Columbia Medicine

Columbia University Vagelos College of Physicians & Surgeons

2019 ANNUAL REPORT

INTO THE FUTURE

TOMORROW'S EDUCATION,
SCIENCE, AND PATIENT CARE

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Whether at the department level, such as efforts to attract more women and people of color to emergency medicine, or at the school level, such as an enhanced parental leave policy, VP&S has shown that efforts to improve diversity and inclusion among its faculty ranks are more about commitment than compliance.

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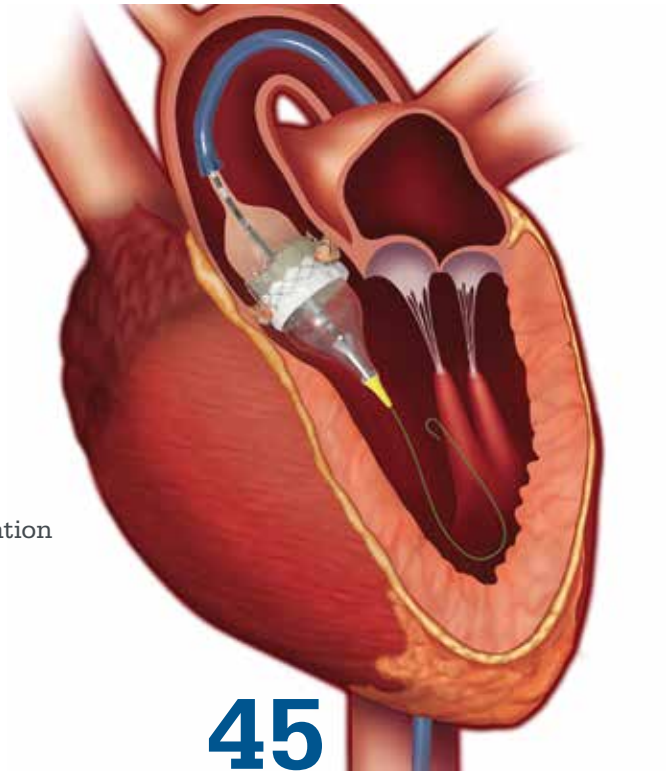
Several innovations in recent years have helped scientists, but CRISPR has been transformative. CRISPR is not merely a way to create gene therapies; it has become an important tool for discovery at VP&S, with basic scientists developing new CRISPR-based tools that translational researchers use to reveal new insights into human disease and how to treat it.

http://ps.columbia.edu/

Departments:



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On the Cover

Whether introducing and validating a new standard of care in heart surgery, improving on the latest scientific tool, strengthening the commitment to diversity and inclusion among the faculty, or complementing Columbia's AIDS programs, VP&S scientists, researchers, clinicians, and teachers have made progress this year that will improve the future for everyone touched by academic medicine.

Illustration by Davide Bonazzi

2019 Annual Report

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TO INFINITY … AND BEYOND

JÖRG MEYER

This 2019 annual report of the Vagelos College of Physicians and Surgeons surely addresses our traditional obligation to review our recent collective accomplishments, but its primary goal is to look to the future. This primary goal is critical because the strength of these ongoing accomplishments has put us in an enviable position to create an even stronger 2020 … and beyond.

We take seriously our legacy and reputation as one of the nation's best medical schools—and second oldest. The values that infuse everything we do reflect our commitment to pursue the best in teaching, scientific investigation, patient care, and community service.

The features in this year's annual report illustrate that range of commitment:

• The move of the Aaron Diamond AIDS Research Center from Rockefeller University to VP&S will augment Columbia's AIDS research efforts with the distinguished career David Ho has built in his many years as an HIV researcher.

• Increasing the diversity of our faculty has been among our most important accomplishments in recent years, and we have reinforced our dedication to diversity and inclusivity by implementing recommendations from two dean's advisory committees. We are committed to ensuring that we meet the career development needs of all of our faculty.

• Despite the important ethical issues it raises, CRISPR is one of the most promising scientific innovations of this generation, and Columbia researchers are at the forefront in using the gene editing tool to advance—and hasten—research discoveries.

