to enable researchers without a large experimental lab or computational expertise to do large-scale, data-intensive studies.”

Preliminary analyses of Dr. Verna’s liver transplant data have revealed a critical insight: Timing matters. “Most patients, to some degree, experience this process of bacterial translocation early after the transplant,” she says. The observation comes as no surprise, given the dysbiosis associated with major abdominal surgery and the drugs used to suppress organ rejection. The data point most relevant for long-term prognosis, then, is how long it takes for a patient’s gut to



Elizabeth C. Verna, MD

recalibrate. “Those who seem to develop disease are those who still have the biomarkers of translocation three months after surgery.”

Of particular importance to the scientific community, says Dr. Verna, are the implications of that preliminary analysis for study design: At least in the case of recovery from a liver transplant, it’s not enough to take a single snapshot of the digestive microbiome. “The key to studying this, which is really missing in the literature, is that you have to study patients over time. If you just have a cross-section of one patient at one moment in time, you’re not really going to understand what’s happening.”

The next phase of analysis will focus on predictive features of the microbial census, as well as correlations with such clinical details as the rate of metabolism of various drugs within the anti-suppression protocol and the incidence of metabolic disruption among transplant survivors. “The idea is that eventually we will know enough to target specific microbes or specific metabolic pathways,” says Dr. Verna, “so we can fine-tune things to maximize each patient’s post-transplant outcomes.”

#### Understanding Why Microbes Go Bad

While Dr. Verna investigates a single clinical outcome—triggers for scarring and inflammation within the liver—Dr. Han has homed in on how a single bacterium can toggle from commensal to pathogen. In the case of *F. nucleatum*, such host

factors as diet, immune status, smoking, and hydration all influence just how much weight the microbe can throw around the ecological playground. Blood chemistry, too—in the form of hormones and blood sugar levels—influences which microbes live or die. Pregnancy, it turns out, is a double whammy for the oral cavity.

Women and their physicians have long known that intense hormonal shifts—puberty, pregnancy, menopause—seem to increase susceptibility to the swollen, bleeding gums and other symptoms of periodontal disease caused by rampant microbial growth in the oral cavity. During pregnancy, the immune suppression that prevents a woman’s body from rejecting her fetus seems to exacerbate the situation. Pregnancy-related gingivitis afflicts approximately 50 percent to 75 percent of pregnant women. “It’s an often overlooked condition because it’s self-limiting,” says Dr. Han. “After childbirth, hormonal levels are restored, and the condition subsides.”

Among healthy individuals with regular access to dental care, *F. nucleatum* is no big deal and it is rarely found beyond the oral cavity. Among those with compromised immune function—someone fighting off a respiratory infection or some other illness—doctors often detect the nonmotile anaerobe far from where it belongs, including within the joints, lungs, and reproductive tract. In an August 2015 review for *Current Opinion in Microbiology*, Dr. Han recorded the microbe’s

association with appendicitis, atherosclerosis, and cerebral aneurysm, among others. “This bacterium has been implicated in a wide array of diseases,” says Dr. Han. “It’s been associated with cardiovascular disease and isolated from abscesses in every organ, even the brain.”

Just how, exactly, does a nonmotile, oral microbe make its way into the joints, across the blood-brain barrier, and throughout the reproductive tract? So far, scientists have identified two modes by which *F. nucleatum* makes its journey: through our digestive

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“New molecular techniques have made it possible to identify organisms that could not be grown in culture. That’s been an enormous boon.”

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tract and in our blood. “We have tons of bacteria in our saliva,” says Dr. Han. “It’s like a washing solution.” And ultimately, the bacteria that mix with our food as we chew and swallow make their way to the stomach. “Whether they proceed to the intestine depends on how resistant or sensitive they are to stomach acid. It’s a numbers game.” Bacte-

ria in the *Shigella* genus, for example, are highly acid-tolerant; exposure to just 20 of the rod-shaped anaerobes can cause a severe case of dysentery. The comma-shaped *Vibrio cholerae*, on the other hand, is extremely acid-sensitive and a very high dose of the shellfish-borne bacterium is required to cause symptoms. “That passage doesn’t need a lot of convincing,” says Dr. Han. “People understand that you swallow these microbes all the time, but your exposure depends on how heavy your oral inoculum is.”

To explain the presence of *F. nucleatum* in meningitis and the joints of people with rheumatoid arthritis, as well as amniotic fluid, placental tissue, and chorioamniotic membranes of women who experienced premature labor, Dr. Han has focused her investigations on blood-borne pathways. “For the bacteria to spread to so many parts, the only logical explanation is the circulation,” she says. “It’s the only passage that can reach every part of the body.”

Like a mosquito inadvertently introducing Zika or West Nile virus as it sucks down its dinner, a nick or cut in the mouth—whether from vigorous flossing or chomping on a piece of toast—allows bacteria within the oral cavity to pass into the bloodstream. As with the symptoms of *H. pylori* infection, host susceptibility factors into the gingivitis equation, along with the unique census of an individual’s oral microbiome. “Each person’s susceptibility to dental bacteremia is different,”

says Dr. Han. “For some people, once you have the bleeding, once the bacteria enter circulation, they survive only a few minutes; for others, the bacteria persist for hours.”

In 2004, the *Journal of Infection and Immunity* published a paper describing the first animal model elucidating the role of *F. nucleatum* in adverse pregnancy outcomes. By injecting the bacterium into the tail vein of pregnant mice, Dr. Han and colleagues mimicked dental bacteremia, demonstrating how *F. nucleatum* invades placental tissue and, ultimately, the amniotic fluid, causing preterm birth and miscarriage without causing systemic maternal infections. In 2007, Dr. Han’s paper in the *Journal of Immunology* revealed the biochemical mechanism at play: *F. nucleatum* stimulates placental inflammation by hijacking receptors in the immune system; treatment with an anti-inflammatory agent reduced the risk of fetal death.

Two years later, a woman who had been afflicted by excessive gum bleeding during an otherwise uncomplicated pregnancy approached Dr. Han after having a miscarriage just two weeks before her due date. Dr. Han’s team dug into the case, confirming that identical strains of *F. nucleatum* isolated during autopsy from the fetus’s lungs and stomach were also present in the woman’s mouth, but not in any of the other samples they collected from her. Almost certainly, they concluded, the woman had suffered pregnancy-related gingivitis; it was only when a brief respiratory illness further weakened her immune system that the oral commensal persisted long enough in her bloodstream to invade the placenta, infuse the amniotic fluid, and infect the fetus. The *Journal of Obstetrics and Gynecology* published the full report in 2010.

While vaginal microbes have frequently been implicated in miscarriage, preterm labor, and other adverse pregnancy outcomes, microbial commensals associated with other parts of the human habitat—like *F. nucleatum*—may be implicated in many of the adverse outcomes doctors previously dismissed as “idiopathic.” Perhaps, Dr. Han and co-authors speculated, the failure to identify *F. nucleatum* as the cause owes to the technical difficulty of microbial detection using conventional culturing techniques, especially for anaerobic species. In the Obstetrics and Gynecology case study, Dr. Han and colleagues deployed a genomic approach, using polymerase chain reactions to amplify genes within the samples they had collected, then checked them against the Human Microbiome database.

## Who’s Who

- Julian Abrams, MD, assistant professor of medicine and epidemiology
- Sankar Ghosh, PhD, the Silverstein and Hutt Family Professor of Microbiology & Immunology and chair, Department of Microbiology & Immunology
- Yiping W. Han, PhD, professor of microbial sciences (in dental medicine, microbiology & immunology, obstetrics & gynecology, and medical sciences in medicine) and a member of the Herbert Irving Comprehensive Cancer Center
- Ivaylo Ivanov, PhD, assistant professor of microbiology & immunology
- W. Ian Lipkin, MD, the John Snow Professor of Epidemiology, director of Columbia’s Center for Infection and Immunity, and professor of neurology and pathology
- Anne-Catrin Uhlemann, MD, PhD, Florence Irving Assistant Professor of Medicine
- Elizabeth C. Verna, MD, assistant professor of medicine and director of clinical research for the Transplant Initiative
- Harris Wang, PhD, assistant professor of systems biology (in pathology & cell biology)
- Timothy C. Wang, MD, the Dorothy L. and Daniel H. Silberberg Professor of Medicine, chief of the Division of Digestive and Liver Diseases in the Department of Medicine, and a member of the Herbert Irving Comprehensive Cancer Center



Timothy C. Wang, MD, and Yiping W. Han, PhD

PCR and other molecular assays have been vital to growth in the field, says Dr. Lipkin, whose team developed VirCapSeq-VERT, a technique that allows simultaneous testing for hundreds of different viruses and provides near complete sequences of their genomes. “New molecular techniques have made it possible to identify organisms that could not be grown in culture,” he says. “That’s been an enormous boon to identify organisms more rapidly, which has allowed us to think in terms of how we might more rapidly respond to acute infectious disease and implicate chronic and viral pathogens in cancer, even in those instances where we can’t grow them.”

Ever more affordable prices for PCR analysis are especially critical for boosting diagnostic accuracy in clinical settings, says Dr. Han. “Currently in the hospital laboratory, the gold standard is still the culturing method but we know that many bacteria that live in or on us are uncultivated or difficult to cultivate.” In the oral cavity, for example, scientists have identified as many as 700 species

(each of us hosts only a few hundred of those species). “Only half have been cultivated. The other half, we know they are there, but we don’t know what kind of growth conditions they require to grow in the laboratory setting.”