In the highlights section of this report, you can read about dozens of patient care advances, research discoveries, and educational programs that show how our faculty and students influence health through prevention, diagnosis, and treatment. Our NIH grant growth has outpaced the NIH budget for 10 years in a row and we now would rank #2 among U.S. medical schools if all awards to our faculty in psychiatry (whose awards are credited instead to the New York State Psychiatric Institute) were included in the calculation. Our researchers were cited in the 2019 Nature Index Annual Tables, which named Columbia University Irving Medical Center the top health care institution for scientific research. The index identifies institutions with the highest output of top-quality research in the natural sciences over the past year, based on articles published in 82 scientific journals. Columbia placed first in the rankings of health care institutions, with 375 publications in leading journals in 2018.

Precision medicine continues to inform our research and patient care programs. The local *All of Us* research program, a consortium led by David Goldstein at CUIMC and joined by Weill Cornell Medicine, NYC Health + Hospitals/Harlem, and NewYork-Presbyterian, has enrolled more than 17,500 New York City participants, over 85% of whom are from communities that have been underrepresented in biomedical research. Our New York City consortium is part of the national NIH *All of Us* program to enroll 1 million or more participants to harness the promise of precision medicine by exploring differences in people's lifestyles,

Artist's rendering of a new research building

environments, and genetic makeup. To complement this effort and address the national shortage of genetic counselors, VP&S recently created a two-year genetic counseling master's degree program, in which the first 12 students began their coursework this fall.

Also new to campus this fall is the VP&S Class of 2023, 140 extraordinary students who are in the second class to be offered scholarships instead of loans to meet their financial needs throughout medical school. The 70 women and 70 men were chosen from among nearly 8,000 applications reviewed by our new admissions dean, Anne Armstrong-Coben, MD, and her admissions committee. Our scholarship program—in which all need-based financial aid is provided by scholarships without loans—was created through the generosity of Roy Vagelos'54 and his wife, Diana, along with many other alumni and friends. This program has further elevated our school and continues to allow us to attract the best and brightest medical school applicants, independent of their financial need. In turn, our students will be able to pursue their passions in medicine and science without the constraints of medical school debt. The makeup of the new class underscores our commitment to diversity and inclusion: 21% of the class members are underrepresented minority students.

This year also saw the completion of the first phase of Haven Plaza, a gathering place we anticipate will be shared enthusiastically by our medical center community and our neighbors. A stretch of Haven Avenue, from 168th Street to 169th Street, was closed to become a pedestrian plaza for all to enjoy either individually or in group events. Please see the latest photos of Haven Plaza on the back cover of this report.

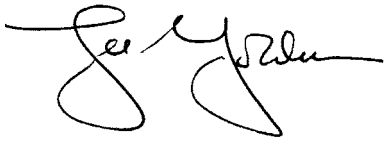
Our celebration of this past year's successes was tempered by the June 2019 loss of Ken Forde, our alumnus, faculty colleague, renowned surgeon, university trustee, and hospital trustee. His generosity was both traditional—he contributed to VP&S scholarships and created a teaching scholars fund that you can read about in this issue—and pioneering—he foresaw the future of surgery in endoscopy and led the way in its implementation in his surgical specialty. Surgeon Spencer Amory, MD, in speaking at Dr. Forde's memorial service in July, thanked his mentor for sharing his skills in endoscopy and for modeling exceptional communication, diagnostic skills, humility, and compassion. Of Dr. Forde's support in promoting minimal access surgery at Columbia and beyond, Dr. Amory said, "Patients and surgeons continue to enjoy the rewards of your foresight." We add our words of appreciation in paying tribute to this physician, mentor, benefactor, and true gentleman who was enormously admired and is now missed by so many.

The late Ken Forde with Lee Goldman and Roy Vagelos in 2017

Although the tradition of an annual report is to look back at the previous year's accomplishments and milestones, it is also important to look forward. And that is particularly important for me. In May, I announced my intention to step down as dean and chief executive of the medical center at the end of the 2019-20 academic year, which will give me the privilege of having stewarded VP&S and CUIMC for 14 years. In my final year, our goals remain lofty yet achievable. Among them are to plan new facilities to increase our faculty's capacity for research and patient care, including a new research building and a new cancer building shared with NewYork-Presbyterian. We also hope to add 50 primary care physicians by 2022 and grow our multispecialty practice sites in Manhattan and Westchester.

Thank you for your continued support of the initiatives that have made this school such an extraordinary place and that will make us even greater in the year to come.

With best wishes,



Lee Goldman, MD, Dean
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THE FUTURE IS NOW: A DIVERSE AND INCLUSIVE FACULTY

BY SHARON TREGASKIS

This spring during her maternity leave, Stephanie Lovinsky-Desir, MD, updated progress reports to the NIH on her research into asthma among kids living in urban areas, reviewed grant applications and abstracts for the American Thoracic Society, flew to Chicago to present an abstract at an American Society for Clinical Investigation meeting, and drove to Baltimore to give an oral presentation of her research at a Pediatric Academic Society meeting. "When an opportunity presents itself, it's really hard to say no," says the pediatric pulmonologist and mother of three. "Junior faculty members are expected to have exponential growth in this early part of our careers—but it overlaps with when we're raising young families."

And yet, says Dr. Lovinsky-Desir, compared with the shorter leaves she had after her older two children were born, the 13-week parental leave policy instituted across Columbia University Irving Medical Center (CUIMC) in January 2018 was a significant benefit. "While it was still hard to come back to work, especially leaving a new baby with a cold, it was really nice to have that extra month of bonding time with her," she says.

In 2017, for the first time, more women than men enrolled in VP&S. This past year, women were the majority of both medical school applicants and enrolled students nationwide. Racial and ethnic diversity likewise continues to increase among medical students, with nearly 50% of medical students in the United States identifying as non-white. And while great strides have been made in diversifying the ranks of academic medical faculty—both at Columbia and across the country—women and people of color remain underrepresented at the highest levels of academic ranks, administration, and leadership. To address the issue, VP&S administrators have dedicated recruitment, hiring, and programmatic efforts to expanding the pipeline of women and underrepresented minority faculty to serve the educational, clinical, and research missions of VP&S and to take on leadership roles.

"Diversity at all levels of medicine, including students, trainees, faculty educators, researchers, and practitioners, is critically important to educate students to understand medical problems that quickly and easily cross global borders; to deliver culturally sensitive health care to a population that is multicultural, multinational, and multilingual; and to bring new and different research perspectives to the research agenda," says Anne Taylor, MD, vice dean for academic affairs. "American medical education, practice, and research can only remain the best by using the full intellectual capital derived from recruiting the most committed, accomplished, and talented workforce from every segment of our population."

The effort at VP&S got a substantial boost in April 2018 when Lee Goldman, MD, dean of the faculties of health sciences and medicine and chief executive of CUIMC, convened two faculty committees—one dedicated to the particular career challenges faced by women and the other to those of underrepresented

minorities—to develop recommendations that would strengthen ongoing efforts to promote opportunities for career success at VP&S for all faculty. Dr. Goldman reviewed the recommendations submitted jointly by the two committees and accepted them in full this year. (See Page 9 for a full list of recommendations.) "While the recommendations were developed by advisory committees, their implementation will position VP&S to be the best place for academic medical faculty to flourish," says Dr. Taylor, whose office provided administrative support for the committees.

Convening the committees was part of the medical school's ongoing efforts over the past decade to be sure that career development needs of all faculty are met. These efforts also recognize that women and underrepresented minority faculty face additional unique challenges to career development that require more professional development efforts. Earlier efforts have resulted in measurable progress. Among VP&S faculty 47% are women, compared with the national average of 39%. Even at the highest ranks, 29% of VP&S full professors are women compared with 25% nationally, and 35% of the medical school's tenure-track faculty are women, leading Columbia's peer group of medical schools. Racially and ethnically diverse people make up 20% of the faculty at VP&S, with 11% (compared with 8% nationally) from groups traditionally underrepresented in the professoriate.

In recent years, the academic tracks were restructured to create a transparent, objective basis for academic advancement and to minimize arbitrary and potentially exclusionary promotion practices. Parameters of equity, such as numbers of women and diverse faculty in leadership positions and on key committees that review candidates for promotion and honors, are closely monitored to assure a balanced representation of the faculty, and salary equity between men and women is regularly measured. To ensure continued efforts, VP&S committed $50 million to programs to recruit and support women and diverse faculty.

Chief among the recommendations Dr. Goldman endorsed to promote the success and retention of new recruits and current faculty is creation of an Office for Women and Diverse Faculty. "All of our programs are driven by faculty interest and faculty demand," says Dr. Taylor. Hired in late 2007, about 18 months after Dr. Goldman became dean, Dr. Taylor now holds the John Lindenbaum Professorship of Medicine and also serves as senior vice president for faculty affairs and career development for CUIMC. From that vantage point, she sees implementation of the committees' recommendations as the latest advance in the work with which she was charged when she joined Columbia. "When I came to the medical school, there were no professional development programs for faculty," says Dr. Taylor. "VP&S hires some of the most gifted faculty members in the country, so it is our responsibility to support their career success and satisfaction." Her office now oversees orientation programs; leadership and management training, including sessions for all women and diverse faculty cohorts; workshops focused on career development and academic advancement for educators, researchers, and clinicians; and workshops focused on teaching skills, negotiation skills, and management of research teams. Working with women faculty, Dr. Taylor helped to develop the Virginia Kneeland Frantz Society for Women Faculty. "Implementation of the advisory committees' recommendations will allow for expanded professional development programs but importantly will offer the opportunity to create further changes in the overall culture and climate around diversity and equity."