Scientists have their work cut out for them and Dr. Han has made the development of new microbial techniques a top priority for her research team. In April 2015, the *Journal of Clinical Microbiology* published Dr. Han’s description of a specialized mass spectrometry technique for identifying subspecies of *F. nucleatum*. In November 2015, Dr. Han and her collaborators received a patent for the polymerase chain reaction technique they used to detect bacterial pathogens in the Obstetrics and Gynecology case study. “One of the frontiers in microbiology is to cultivate the uncultivated,” she says. “In order to study pathogenic mechanisms, we need to know the conditions under which they thrive or die and we have to be able to cultivate them so we can manipulate and study them in the laboratory setting.”

Among the vital insights *F. nucleatum* has yielded to Dr. Han’s manipulations is its reliance on a unique adhesin protein the scientist dubbed FadA. “It’s one small molecule of only 129 amino acids,” she says, “but it can do a lot of things.” Key to *F. nucleatum*’s ability to colonize so many parts of the body is FadA’s connectivity with a type of receptor known as a cadherin, which serves as a cellular gatekeeper. “Cadherins are ubiquitous in our cells. You have vascular-endothelial, VE-cadherins, and epithelial, E-cadherins; neuron cells have N-cadherins, and in the placenta are P-cadherins.”

Like Spider-Man clinging to a wall, FadA can lock on to a wide array of sites by binding to the specialized cadherins it encounters throughout our bodies. “As a microbiologist, I’m amazed by how smart and efficient these bugs are,” says Dr. Han. “They have such a tiny genome—only 2 million base pairs. However, they can manipulate us, their hosts, so efficiently, making us work for them.”

FadA goes far beyond merely clinging to the cadherins; it leverages something of a Trojan horse effect. “Once FadA binds to cadherin, it loosens the tight junction, like a key,” Dr. Han explains. “Not only can *Fusobacterium* get into the circulation by itself, but whatever bacteria are in the vicinity can come along. It’s like a facilitator, an enabler.”

In their investigation of the role of *Fusobacterium nucleatum* in colorectal cancer, Timothy Wang and Dr. Han are drawing on her investigations of the particularly diabolical synergy of FadA with E-cadherin, a well-known cancer suppressor, as well as his expertise in *H. pylori*, particularly its knack for altering its environment. Already, they have demonstrated that in knockout mice engineered with a predisposition for colon polyps, *F. nucleatum* can accelerate activation of the cancer. “It’s proof of principle that the bacteria alone are not sufficient to cause colon cancer,” says Dr. Wang, “but can wake up dormant cancer stem cells to go on to become tumors in the large intestine.”

The prospect of showing that a single bacterium can induce cancer is an exciting one, says Dr. Wang, but the work will not be that simple. “In most cases, it’s not going to be a single bacterium,” says Dr. Wang, noting that he and Dr. Han have a lot of genomic sequencing and bioinformatics work in their future. “These things live in student dorms with a lot of their friends. They’re like fraternities, in a way. Just looking at one at a time makes it really difficult to figure out the source of the noise late at night.” ❖

# Medical (In) Equality

Scientists  
Work to Level  
the Field for  
Medical Care

**From Shanghai to Kinshasa**, humans have most of the same DNA. But in the matter of longevity and well-being, nurture—including such personal choices as the foods we eat and the amount of exercise we get—often trumps nature. Disparities researchers seek to untangle the relative power of social and environmental factors, including race, education, and income, from the influence of shared genetic predispositions, such as the APOE Alzheimer’s gene more common among African-Americans or the tendency toward Tay-Sachs disease among Ashkenazi Jews, to identify interventions that can boost longevity for all Americans.

From their vantage in Northern Manhattan, P&S investigators have a unique opportunity to identify and explain health disparities and develop interventions to boost the well-being of the people who call the medical center area home—especially the working-class Hispanic immigrants of Washington Heights, the denizens of Harlem’s vibrant African-American community, and the Caucasian residents of Northern Manhattan.

Perhaps the most ambitious of those projects, the multiethnic Washington Heights, Hamilton Heights, Inwood, Columbia Aging Project—WHICAP—is led by Richard Mayeux, MD, the Sergievsky Professor of Neurology, Psychiatry, and Epidemiology. Con-

tinuously funded by the NIH since 1989, WHICAP has enrolled more than 5,900 participants and collected some 40,000 biological samples, 1,300 MRI and 200 PET scans, and longitudinal data on cognitive performance, emotional health, independence in daily activities, blood pres-

sure, anthropometric measures, and cardiovascular status. On Aug. 1, the National Institute on Aging awarded another \$8.8 million to Dr. Mayeux and his collaborators to continue their work in the community.

Designed to investigate dementias related to stroke, Parkinson’s disease, and Alzheimer’s disease, WHICAP quantifies the rates of late onset Alzheimer’s disease, mild cognitive impairment, and age-related cognitive decline among the three major ethnic groups in the community. WHICAP investigators have authored scores of papers that untangle the relationships among age, sex, race and ethnicity, and clinical risk factors to guide prevention, clinical care, and future research. Their findings include the discovery—after controlling for an array of correlated factors—that African-American and Caribbean-American elders are at greater risk for Alzheimer’s and identification of a new gene associated with late-onset Alzheimer’s.

“Disparities research is intended to generate new knowledge that will help us improve health through prevention and treatment. Investigations of ethnic populations that have migrated across several cultures offer the opportunity to study groups for which genetic factors essentially remain the same but environmental and cultural forces undergo dramatic change,” says Dr. Mayeux. “At the same time, comparing groups residing in the same environment with similar socio-economic status and equal exposure to risk factors helps us uncover genetic factors responsible for all kinds of health conditions.”

Being located in Washington Heights, Dr. Mayeux says, has given researchers an extraordinary opportunity to contribute to new knowledge about the health of Hispanics of Caribbean descent. “Our local community is the most ethnically diverse in New York, home to the largest population of individuals from the Dominican Republic outside of the Dominican Republic, and we have long been dedicated to not only treating this population, but also partnering with them to understand how to improve the health of the community.”

The following pages profile four researchers who are studying disparities in diabetes, obesity, cardiovascular disease, and Alzheimer’s and other neurodegenerative diseases.



Richard Mayeux, MD

By Sharon Tregaskis | Photographs by Jörg Meyer



# Implementation Science

## Nathalie Moise

**A**n African-American woman in her 60s who was hospitalized frequently for heart failure struggled to follow what doctors had prescribed to control her cardiovascular disease and depressive symptoms— aspirin, prescription medication, exercise, and diet changes—and she had limited social support. For her doctor, Nathalie Moise, MD, then a research fellow in Columbia’s Division of General Medicine while earning a master’s degree in public health at Columbia, the patient’s case crystallized a plan she had been thinking about for more than a decade: Identify barriers and scale implementation of

**A model for depression treatment would have a care manager collaborate with the patient’s physician and a psychiatrist.**

evidence-based guidelines in minority patient groups.

“In college, I was struck by how evidence-based guidelines are poorly disseminated in minority communities,” says Dr. Moise, whose first foray into research was as an undergraduate at Princeton University, where she designed and implemented a randomized, controlled trial to compare the effectiveness of four behavioral change

theories to boost breast cancer screening among African-American women. More than a decade later, Dr. Moise is assistant professor of medicine in Columbia’s Center for Behavioral Cardiovascular Health. She acknowledges that health care professionals still struggle to provide optimal care for minority patients. “While there were clear, evidence-based strategies for treating my patient’s disease,” she says, “it was difficult to implement them in real-world settings.”

African-American and Hispanic individuals, who are at greater risk for both depression and cardiovascular disease, need clarity about the relationships among gender, socioeconomic status, race, depression, and cardiovascular disease. “The barriers to implementing cardiovascular disease guidelines in my own clinic revolve around my patients’ mental illnesses, inadequate psychosocial resources, and uncertainty about their adherence,” says Dr. Moise, who sees patients at Columbia’s Associates in Internal Medicine Clinic and CoSMO, the free, student-run clinic for uninsured residents of Washington Heights. For someone struggling with depression and other chronic diseases, implementing a regimen of diet change and exercise—plus the daily handful of pills to control both conditions—can be especially challenging. From the vantage point of the treating physician, uneven adherence complicates the process of tailoring treatment over time.



Dr. Moise has conducted computer simulation analyses to assess how medication costs, adherence, and race influence the cost-effectiveness of hypertension guidelines, published recently in *Hypertension* and the *American Journal of Hypertension*. Last fall, Dr. Moise was awarded funds from the Columbia Provost’s Grants Program for Junior Faculty Who Contribute to the Diversity Goals of the University to conduct interviews of predominantly minority and Spanish-speaking patients with depression to better understand the barriers to care that they encounter. The insights Dr. Moise gains will inform a subsequent study to assess the effectiveness of an electronic, shared decision-making tool to engage minority patients in their own treatment. As the site primary investigator

for a multicenter grant from the National Heart, Lung, and Blood Institute, Dr. Moise is investigating the American Heart Association guideline that recommends depression screening in patients following stroke and heart attack. As a policy scholar with the New York State Office of Mental Health she is investigating a model for depression treatment in which a care manager collaborates with the patient’s physician and a psychiatrist; the model has been especially effective among minority populations but difficult to implement with patients and doctors. “To truly impact health disparities,” she says, “systems-level interventions in real-world settings will be just as integral as tailored, patient-level approaches. Involving minority patients as stakeholders in creating interventions is also key.”

# A Clear Picture

José Luchsinger

Last fall, the National Institute on Aging awarded José Luchsinger, MD, associate professor of medicine, two five-year grants: \$3,238,671 to investigate diabetes status and brain amyloid in middle-aged Hispanics from Northern Manhattan and \$5,294,619 to pursue interdisciplinary research to understand the relationship among diabetes, cerebrovascular disease, and Alzheimer's disease.