When Hilda Hutcherson, MD, arrived at Columbia in 1981, she was the first African American woman

Anne Taylor

PHOTOS BY JÖRG MEYER

Hilda Hutcherson

Christine Rohde

resident in obstetrics & gynecology. "On this campus, there were few African American residents at the time in any department, or even faculty members," she recalls. "When I started as an assistant professor in '85, there were no programs to encourage minorities or women to pursue academic medicine." Now a professor of obstetrics & gynecology and senior associate dean for diversity and multicultural affairs, Dr. Hutcherson served on the Committee for Faculty Diversity and Inclusion—and she is pleased that the committee's work has been so enthusiastically endorsed by the dean. "When the list of recommendations was put together, I don't think anyone was thinking we'd get 100%," she says. "I'm so happy that Dr. Goldman took all of the recommendations."

In the absence of formal programs to support her own career development, says Dr. Hutcherson, informal relationships were key to her success. During her early years on the faculty, Gerald E. Thomson, MD, now the Samuel Lambert and Robert Sonneborn Professor Emeritus of Medicine, took note of her passion for encouraging students from diverse backgrounds and urged her to consider formal opportunities to mentor others. "It wasn't something I was pursuing at first," says Dr. Hutcherson. "Dr. Thomson thought I would be really good and a natural fit and encouraged me to apply—that's how I ended up in this position." She not only transformed what was once a small office dedicated to recruitment of underrepresented minority medical students into an office with a broader set of programs that support all medical center students, she founded and leads the Kenneth A. Forde Diversity Alliance, which is dedicated to recruiting, retaining, and recognizing a diverse community among students, residents, faculty, and alumni.

All departments will offer training in detecting and fighting implicit bias—the unconscious attitudes and stereotypes that can affect behavior.

Informal associations like that with Dr. Hutcherson and Dr. Thomson—whereby higher-ranking professionals in the field champion the career trajectories of junior faculty—play a critical role in sustaining diversification of leadership of academic medicine, says plastic surgeon Christine Rohde, MD. These relationships, which differ significantly from the peer-to-peer mentorship and networking many professionals already enjoy, are important but should be supplemented by formal mentoring and sponsorship opportunities available to all, says Dr. Rohde. The Office of Faculty Professional Development, Diversity & Inclusion led by Clara Lapiner, MPH, pro-

Richard Francis

Angela Mills

motes mentorship and sponsorship for faculty within departments but also has made sponsorship of faculty for outside career development part of its mission.

A sponsorship opportunity from the Office of Faculty Professional Development, Diversity & Inclusion provided funding support from the Virginia Kneeland Frantz Society for Dr. Rohde to attend an AAMC mid-career development training program for women faculty. Since the program began in 2016, 29 women and 20 underrepresented faculty have received funding support to attend AAMC career development seminars. Faculty who have received such support share what they have learned with others. "At the end of that course I wrote a list of the things I wanted to try to do in my work life and some were very, very specific—talking to a particular individual about things I wanted to achieve in the future—and others were more general about how I could grow, contribute, increase visibility," says Dr. Rohde. "Sponsors have really put me forward for things I wouldn't have thought of myself."

As vice chair of faculty development and diversity for the Department of Surgery and chief of microvascular services at CUIMC, Dr. Rohde now has opportunities to mentor and sponsor colleagues earlier in their careers, with a particular eye on cultivating diversity among those being recommended for leadership. "There are scholarships geared toward women, underrepresented minorities, and I'll find people in my department who are eligible, encourage them to go for it, talk to people who will nominate them," she says. And as a Chinese American mother of three, she chooses to take on high-visibility roles—as co-chair of the Women Physicians of NewYork-Presbyterian, as a leader in her professional societies, as a member of the dean's advisory committee for women faculty, and now as she applies for a full pro-