He focuses on study participants of Hispanic origins, most of whom

are recruited from the Washington Heights neighborhood, because they are at higher risk for type 2 diabetes and dementia. His hypothesis is that diabetes can cause both Alzheimer's disease and stroke and that the memory impairment common among people with type 2 diabetes is actually the earliest symptom of that pathogenic process. Dr. Luchsinger and his collaborators hope to reveal the biochemical process underway and identify therapeutic targets or biomarkers to enhance

clinical care. "There are a lot of studies showing that the presence of diabetes is related to various forms of cognitive impairment, particularly Alzheimer's," says Dr. Luchsinger, who also has investigated the benefits of exercise and a Mediterranean diet to slow cognitive decline among different racial

**"I'm looking at a group in their early 60s. That's the best time to see what's happening in the brain, instead of waiting until they already have dementia."**

and ethnic groups. "Diabetes is also a very well known cause of vascular disease, which in the brain translates to strokes.

"In the clinic, doctors see memory impairment that worsens over time and diagnose Alzheimer's without really knowing for sure if the symptoms are caused by the presence of amyloid plaques and neurofibrillary tangles containing abnormal tau," he adds. The only definitive diagnosis of the disease, however, depends on autopsy. Emerging imaging techniques could allow the team to definitively reveal how diabetes corresponds to amyloid deposition and tau formation. "I'm very excited, because our imaging is going to be unique. Even if we find that diabetes has nothing to do with the amyloid, that will be very informative."

In addition to brain imaging, the team, which includes Adam Brickman, PhD, associate professor of neuropsychology in neurology, and Herman Moreno, MD, of SUNY Downstate Medical Center, also will use mouse models and clinical data from 200 Hispanic study participants to explore the hypothesis. "Traditionally, studies looking at this question have looked at older people, 70 or 75," says Dr. Luchsinger. "I'm looking at a group in their early 60s. This is important because we hope we're collecting our first observations before they actually manifest the dementia, or when they're just beginning to have a deficit. That's the best time to see what's happening in the brain, instead of waiting until they already have dementia."

By examining a broad range of data, the team hopes to elucidate some of the mechanisms explaining the contributions of diabetes, cerebrovascular disease, and Alzheimer's disease to dementia, which disproportionately affects minorities in Northern Manhattan. "Societies are getting older," says Dr. Luchsinger, "and there's some controversy as to whether AD rates are stable, getting worse, or getting better. Regardless, because we're living much longer and the older population is getting larger, we're absolutely going to have more numbers of people with dementia, which affects spouses, families, and children, and this problem is worse for minorities, who tend to have fewer resources to cope."



# Giving Kids a Chance

Jennifer Woo Baidal

Jennifer Woo Baidal, MD, was a college freshman working as a teacher's assistant on the affluent West Side of Los Angeles when she came across a youngster distressed that his mother had forgotten his snack. Just then, a woman came dashing across the playground. "Here you are," she called, "I packed your favorite—bell peppers."

For Dr. Woo Baidal, raised in the lower-income, predominantly

**"I'm thinking about how we best institute better practices to really help patients who need it the most."**

minority neighborhoods of LA's East Side, the difference from her own childhood was stark. "These kids knew the names of fruits and vegetables and they ate so much more healthfully," says Dr. Woo Baidal, assistant professor of pediatrics and director of pediatric weight management for the Division of Pediatric Gastroenterology, Hepatology, and Nutrition. "On the East Side, kids were eating highly processed foods for lunch—chicken nuggets, French fries—and ketchup was considered a vegetable."

National rates of obesity seem to have plateaued but remain historically high, and rates of overweight and obesity among

minorities show no signs of falling. In Washington Heights and Inwood, where Dr. Woo Baidal investigates strategies to promote healthy weight, 47 percent of children are overweight or obese. "At the root of obesity disparities are a lot of social determinants of health like socio-economic status and other inequities," she says. "I'm looking at the outcome and thinking about how we best leverage our health care system, institute better practices to really help patients who need it the most."

In a series of papers published earlier this year—co-authored with her mentor at Harvard, where she earned her MD and a master's of public health—Dr. Woo Baidal and her colleagues explore "the first 1,000 days," from conception through 24 months, a period that seems critical to modifying childhood obesity risk. The team recruited 49 low-income Hispanic women at a federal community health clinic and engaged them in a series of focus group conversations—in Spanish—between pregnancies through their children's second birthdays. To boost retention rates, the team provided stipends for travel and child care associated with the meetings and hired a bilingual facilitator. "It's always a consideration who's on the research staff," says Dr. Woo Baidal, "finding people from diverse backgrounds to connect with research participants."

With funding from Columbia's KL2 Career Development

program, the New York Obesity Nutrition Research Center, and the National Institute on Minority Health and Health Disparities, Dr. Woo Baidal currently serves as principal investigator on a suite of studies intent on developing non-invasive techniques to diagnose nonalcoholic fatty liver disease, which afflicts 40 percent to 70 percent of overweight and obese children and can lead to cirrhosis and even liver failure. The disease, which disproportionately affects Hispanic children, is not well

enough understood for scientists to explain why some who are merely overweight develop the disease while some obese individuals do not, says Dr. Woo Baidal. "If we can reduce the burden of obesity and fatty liver early in life, we can have a positive effect on everything that comes later by having a healthier workforce, reducing health care costs, and giving children from all backgrounds the chance to start out on the same foot," she says. "It's a social justice issue."





# School Daze

Jennifer Manly

To quantify memory loss over time, investigators must be able to measure and compare individual function. Yet in a study with a diverse sample, participants' vocabulary, analytical skills, and spatial skills vary broadly—often directly reflecting their life experiences. And those experiences often reflect a person's race, culture, gender, and socio-economic status. So how is a disparities researcher intent on untangling the influence of nature and nurture to make sense of the data? “If cultural differences get in the way of a person's performance so much that we're not measuring anything to do with memory,” says neuropsychologist Jennifer Manly, PhD, “the study's results will be misleading.”

Dr. Manly has made it her mission to impose scientific rigor on data collection and analysis associated with cognitive assessments of African-American and Hispanic elders in studies of aging-related disparities in multiethnic populations. “Most of us who see diverse older adults are seeing a lot of different educational experiences and language competencies,” says the associate professor of neuropsychology. “There's always a role of background and experience in terms of what you bring to cognitive testing.”

In addition to collecting quantitative data on years of schooling and other demographic details from study participants, Dr. Manly chooses tests likely to reveal details

about cognitive function most relevant to the study hypothesis. The majority of older Hispanics recruited by P&S investigators in Washington Heights, for example, grew up in rural communities in the Dominican Republic. Many African-American elders living in the Northeast attended segregated schools in the South. “The things we think about are, ‘Has this person held a pencil before? Have they drawn or copied something before? Does this person know the rules of scanning a multiple-choice array? Do they value—as the people do who developed this test—speed over accuracy? Have they ever seen this visual representation? How familiar are they with two-dimen-

**“More time in the classroom as a kid and a lower student-teacher ratio translates into better cognitive function 70 years later.”**

sional line drawings to represent three-dimensional visual stimuli?”

In the past year, Dr. Manly has co-authored papers that explore the effect of the Mediterranean diet on brain structure and function, the relationship between type 2 diabetes and cognitive change, and the association of late-life depression with cognitive function and brain volume. In August 2015, *Journals of Gerontology*



published her work with a team of investigators from across the United States that concluded that quality of education appears to be more important than cerebrovascular risk factors in explaining differences in memory and executive function between white and African-American older adults. “More time in the classroom as a kid and a lower student-teacher ratio translates into better cognitive function 70 years later,” says Dr. Manly, noting that Southern schools attended by African-American children a generation ago were open for fewer days each year because of lack of funding

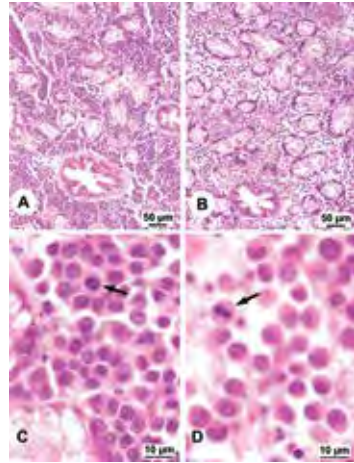
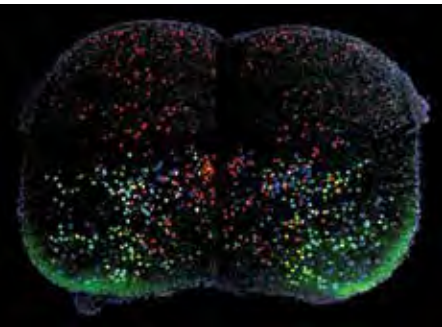
and because kids were expected to work in the fields. “In general, the amount of money spent on the school system relates to better cognitive function for people who attended those schools.”

A series of studies underway collects data on middle-aged study participants to reveal factors that may provide protection against disparities early in life. “This is a life-course process,” says Dr. Manly. “We find links between cognitive impairment late in life and early childhood experiences, but a lot of things happen between those two points that could confer resilience or vulnerability.” ❖

# 2016 Research Highlights

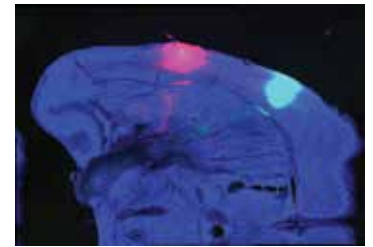
## Counting Neurons in the Spinal Cord

Researchers at Columbia's Mortimer B. Zuckerman Mind Brain Behavior Institute have described new approaches to identify individual classes of neurons in the spinal cord. Two papers published in *Cell* highlight how statistical approaches could provide neuroscientists with a critical tool to quantify cellular diversity of any brain region. The research focused on a group of neurons in the spinal cord called V1 interneurons that orchestrate the activity and output of motor neurons, the class of neurons that give muscles the power to move. Researchers looked at these neurons in laboratory mice and were able to distinguish 50 distinct types of V1 interneurons.



## Contagious Cancers Seen in Shellfish

Direct transmission of cancer among some marine animals may be more common than once thought, suggests a study published in *Nature*. A study led by Stephen Goff, PhD, the Higgins Professor of Biochemistry & Molecular Biophysics and professor of microbiology & immunology, in collaboration with researchers from Canada and Spain, revealed that in several species of bivalves, including mussels, cockles, and clams, cancer cells spread from animal to animal through sea water. The cancer, known as disseminated neoplasia, is a leukemia-like disease that affects bivalves in many parts of the world. Until recently, direct transmission of cancer cells had been observed in only two species of mammals.



## Turning Taste On and Off

In research published in *Nature*, scientists demonstrated in mice the ability to change the way something tastes by manipulating cells in the brain. In one experiment, researchers used optogenetics to activate neurons to trick mice into thinking they were tasting bitter or sweet even when drinking water. "These experiments formally prove that the sense of taste is completely hardwired, independent of learning or experience," says Charles S. Zuker, PhD, professor of biochemistry & molecular biophysics and of neuroscience.

### Brain Tumor Differences

Pathologists currently determine if a glioma, the most common malignant brain tumor, is low-grade or high-grade based on the tissue's appearance under the microscope. Research published in *Cell* explains why some patients diagnosed with slow-growing or low-grade tumors succumb to the disease faster than those with more aggressive tumors. Researchers analyzed samples to look for epigenetic changes in the tumors' DNA. They found that DNA methylation levels might influence tumor progression. Co-senior author Antonio Iavarone, MD, professor of neurology and of pathology & cell biology, says the results may help identify patients who require more aggressive treatment.



### Drug Activates Brain's 'Garbage Disposal'

To remain healthy, brain cells must continually clear out old, worn, or damaged proteins, a task performed by a small molecular cylinder called the proteasome. The proteasome acts as a kind of garbage disposal, but in neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's, proteins tagged for destruction accumulate in the brain's neurons, suggesting that the cell's proteasomes are impaired. Researchers identified a new way to activate the brain's garbage disposal system, successfully using a drug to activate the system and slow down disease in a mouse model. Even though the drug used in the research, rolipram, is not a good drug for humans because it causes nausea, similar drugs without that side effect could be tested, says study leader Karen E. Duff, PhD, professor of pathology & cell biology (in psychiatry and in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain). "This has the potential to open up new avenues of treatment for Alzheimer's and many other neurodegenerative diseases."

### Cellular 'Switch' and the Perception of Danger

In a study published in *Science*, Jayeeta Basu, PhD, then a post-doctoral fellow in the laboratory of neuroscience chair Steven Siegelbaum, PhD, examined how a cellular circuit in a mouse helps the brain remember which environments are safe or harmful. The findings suggest that disruptions in neural pathways may contribute to an inappropriate fear response, a key characteristic of conditions such as anxiety or post-traumatic stress disorder.

### Protein 'Raptor' Prevents Fatty Liver Disease

Researchers at Columbia's Naomi Berrie Diabetes Center have identified a pathway that prevents insulin or insulin-sensitizing therapy from causing fatty liver without getting rid of the favorable effects of insulin to reduce blood sugar. They found a protein called Raptor that exists within a protein complex known as mTORC1 that is involved in cell growth and cell differentiation. "As it turns out, young healthy mice—and, we assume, young, healthy people—have a lot of this free Raptor," says Utpal Pajvani, MD, PhD, assistant professor of medicine. "As mice age or get fat, free Raptor disappears. When free Raptor disappears, mice get fatty liver. If you give them back free Raptor, fatty liver goes away but leaves insulin's ability to lower blood sugar intact."

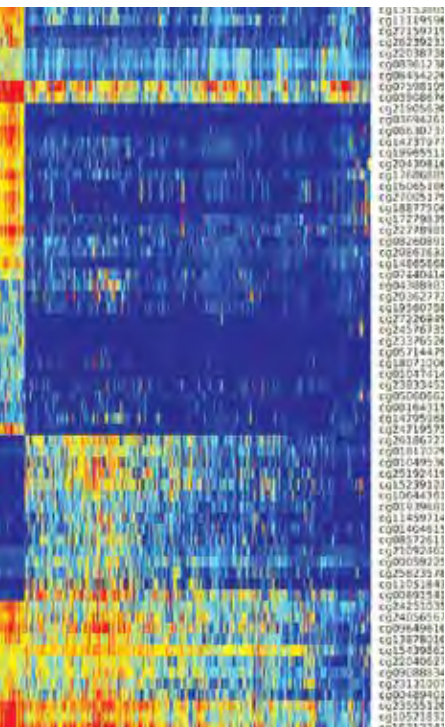
### New Embryonic Stem Cell

P&S partnered with researchers at the Hebrew University of Jerusalem and the New York Stem Cell

Foundation Research Institute to create a new type of embryonic stem cell that carries a single copy of the human genome. It is the first time human cells have been known to be capable of cell division with just one copy of the parent cell's genome. The researchers were able to show that these haploid cells were pluripotent or able to differentiate into many other cell types, including heart, nerve, and pancreatic cells, while retaining a single set of chromosomes. The findings, published in *Nature*, show the potential for the cells to be used to develop cell-based therapies for diseases in which genetically identical cells offer a therapeutic advantage.

### Fighting 'Superbugs'

Bugs like *E. coli*, *Salmonella*, and *Klebsiella pneumoniae*—all gram-negative bacteria—alter their electrostatic charge to evade detection by polymyxin antibiotics, our last line of defense against some "superbug" infections. Researchers using high-resolution imaging techniques to peer inside the bacteria have found places where drugs could disrupt the bugs' defense and restore their susceptibility to powerful antibiotics. Bacteria become resistant to polymyxins by placing a cap, made from a sugar molecule, over the negative charge, altering the electrostatic forces between bacteria and antibiotics. An enzyme called ArnT in the membrane of bacteria is responsible for the capping. The researchers were able to visualize the precise details of the process by using X-ray crystallography to reveal the location of



each individual atom in the ArnT enzyme before and after it grabs the sugar. Because the images reveal places where the enzyme could be disabled, the researchers are using computerized techniques to screen millions of potential drug candidates that might work with polymyxins to eliminate antibiotic-resistant bacteria.

### Understanding Schizophrenia

P&S and Mortimer B. Zuckerman Mind Brain Behavior Institute investigators made significant findings in schizophrenia this year. Zuckerman Institute researchers Joseph Gogos, MD, PhD, and Joshua Gordon, MD, PhD, successfully disrupted a genetic

chain of events in a mouse model of schizophrenia and reversed memory deficits, one of the disorder's most difficult-to-treat symptoms. In a paper published in *Neuron*, scientists used a chemical compound to regrow connections between neurons, which in turn restored memory. In another study published in *Neuron*, Zuckerman researchers found that deficits in social memory, the inability to recognize familiar faces, may be due to a decrease in the number of inhibitory neurons in a little-explored region within the brain's memory center. "We can now examine the effects of schizophrenia at the cellular level and at the behavioral level," says Steven Siegelbaum, PhD, chair of neuroscience, who led this study along with Dr. Gogos. "This essentially opens up a whole new avenue for research that could lead to earlier diagnosis and more effective treatments for schizophrenia." A study by P&S and New York State Psychiatric Institute researchers, this one published in *Biological Psychiatry*, identified a pattern of brain activity that may be a sign of memory problems in people with schizophrenia. The research for the first time linked a brain signal in the dorsolateral prefrontal cortex directly to working memory performance in patients with schizophrenia.

### Turning Back Time

As people reach their 30s and 40s, muscle strength and endurance decline. New research now suggests that changes in a protein from bones may be partly responsible. Researchers in the lab of Gerard Karsenty, MD, PhD, chair and the Paul A. Marks Professor of Genetics & Development and professor of medicine, years ago discovered that osteocalcin, a protein that is produced by bone cells in both mice and humans, is present in the bloodstream and delivered to other organs where it acts

as a hormone. Their newest studies show that osteocalcin has a profound effect on muscle and exercise capacity. When the hormone is injected into old mice, the animals are able to run as far and as fast as young mice. The researchers found that osteocalcin is able to improve exercise capacity by increasing the amount of glucose and fatty acids that skeletal muscle can take in and consume during exercise.

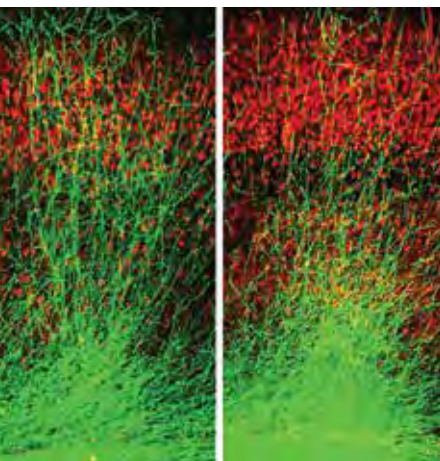
### Clinical Practice by the Numbers

An international observational study has uncovered widespread differences in the treatment of patients with common chronic diseases, including type 2 diabetes, hypertension, and depression. Using data from 250 million records of patients from four countries, researchers demonstrated the feasibility of performing large-scale observational research to obtain information about clinical practice among diverse groups of patients. "We found that while the world is moving toward more consistent therapy over time for the three diseases, there remain significant differences in how they are treated," says George Hripcsak, MD, the chair and Vivian Beaumont Allen Professor of Biomedical Informatics. Observational research, in which patterns of care are gleaned from large data sets—such as electronic health records, insurance claims, and pharmacy records—has the potential to offer insight into real-world treatment scenarios that may inform clinical trial design and, ultimately, clinical practice. An international group of scientists

formed the Observational Health Data Sciences and Informatics program, which allows researchers to combine and analyze patient data from widely different sources in the United States and abroad. Columbia University serves as the program's coordinating center.