Who's Who

- **Richard Francis, MD, PhD,** assistant professor of pathology & cell biology
- **Hilda Hutcherson, MD,** professor of obstetrics & gynecology at CUMC and senior associate dean for diversity and multicultural affairs at VP&S
- **Stephanie Lovinsky-Desir, MD,** assistant professor of pediatrics
- **Angela Mills, MD,** the J.E. Beaumont Professor of Emergency Medicine and department chair
- **Christine Rohde, MD,** associate professor of surgery at CUMC
- **Anne Taylor, MD,** the John Lindenbaum Professor of Medicine at CUMC, vice dean for academic affairs at VP&S, and senior vice president for faculty affairs and career development at CUIMC

fessorship, a pursuit relatively rare among female surgical faculty. "I'm very conscious of what I do and what that means for other people who may want to follow my career path in academic plastic surgery," she says. "The kids are watching—if we say diversity is important, but the field is not, I think they pick up on that."

Pathologist Richard Francis says he has seen significant shifts in the institutional culture at VP&S since he was a student in the MD-PhD program and since he was hired as faculty in 2011. "I feel like it is sincere, the idea of making this a better place for people to work, for patients to be seen, for people to receive their education," says Dr. Francis, who directs the Special Hematology and Coagulation Laboratory and served with Dr. Hutcherson on the dean's advisory committee for faculty diversity and inclusion. "I don't get the impression that it's just lip service, but real follow-through where you can see differences."

He sees particular promise in the dean's endorsement of the faculty recommendation that all departments offer training in detecting and fighting implicit bias—the unconscious attitudes and stereotypes that can affect behavior. "It feeds back into interviewing students, residents, faculty," he says. "People need to understand how they view people, how that affects who they recommend, and how they approach trainees and job offers."

In his own career, he has found connection through programs like a Harold Amos Medical Faculty Development Program award from the Robert Wood Johnson Foundation, which expanded his access to mentors. "As you get further along, having people to mentor you who are more like you, look like you, have gone through things that you've experienced matters more."

To provide that kind of access among the residents he meets in clinical rotations, Dr. Francis keeps lines of communication open, often helping trainees process their own encounters with implicit bias. Much of that work boils down to acknowledging and validating painful experiences. Sometimes he shares insights from his own journey or offers advice. "It's not that someone's trying to disrespect you," says Dr. Francis. "They're updating their schema—sometimes it works and sometimes it doesn't and there's friction in that process."

Diverse perspectives advance the kind of problem-solving central to academic medicine, Dr. Francis notes. Acknowledging the friction that can sometimes emerge and working through difficult processes are critical steps for achieving the potential a diverse workforce promises. "You have to do something to foster that environment, make sure everyone has an equal voice, that they know that what they have is something of value," he says. "Everyone needs to know that their perspective will be heard."

PHOTOS BY JÖRG MEYER

Faculty Initiatives Accepted and Funded

The list of recommendations submitted to VP&S Dean Lee Goldman, MD, about ways to strengthen women faculty and faculty diversity and inclusion was a comprehensive one, but it took little time for Dr. Goldman to accept them in full—and pledge funding for their implementation.

Below are the recommendations made by the Dean's Advisory Committee for Women Faculty and the Dean's Advisory Committee for Faculty Diversity and Inclusion.

- Create an Office for Women and Diverse Faculty.
- Expand the work of successful faculty development programs, such as the Virginia Kneeland Frantz Society for Women Faculty and the Kenneth A. Forde Diversity Alliance.
- Require each department to submit an annual diversity update.
- Emphasize broad engagement with faculty and the VP&S community around issues of gender and diversity.
- Seek funding to create an endowment to expand leadership training and other ongoing development programs for women and diverse faculty.
- Increase transparency around service on key school committees, leadership positions, and opportunities.
- Expand implicit bias training for all departments, key committees, and searches at all levels.
- Strengthen the medical school's existing successful initiatives, such as regular salary equity reviews, parental leave, and work/life services, including child care options.

As chair of the Department of Emergency Medicine since January 2018, Angela Mills, MD, has hired 34 new faculty. Among them are 21 women and nine people of color. "Diverse teams are smarter, and teams that are both gender and culturally diverse are more likely to introduce innovations," says Dr. Mills. Both as problem solvers and as educators, she says, leaders in academic medicine must innovate. Yet implicit bias often interferes with the recruitment and retention of a diverse team. To reduce that risk, Dr. Mills has standardized as much of the process as possible by requiring that nominating committees define hiring criteria

JÖRG MEYER

Stephanie Lovinsky-Desir

"It's important to see people in leadership who look like you, who have gone through similar experiences. If they've made it, I too can make it."

in advance and search committees develop a panel of questions each candidate must answer. "What we ask candidates and how we evaluate them is really important when we're talking about diversity," she says. "Without clearly defined criteria, people tend to redefine characteristics of what they're seeking to promote male candidates, less diverse candidates."