### New Mouse Model of Anorexia

Columbia researchers have described a new mouse model that features a combination of genetic and environmental risk factors that can trigger the compulsive restriction of food intake seen in patients with anorexia nervosa. Previous models of anorexia included some of the variables thought to raise the risk of anorexia (genetic, biological, psychological, and sociocultural), but no model captured the elements of social stress and genetic susceptibility to anxiety and anorexia that appear to contribute to the onset of the disorder in humans, particularly in adolescents. "This model not only shows us the most important factors that contribute to the onset of anorexia, it's also helping us to identify signaling pathways in the brain that ultimately drive this potentially fatal eating disorder," says study leader Lori Zeltser, PhD, associate professor of pathology & cell biology. For the new mouse model, the researchers exposed adolescent mice with at least one copy of a variant of the BDNF gene, which has been associated with anorexia and anxiety in mice and humans, and also exposed the mice to social stress and caloric restriction.



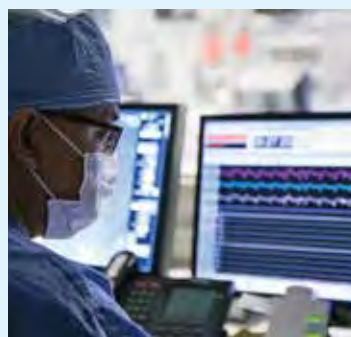
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# 2016 Clinical Highlights



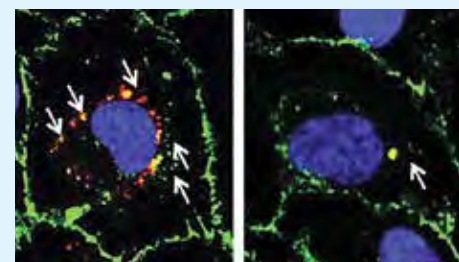
## **Killing Drug-Resistant Bacteria**

Scientists from Columbia's Center for Radiological Research have shown that a narrow wavelength of ultraviolet light killed drug-resistant MRSA bacteria in mice, demonstrating a potentially safe and cost-effective way to reduce surgical site infections. A particular wavelength of UV light known as "far-UVC" is as effective as conventional germicidal UV light in killing MRSA, as shown in a previous study, but the new study shows for the first time that, unlike conventional germicidal UV, far-UVC does not cause biological damage to exposed skin, reports David J. Brenner, PhD, the Higgins Professor of Radiation Biophysics and director of the Center for Radiological Research.



## **Alternative to Open Heart Surgery**

A study conducted by the Columbia Heart Valve Center found that women undergoing transcatheter aortic valve replacement—TAVR—have better survival rates than men one year after the procedure. The results, published in the *Annals of Internal Medicine*, are opposite of results seen in surgical aortic valve replacement, for which women had poorer outcomes. Another Columbia study, published in the *New England Journal of Medicine*, showed that TAVR is a viable alternative to traditional open heart surgery for patients with severe aortic stenosis at intermediate risk for surgery.



## **Heart Disease Risk and Sleep Apnea**

For millions of adults, obstructive sleep apnea results in sleep disruption and then daytime sleepiness and difficulty concentrating. Sleep apnea also triples the risk for developing heart disease, including hypertension and ischemic stroke. A study has revealed some of the underlying mechanisms that may increase the risk and also found that statins may reverse the process. "We were surprised to discover that these commonly prescribed drugs appeared to reverse the process that leads to vascular injury, and ultimately heart disease, in people with sleep apnea," says Sanja Jelic, MD, associate professor of medicine at CUMC.

### **Steroids Benefit Late Preterm Babies**

Babies born to women at risk for late preterm delivery may benefit from corticosteroids, reports new research published in the *New England Journal of Medicine*. Cynthia Gyamfi-Bannerman, MD, the Ellen Jacobson Levine and Eugene Jacobson Associate Professor of Women's Health (in Obstetrics & Gynecology), found that babies whose mothers received the corticosteroid betamethasone had significantly lower rates of severe respiratory complications shortly after birth compared with those whose mothers received a placebo. Babies in the study's treatment group also were significantly less likely to require long-term stays in the hospital's NICU or require respiratory treatment. Since the early 1990s, corticosteroids have been used in mothers at risk of delivering before 34 weeks of gestation to accelerate the development of the baby's lungs, but researchers believed that corticosteroids were unnecessary for later preterm births because 99 percent of babies born after 34 to 35 weeks survive. Research shows that even infants born during the "late" preterm period (between 34 and 36 weeks) have increased neonatal and childhood respiratory complications compared with newborns born at 37 weeks or later.

### **Precision Medicine Tools Link Congenital Disorders**

A study published in *Science* explains why many children with congenital heart disease

also have other health problems, including neurodevelopmental disorders and other congenital problems. Researchers looked at genetic information from 1,213 children with congenital heart disease and their parents to analyze more than 4,000 genes. After comparing the findings with data on families not affected by congenital heart disease, the researchers showed that many children with congenital heart disease had spontaneous mutations in heart development genes. A single genetic mutation was responsible for about 20 percent of cases of severe congenital heart disease accompanied by neurodevelopmental disorders and/or other congenital problems. Mutations in children born with a combination of heart, brain, and other congenital disorders occurred in a subset of genes that act like conductors, orchestrating the formation and function of organs. Knowing these links could help doctors predict risk and may allow interventions to be put in place while the brain is still developing.

### **Infants, Immune System, and Vaccines**

A study published in *Nature Medicine* provides new insights into how the infant immune system functions and suggests strategies for enhancing vaccination programs. Researchers took tissue from 64 organ donors to measure T cells and found that children under age 2 had more regulatory T cells in their tissues and lower levels of infection-fighting cyto-

kines than adults. The results suggest that health officials may be able to enhance the effectiveness of vaccines given in early infancy, says author Donna Farber, PhD, professor of surgical sciences (in surgery and microbiology & immunology).

### **Model Cancer Care**

The Centers for Medicare & Medicaid Services selected Columbia, New York-Presbyterian Hospital, and Weill Cornell Medical College to participate in a care delivery model that supports and encourages higher quality, more coordinated cancer care. Nearly 200 physician group practices and 17 health insurance companies are participating in the Medicare arm of the Oncology Care Model, which includes more than 3,200 oncologists and will cover approximately 155,000 Medicare beneficiaries nationwide. Participants in the five-year Oncology Care Model will provide treatment following nationally recognized clinical guidelines for beneficiaries undergoing chemotherapy, with an emphasis on person-centered care.

### **Safety of Anesthesia for the Young**

Columbia participated in a multicenter study that found that a single exposure to general anesthesia poses no cognitive risk to healthy children under age 3. Findings from the Pediatric Anesthesia Neurodevelopment Assessment study were published in the *Journal of the American Medical Association*. "A number

of animal studies have suggested that exposure to commonly used anesthetic agents in early development could lead to deficits in learning, memory, attention, and other cognitive functions," says Lena S. Sun, MD, the Emanuel M. Papper Professor of Pediatric Anesthesiology and professor of pediatrics at CUMC. "However, few clinical studies have adequately addressed whether this is also true in humans. Based on our findings, we can reassure parents that one exposure to anesthesia is safe for healthy young children."

### **Pioneering Public-Private Cancer Initiative**

Columbia's Herbert Irving Comprehensive Cancer Center is one of four cancer centers that have formed a research consortium to accelerate the discovery and development of novel cancer therapeutics and diagnostics. The four cancer centers also entered into public-private collaboration agreements with Celgene Corporation in which Celgene will pay each institution \$12.5 million for the option to enter into future agreements to develop and commercialize novel cancer therapeutics arising from the consortium's efforts. Over the next 10 years the institutions plan to present research programs to Celgene with the goal of developing new life-saving therapeutics.

### **Surgical Treatment for Spasticity**

Spasticity, an involuntary stretching reflex that stiffens



#### 467-Gene Cancer Panel

The New York State Department of Health approved the Columbia Combined Cancer Panel, which queries 467 cancer-related genes. The panel was designed by the Laboratory of Personalized Genomic Medicine at CUMC in collaboration with Columbia oncologists.

muscles, is a common problem for people with cerebral palsy. One way to reduce spasticity is with a procedure called selective dorsal rhizotomy, in which a surgeon disconnects overactive sensory nerves that tell muscles to contract. CUMC is one of only a few medical centers in the United States to offer a less-invasive procedure that reaches the crucial sensory nerve roots by removing a much smaller piece of bone from the spine than is standard. Once the nerve roots are accessible, the surgeon uses electrical signals to differentiate motor nerve roots from sensory nerve roots and determine which sensory nerves are causing the most spasticity. Physical and occupational therapists in the OR confirm the results before the surgeon disconnects any nerve roots.

#### Combining Genomic Information and Electronic Records

A group of researchers will incorporate genomic information into electronic health records for thousands of Columbia patients

as part of the Electronic Medical Records and Genomics Network administered by the National Human Genome Research Institute. The goal is to combine genetic data with electronic medical record systems to improve diagnosis, disease risk assessment, prevention strategies, and treatment options. Researchers will look for new disease-causing variations in about 100 genes that have been linked to cancer, cardiovascular disease, stroke, kidney disease, and other health problems. The research is led by principal investigators Chunhua Weng, PhD, associate professor of biomedical informatics; George Hripcsak, MD, the Vivian Beaumont Allen Professor of Biomedical Informatics and chair of biomedical informatics; and Ali Gharavi, MD, professor of medicine and chief of nephrology.

#### Slowing Cognitive Decline with Hearing Aids

Though more than half of adults over the age of 75 have hearing loss, less than 15 percent of this population uses a hearing aid. A

Columbia study published in the *American Journal of Geriatric Psychiatry* found that adults who used a hearing aid performed significantly better on cognitive tests. The study showed that adults with hearing loss who used a hearing aid performed significantly better on the Mini-Mental State Examination, in which participants give vocal responses to verbal commands. The research suggests that using a hearing aid could prevent or slow the development of dementia, says Anil K. Lalwani, MD, professor of otolaryngology/head & neck surgery.

#### Treating Opioid Addiction

Opioid addiction is a growing problem in the general population, but it is disproportionately high in prison populations. A study published in the *New England Journal of Medicine* found that ex-prisoners who received six monthly injections of naltrexone, a long-acting medication that blocks opioid receptors in the brain, were significantly less likely to resume opioid use than

those who received counseling and referrals to community treatment centers without the injections. “Medications like methadone and buprenorphine have proved essential to the treatment of opioid dependence,” notes study co-author Edward V. Nunes, MD, professor of psychiatry at CUMC. “But people with opioid dependence are better served by having a range of options to prevent relapse and reduce the risk of death from overdose. Naltrexone injections offer another effective therapeutic option for people struggling with opioid addiction in a variety of settings.”

#### New Option for Some Forms of Lung Cancer

The FDA approval of pembrolizumab (brand name Keytruda) provides a new immunotherapy option to treat some patients with metastatic non-small cell lung cancer. “The durability of response with immune checkpoint inhibitors is exciting and has given new options for our patients,” says Naiyer Rizvi, MD,

professor of medicine at CUMC and director of thoracic oncology, who was a principal investigator for Keytruda clinical research.

#### **Fecal Transplants Treat Severe *C. Diff***

Cases of *Clostridium difficile* infections are hard to treat, but several children with recurrent *C. diff* have been treated at Columbia with transplants involving an infusion of a fecal preparation from a healthy donor into the patient's gastrointestinal tract. The goal is to replace harmful microbiota with bacteria that support a healthy gastrointestinal milieu. "The families we have worked with describe the therapy as life-changing," says Norelle Reilly, MD, director of the pediatric celiac disease program and assistant professor of pediatrics. "Many of the children we have treated have experienced years of refractory *C. diff* infection. It is gratifying to be able to intervene in such a novel and meaningful way."

#### **Leukemia Drug with Fewer Side Effects**

While the cancer drug ibrutinib has significantly improved treatment for patients with chronic lymphocytic leukemia, it may increase the risk of bleeding, particularly in older patients who are taking blood thinners for heart disease. A study published in the *New England Journal of Medicine* suggests that a similar class of drug, acalabrutinib, has the same cancer-fighting ability as ibrutinib but reduces the risk of bleeding. Thomas Diacovo, MD, associate professor of pedi-

atrics and of pathology & cell biology, found that acalabrutinib has less effect on platelet function than ibrutinib because the drug hits its target with greater precision. Both drugs are designed to inhibit the cancer-promoting molecule Bruton's tyrosine kinase, but ibrutinib also blocks molecules essential to platelet function, which can cause hemorrhaging.

#### **Autism and GI Problems**

Children with autism spectrum disorder are four times more likely to suffer from gastrointestinal problems than other children. A study published in the *Journal of Clinical Investigation* found evidence in mice that in some types of autism, gastrointestinal difficulties may originate from the same genetic changes attributed to behavioral and social characteristics of the disorder. "Because serotonin plays an important role in the gastrointestinal system as well as the brain, we wanted to see if there was a direct relationship between these genes and GI development and function," says Kara Margolis, MD, associate professor of pediatrics, who conducted the study with Michael Gershon, MD, professor of pathology & cell biology. The researchers investigated gastrointestinal development in a mouse model that carries a mutation found in some patients with autism. The mutation decreases serotonin activity by increasing the activity of the serotonin reuptake transporter, which pulls serotonin back into the neuron after it is released for

neurotransmission. Drs. Margolis and Gershon discovered that these mice have fewer neurons than normally found in the gut, a poorly maintained gut lining, and slower movement of gut contents. Dr. Margolis says families and physicians should recognize that gastrointestinal problems are common in children with autism, who may present in a different way. "Often, they're not verbal or they have sensory issues so they can't pinpoint where the pain is coming from. It's important that when these patients present with distress or behavioral problems, a gastrointestinal source is considered."

#### **Treatment-Resistant Schizophrenia**

A study published in the *American Journal of Psychiatry* looked at the use of clozapine for patients with treatment-resistant schizophrenia, which accounts for 30 percent of schizophrenia cases. Even though clozapine is the only medication approved by the FDA for treatment-resistant schizophrenia, the drug is seen as a last resort and its use in clinical practice has not been studied in depth. The results of a study led by T. Scott Stroup, MD, professor of psychiatry, found that patients with schizophrenia who do not respond to standard antipsychotic medications have better outcomes if they switch to clozapine instead of another standard antipsychotic. They have fewer hospitalizations, stay on the new medication longer, and are less likely to need additional antipsychotics.



### A New Medical School in Lesotho

P&S student Dylan O'Connor'17 contributed to the development of a new medical school in the southern African nation of Lesotho with a hands-on international project that satisfied his passion for global health and



development. “When I came to Columbia, I knew that global health was going to be part of my package,” says Mr. O'Connor. “My experience in Lesotho was truly transformative. It showed me why it’s important for institutions like Columbia to guide the development of new schools.” Mr. O'Connor worked with the dean of the new Lesotho School of Medicine to develop a curriculum that would help address the shortage of doctors in sub-Saharan Africa.

### The Newest MD/PhDs

The first two enrollees in a PhD-to-MD program graduated in May 2016. The three-year program was launched to give PhD-trained research scientists an opportunity to move through an accelerated medical school curriculum that would prepare them for careers as physician-scientists.

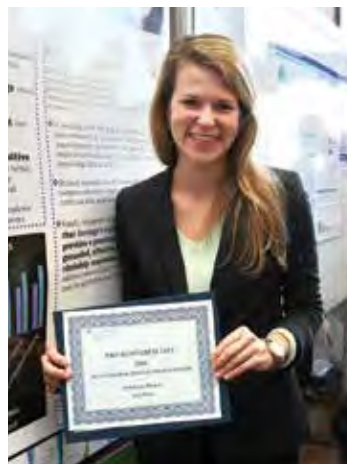
The first graduates are Siyan “Stewart” Cao, who matched to an internal medicine residency at UCSF, and Matthew Fleming, who matched to an internal medicine residency at Vanderbilt.

### Student-Led Events Highlight Health Care Issues

Medical students hosted and participated in several national health care events this year. The events they organized helped broaden their understanding of topics such as health care reform, human rights, and new technologies, including mobile diagnostic technologies. Universal health care was a focus for students across the nation at the #TenOne National Medicare-for-All Student Day of Action on Oct. 1. Human rights work was the focus at the 2015 Physicians for Human Rights National Student Conference, hosted by P&S, where students discussed medicine, economics, law, sociology, and



humanitarianism. The P&S Innovative Medicine Interest Group hosted the second annual InnovateMED conference with student leaders in health and medicine presenting a TED-style event.



### Scholarly Project Impacts Clerkship

Emily Woodbury'16 not only satisfied her scholarly project requirement, she also made an impact on the obstetrics & gynecology clerkship. The scholarly project requirement gives students a chance to delve into topics that most interest them. For Dr. Woodbury it was a chance to engage and mentor medical students in ob/gyn. She worked with the clerkship’s director to pilot a new ob/gyn rotation, which included a new set of interactive lectures. To maximize opportunities for students to observe how ob/gyn care is practiced, the new clerkship consolidates the number of days a student performs each activity and increases the amount of time spent with each clinical team.

### Teaching Next-Generation Tools to the Next Generation

A new multidisciplinary, graduate-level course organized by the Department of Systems Biology is helping young investigators incorporate new genomics tools into their research. The course covers both the experimental principles of next-generation sequencing and key statistical methods for analyzing the enormous datasets that such technologies produce. The stu-

dents also gain valuable practice applying deep sequencing technologies. “We ask students to find a question that has never been systematically investigated before,” says one of the course designers, assistant professor Yufeng Shen, PhD. “We believe the best training is to solve a real world problem using the arsenal of experimental and computational knowledge that they take away from the lectures.”

### Asylum Clinic

The Asylum Clinic, part of the P&S Human Rights Initiative, is one of several learning and community service opportunities for medical students. The clinic is among a group of student-



run clinics that offer students the opportunity to work with underserved populations to help alleviate health care disparities afflicting minority, immigrant, and low-income populations. The Asylum Clinic helps asylum seekers in the New York City metropolitan area gain access to pro bono medical evaluations; medical affidavits are thought to considerably increase the chance of receiving asylum.



# HELP FROM OUR FRIENDS

Numerous individuals and foundations have advanced the P&S missions over this past fiscal year, with philanthropic donations exceeding \$200 million. Below are just a few of the projects that have benefited from the generosity of donors.



The Kempner Foundation has supported several Department of Medicine junior investigators through current and previous gifts. Some of those recipients, from left: Emily M. Stein, Serge Cremers, Thuy-Tien Dam, Kyle K. Nishiyama, Mishaela R. Rubin, Thomas Nickolas, and Natalie E. Cusano.

## Junior Faculty in Endocrinology

The Thomas L. Kempner Jr. Foundation has pledged \$1.2 million to support junior investigators in the Department of Medicine's Division of Endocrinology. The gift honors Elizabeth Shane, MD, professor of medicine, vice chair for clinical and epidemiological research, and associate dean for student research. The gift will provide salary and administrative support for junior faculty to conduct research in osteoporosis, helping young physician-scientists establish a career path in research while strengthening the division's ability to retain and recruit the most promising young endocrinologists.

## Psychiatric Care for At-Risk Children

The Viola W. Bernard Foundation has given \$1.1 million to support programs in the Department of Psychiatry's Division of Child and Adolescent Psychiatry. The gift will advance efforts in research, training for child psychiatry fellows and faculty, and clinical services with an emphasis on the needs of children in underserved communities. It represents a significant expansion of an endowed fund established at Columbia in 1982 to provide permanent support for the Division of Child and Adolescent Psychiatry. The fund honors and extends the legacy of Viola W. Bernard, MD, a longtime P&S psychiatry faculty member who died in 1998. Dr. Bernard, who was associated with Columbia for more than five decades, dedicated her career in psychiatry to understanding and helping adopted and foster children. An authority on community and social psychiatry, child psychiatry, and adoption, she played an important role in the evolution of Columbia's Division of Child and Adolescent Psychiatry.



Viola W. Bernard

## Allen I. Hyman Establishes Professorship

Allen I. Hyman, MD, professor emeritus of anesthesiology at P&S, has established the Allen I. Hyman, MD, Professorship of Critical Care Anesthesiology. Through his clinical, investigative, and advisory work, Dr. Hyman played a lead role in shaping critical care anesthesiology at Columbia, and this gift represents his additional investment in the future of the field. The current holder of the Hyman Professorship is Vivek K. Moitra, MD, chief of the Division of Critical Care in the Department of Anesthesiology and medical director of the cardiothoracic and surgical intensive care units.



Allen Hyman, center, with his wife, Valerie, and P&S Dean Lee Goldman



Tyler and Kate Ilie, with their baby, Caroline, benefited from the Nurture Science Program.

## Advancing Nurture Science

**The Einhorn Family Charitable Trust** has made a commitment to support the CUMC Nurture Science Program, which plans to roll out a major initiative to develop, test, and disseminate nurture-based therapies for U.S. health care providers. The goal of the initiative is to provide families across the country with easy-to-follow techniques that prevent emotional, behavioral, and developmental problems in children. The program has received longstanding support from the Einhorn Family Charitable Trust, which supported the program's launch. Under the leadership of director Martha G. Welch, MD, and co-director Michael M. Myers, PhD, the Nurture Science Program has established a scientific link between family emotional connection and healthy child devel-

opment. Previous research conducted by program researchers showed that mother-child communication begins before birth, conditioning the bodies of both mother and child to respond to each other throughout development. Mother and child continue to draw on these responses after birth to achieve a state of emotional and physiological co-regulation. The program has developed a parenting strategy to establish and maintain this state of co-regulation and is working to introduce therapies based on this concept in a variety of health care settings. The Einhorn Trust's latest gift includes \$6 million designated as matching funds. Columbia and the Nurture Science Program have until 2020 to raise \$6 million from other sources.

## Support for Cardiology

**The Mallah Family Foundation** has committed \$2.5 million to establish the Mallah Family Professorship of Cardiology in the Department of Medicine's Division of Cardiology. The gift honors Allan Schwartz, MD, chief of the Division of Cardiology, and will enhance the division's ability to recruit and retain outstanding cardiologists whose goal is to provide a holistic approach to the care of cardiac patients, specifically geriatric patients.

## Substance Abuse Research and Awareness

**The Eric D. Hadar Family Foundation** has committed \$2 million to support the Division on Substance Abuse within the Department of Psychiatry. The gift will establish an endowed fund of \$750,000 for the Eric D. Hadar Distinguished Lecture, an annual lecture series focused on substance abuse, and \$1.25 million for the Eric D. Hadar Research Fund, which will advance research by providing resources for fellowship and faculty support, research projects, and laboratory infrastructure. The inaugural Eric D. Hadar Distinguished Lecture is scheduled for Nov. 2, 2016. This gift represents the foundation's first significant gift since its formation late last year. The foundation plans to announce additional support targeted toward substance abuse research and treatment, with an emphasis on inner city children.

## Pediatric Precision Medicine

**The Sohn Conference Foundation** is giving CUMC a \$1.5 million grant over three years to establish a pediatric oncology precision medicine program that provides immediate access to next-generation genomic technologies for pediatric cancer patients throughout New York City. The goal of the program is to demonstrate the value of the platform to insurers and regulatory bodies and to advocate for policy changes to cover these approaches for future patients. At a January 2016 press event to announce the program, Evan Sohn, vice president and co-founder of the foundation, joined CUMC leadership in discussing the importance of translational research to developing a new generation of targeted treatments for pediatric cancer.

## Translational Neuroscience

**The Belle and Murray Nathan Philanthropic Fund** gave \$2.5 million through the Jewish Communal Fund to establish the Belle and Murray Nathan Professorship of Neurology. This professorship, named in memory of Columbia College alumni Belle and Murray Nathan, will support a faculty member specializing in translational neuroscience, including the genetics of neurodegenerative diseases. This gift is just one example of the Nathans' longtime commitment to Columbia and to medical research. Belle and Murray Nathan also established a scholarship at Columbia College and a lecture series at Columbia's law school and have funded scientific research at other institutions, including Ben Gurion University.

## New Building Opens to Fanfare (and a Few Healthy Babies)



PHOTOGRAPHS BY NIC LEHOUX,  
COURTESY OF DILLER SCOFIDIO + RENFRO





**M**ost building dedications follow a traditional agenda: a ceremonial ribbon-cutting, tours of the facilities, photo opportunities, and cocktail conversations. The June 9 dedication of the new medical and graduate education building—the Roy and Diana Vagelos Education Center—had an added feature when participants were invited to test their clinical expertise in the building’s simulation center.

The centerpiece of the building is the simulation center, four floors covering 18,000 square feet and including standardized patient exam rooms, mock emergency rooms, and surgical suites. Students will use the center’s advanced equipment and software to hone clinical skills

and receive immediate feedback through the use of one-way mirrors and video monitors that will allow teachers to observe and comment on student performance. Video recording is available from multiple angles.

It was in the simulation center on the night of the dedication that invitees veered from the traditional ribbon-cutting agenda. In the labor and delivery suite, dedication attendees practiced delivering babies. “I would estimate that we had about 15 deliveries in the span of three hours,” says Leslie Moroz, MD, a clinical fellow in maternal-fetal medicine and critical care. “Our obstetricians-in-training ranged in age from 7 to 70 years old. Sim Mom looked tired but happy at the



## Built for Success

IN ADDITION TO THE SIMULATION CENTER, NAMED FOR MARY JAHARIS AND HER LATE HUSBAND, MICHAEL JAHARIS, THE BUILDING INCLUDES:

- A multipurpose auditorium, a 270-seat flexible space for lectures, screenings, and concerts
- “Academic Neighborhoods,” groups of classrooms that can be configured according to need by partitions, drop-down screens, large-scale multi-user touch screens, and suspended ceilings
- “Anatomy Quad,” a flexible learning space with integrated screens and task lighting
- Ground floor lobby and café, which adjoin a “study bar” with views of the Palisades
- Student Commons, which features a café, computer work area, and computer labs
- South and West Courts, outdoor spaces featuring local plant species



BRIAN HATTON PHOTOGRAPHY

**Left:** Pictured at the dedication of the Vagelos Education Center—in front of a wall that spells out the Hippocratic Oath—are, from left, Roy Vagelos, Columbia University President Lee Bollinger, building designer Elizabeth Diller, Philip Milstein, and P&S Dean Lee Goldman.

end of the evening, and all of the babies went to the well-baby nursery.”

In the simulation center’s operating room, dedication participants were introduced to a scenario of a 56-year-old male undergoing heart-lung bypass for coronary artery bypass grafting surgery. The patient was under the care of a surgeon, an anesthesiologist, and a perfusionist during the procedure. After the patient came off bypass, his oxygenation deteriorated and he required emergency initiation of extracorporeal membrane oxygenation—ECMO—to save his life. “It was exciting to showcase the simulator’s capabilities throughout the evening,” says Cara Agerstrand, MD, assistant director of the medical ECMO program. “Attendees participated in saving the

patient’s life by assisting the team in adjusting the settings of cardiac bypass and learning how to initiate ECMO.”

The new building, which officially opened in August when the Class of 2020 matriculated, is named for the couple who provided the lead gift for the building’s construction, Diana and P. Roy Vagelos, a 1954 graduate of P&S. Other major donors on hand at the June dedication were Cheryl and Philip Milstein; Kathryn and Mary Jaharis, representing the Jaharis family; Roger Wu and David Wu, representing their parents, the late Helen and Clyde Wu; and Sudhir, Anita, and Dhairya Choudhrie, representing the Choudhrie Family Foundation.

The 14-story glass tower, designed by Diller Scofidio + Renfro in collaboration with Gensler as executive architect, features a distinctive cascade design that creates flexible social spaces to facilitate team-based learning. The building’s 100,000 square feet of technologically advanced classrooms and collaborative spaces integrates a range of environmentally sustainable features, including locally sourced materials, green roof technologies, and an innovative mechanical system to minimize energy and water use. Construction on the building began in 2013.

## Vagelos Education Center Visionary Leaders

### TOP DONORS TO THE VAGELOS CENTER:

- The Russell Berrie Foundation
- Margo and John A. Catsimatidis
- The Choudhrie Family Foundation
- Mary and Michael Jaharis
- Merck & Co. Inc.
- Cheryl and Philip Milstein Family
- P. Roy Vagelos, MD P&S ‘54, and Diana T. Vagelos
- Clyde Wu, MD P&S ‘56, and Helen Wu
- George D. Yancopoulos, MD, PhD P&S ‘87

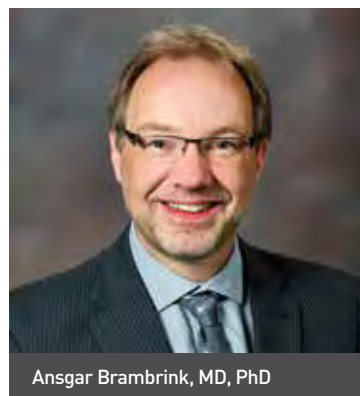
## New Chair, Initiative Director Named

**Two leadership appointments** were made this year. Ansgar Brambrink, MD, PhD, was named chair of the Department of Anesthesiology, and Emmanuelle Passegué, PhD, was appointed director of the Columbia Stem Cell Initiative, which was launched in 2008 to bring together researchers to explore the potential of using stem cells to improve human health.

Dr. Brambrink, who also will serve as anesthesiologist-in-chief at NewYork-Presbyterian/Columbia, succeeds Margaret Wood, MD, who retired after more than 20 years as chair.

An internationally renowned expert in brain injury, Dr. Brambrink joined P&S after serving as professor and vice chair of faculty development and advancement in the Department of Anesthesiology and Perioperative Medicine at Oregon Health & Science University. Dr. Brambrink received his doctorate and medical degrees from Westfälische Wilhelms-University School of Medicine in Germany.

Dr. Passegué spent 11 years in the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of Cali-



Ansgar Brambrink, MD, PhD



Emmanuelle Passegué, PhD

fornia San Francisco, where she was a tenured professor in the Department of Medicine’s Division of Hematology/Oncology.

An expert in hematopoietic stem cells, Dr. Passegué was an active member of the UCSF stem cell program and helped shape its programmatic activities for the past decade. Before joining UCSF, she earned a PhD in endocrinology summa cum laude from Paris-XI University.

## Grants Support Faculty Diversity Efforts

Six P&S faculty members received support through the Columbia University Provost's Grants Program for Junior Faculty Who Contribute to the Diversity Goals of the University. The program is part of a \$33 million commitment announced last year to reinforce and expand the University's faculty diversity efforts.

The six faculty members received support during two rounds of funding in 2015-16. Since the program began in 2013, 75 projects throughout the university have been funded.

The 2015-16 P&S recipients and their project titles:



### *Targeting Systemic Mediators in Cancer*

**Swarnali Acharyya, PhD**

assistant professor of pathology & cell biology  
(in the Institute for Cancer Genetics)



### *Modulation of Circuit Elements for Motion Detection by Locomotion*

**Rudy Behnia, PhD**

assistant professor of neuroscience



### *Innovative Models for Delivery of Depression Care and Reducing Cardiovascular Disease*

**Nathalie Moise, MD**

assistant professor of medicine



### *Sex Differences and the Role of Novel Calcium Kinase Signaling*

**Lale Ozcan, MD**

assistant professor of medical sciences  
(in medicine)



### *Immune Editing of Glioblastoma Genome During Tumor Progression*

**Adam Sonabend, MD**

assistant professor of neurological surgery



### *Understanding the Molecular Pathobiology of Right Ventricular Dysfunction as a Determinant of Gender Differences in Heart Failure*

**Emily Tsai, MD**

assistant professor of medicine



AMELIA PANICO

## ABOUT THE CLASS OF 2016

**166** MD graduates, **50** percent of them women

**12** also received PhD degrees

**2** also have MPH degrees

**2** were inaugural graduates of the three-year PhD-to-MD program

**2** also received MBA degrees from Columbia

**2** also have DDS degrees

**1** also received an MS degree in biomedical engineering

**28** took an extra year for research

**29** percent took extra time for either research or to complete a dual degree

**27** percent went abroad for senior electives or scholarly projects, mostly to developing countries

**30** students got married during medical school

**20** babies were born to students in the class during medical school, and three students had two children during medical school

Graduates completed **55** triathlons or full or half marathons

**47** percent matched to residencies in New York City

**26.7** percent matched at Columbia for all or part of their training

**11** couples participated in the match, including **4** in which both were P&S students

**One-third** of the class volunteered as senior student advisers for the class below

**Many members** of the class volunteered for one of the five student-run free clinics

## New Academy Recognizes Clinical Excellence

P&S has launched the Academy of Clinical Mentoring and Excellence to measure, recognize, and reward achievements of clinical faculty members who contribute to the school predominantly through patient care.

“P&S is ranked consistently among the best U.S. medical schools and is one of the most research intensive, but we also are home to excellence in clinical care in more than 230 medical specialties and subspecialties,” says Dean Lee Goldman, MD. “The creation of the academy is a way of honoring our faculty who have achieved the very best in patient care. Excellence in clinical care combines compassion with knowledge informed by research, evidence-based practices, and experience to benefit patients and their families.”

Adds James McKiernan, MD, the John K. Lattimer Professor of Urology, chair of the Department of Urology, and chair of the P&S faculty committee that developed the academy: “Membership in the academy will honor our expert Columbia clinicians and provide opportunities for inductees to also serve the academy as teachers, mentors, and champions of clinical excellence.”

Induction into the academy will take place annually with an awards ceremony and lecture. In its inaugural year, the academy will induct its first class of members who are P&S full professors



JORG MEYER

and have been at CUMC for at least the past five years. Inductees will have devoted more than 50 percent of their time to patient care and training the next generation of clinicians. In 2017, after the inaugural class, nominations for membership will be made by full-time active clinical faculty members and will be open to all ranks at P&S.

“The creation of the academy enables P&S to honor and foster what makes these faculty members so special. They have qualities as clinicians that make you want them treating yourself, your family member, or close friends,” says Robert Whittington, MD, professor of anesthesiology and academy committee member.

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## Global Innovation

Two projects led by P&S faculty were among 12 projects that received funding during the fourth round of grants from the Columbia President’s Global Innovation Fund. Grants are awarded to faculty members to leverage and engage Columbia Global Centers in developing new projects and research collaborations that will increase global opportunities for research, teaching, and service.

The projects make use of the network of eight Columbia Global Centers to provide opportunities for faculty and students to address important global issues. In the three previous rounds of funding, 49 projects were supported. “Collectively, these projects play an essential role in realizing the potential of the Columbia Global Centers to create new opportunities for faculty and students and in defining in tangible ways what it means for Columbia to explore new frontiers of knowledge in the 21st century,” said Provost John H. Coatsworth in announcing the 2016 funded projects.

The two projects led by P&S faculty:

**Adolescents Living with HIV: Engaging and Empowering through Photography**

**Elaine Abrams, MD**  
professor of pediatrics at CUMC

**Laboratory-based PhD Training in Nutritional and Agricultural Sciences in East Africa**

**Debra Wolgemuth, PhD**  
professor of genetics & development  
(in obstetrics & gynecology and in the Institute of Human Nutrition)



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Lawrence Hospital,  
Bronxville, NY

# FACTS & STATISTICS, FY16

## MEDICAL SCHOOL ENROLLMENT, FALL 2015

Total medical school enrollment .....	670
Enrollment of underrepresented minorities .....	166
Enrollment of minorities .....	271
Enrollment of international/nonresident students .....	21
Enrollment of in-state residents .....	209
Enrollment of men .....	334
Enrollment of women .....	336

## ENROLLMENT BY YEAR

	MALE	FEMALE
First-Year Class	81	79
Second-Year Class	80	77
Third-Year Class	89	97
Fourth-Year Class	84	83
Total Enrollment	334	336

## MEDICAL SCHOOL ETHNICITIES

Nonresident aliens .....	21
Hispanic/Latino .....	79
Black or African-American, non-Hispanic/Latino .....	68
White, non-Hispanic/Latino .....	318
American Indian or Alaskan Native, non-Hispanic/Latino .....	1
Asian, non-Hispanic/Latino .....	105
Native Hawaiian or other Pacific Islander, non-Hispanic/Latino ...	1
Two or more races, non-Hispanic/Latino .....	17
Race and/or ethnicity unknown .....	60

## OTHER STUDENTS

MD/PhD students .....	120
PhD students .....	317
Other students (PT, OT, Nutrition, Informatics) .....	506

## DEGREES GRANTED, FY16

MD .....	168
PhD .....	55
Doctor of physical therapy .....	54
MS in nutrition .....	78
MS in occupational therapy .....	51
Certificate in psychoanalysis .....	1

## APPLICATIONS (ENTERING CLASS 2015)

Number of applicants .....	7,878
Number of applications considered .....	7,366
Number of applicants interviewed .....	1,090
Number of acceptance letters issued .....	313
Number of new entrants .....	161
Bassett Program applications .....	637
Number of new Bassett Program entrants .....	10

## FACULTY, 2015-2016 ACADEMIC YEAR

	FULL TIME	PART TIME
Number of clinical faculty	1,675	2,009
Number of basic sciences faculty	238	68

## FACULTY HONORS

Nobel Prize in Medicine .....	2
National Academy of Sciences .....	19
National Academy of Medicine .....	47
American Academy of Arts and Sciences .....	25
Howard Hughes Medical Institute .....	9

## FINANCIALS, FY16 (except where noted)

Budget .....	\$1.7 billion
Philanthropic support .....	\$204 million
Endowment .....	\$1.7 billion
Endowed chairs/professorships .....	254
NIH research support (FY 2015) .....	\$356.5 million



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# Space MATTERS



Our new education building will ensure that Columbia continues to train superior doctors and researchers, educated in the latest techniques, as medicine continues to evolve rapidly throughout the 21st century. The building also will allow us to centralize key activities in a state-of-the-art facility that reflects our commitment to providing world-class instruction and a superb learning environment for students.”

— Lee Goldman, MD, Dean

More about the new building: Page 42