As a member of the dean's advisory committee for women faculty, Dr. Mills brought to the table her personal experience as a first-generation college student, woman, and mother of two rising through the ranks of emergency medicine, as well as her scholarship on the gender gap in her field. In February, the Society for Academic Emergency Medicine published her analysis—co-authored with colleagues at Harvard—on gender differences in faculty rank among academic emergency physicians in the United States. Later that month, she gave a VP&S grand rounds lecture on the gender gap in academic medicine. Nationally, Dr. Mills notes, more than 50% of medical students are women. Among all residents, 46% are women; in emergency medicine, however, only 37% of residents are women. "And the number keeps falling off," she says. "The question is how do we promote emergency medicine as a specialty that supports women, promotes women, and allows women to successfully transition into academic medicine if they choose?"

She has found that the new 13-week parental leave policy helps recruitment. "I use that as a selling tool, and I've had just as many men as women take parental leave," she says. "It's a great benefit to all parents." She also is optimistic about the potential of #SHEmergency, a professional development group that fosters community and develops methods for awareness of gender bias among female-identified residents and emergency medicine faculty. The group's article, "#Shemergency Presents: Recruitment & Retention of Female Residents," appeared this summer in AAMC's journal, Academic Medicine. "We developed specific events where residents and faculty partner on strategies and plans to combat disparities—everything from mentorship to speaking invitations, awards and recognition, salaries."

Like Dr. Francis and Dr. Rohde, Dr. Lovinsky-Desir credits an early career development award for providing the professional connections and coaching she needed to take a tactical approach to her own career advancement. "In my regular circles on the academic campus, often I'm the only woman of color," she says. "It's important to see people in leadership who look like you, who have gone through similar experiences. If they've made it, I too can make it."

Among members of the dean's advisory committee for faculty diversity and inclusion, the power of solidarity and connection made the idea of an Office for Women and Diverse Faculty particularly attractive, says Dr. Lovinsky-Desir. "As the odd person out, sometimes your voice gets lost. It's a little harder to speak up," she notes. "If there's a space where we can unite, uplift one another, I think it will empower us as we go back into our teams."

Already, says Dr. Lovinsky-Desir, she sees other changes emerging from the recommendations advanced by the dean's advisory committees—a powerful, self-reinforcing effect both on campus culture and the advancement of women and minorities across VP&S. She was recently invited to serve on a search committee. Not only was she able to lend her perspective on the search itself, Dr. Lovinsky-Desir was fascinated by the insights she gleaned about what search committees prioritize when assessing candidates for senior leadership positions. "We often don't get that as junior faculty, women, minorities," she says. "I learned so much about what features are valued in a person in senior administrative leadership, and that perspective will enhance my growth here as a junior faculty member." ❖

THE **FUTURE** — AND THE **END?** — OF **AIDS**

BY **KRISTIN BUNDY**

Throughout much of the world, a diagnosis of HIV/AIDS that once meant a certain death sentence now means living with a chronic, controllable disease. "If you think about the fact that this epidemic was only recognized in 1981, the progress has been enormous," says David Ho, MD, the AIDS pioneer who was recruited to VP&S this year as the Clyde'56 and Helen Wu Professor of Medicine. "We do not have a vaccine. We do not have a cure. But we have turned a deadly disease into a manageable condition."

Dr. Ho has witnessed that transformation firsthand. He saw some of the earliest AIDS cases in the United States as a resident at Cedars-Sinai Medical Center in Los Angeles in 1980. "I will always remember the young man who came to the hospital with a multitude of infections," he recalls of his first case. "He was treated but, nevertheless, died within a few weeks after leaving the hospital."

Soon, another young man with pneumonia and other infections came to the hospital, was treated, and, again, died very quickly. "It was this second, then third case, that began to raise alarm," says Dr. Ho. Within a year, those patients were included in the first case report submitted to the Centers for Disease Control and Prevention on what would become known as the AIDS epidemic.

What he saw in the clinic moved Dr. Ho to pursue HIV research throughout the 1980s. His renown grew, and by 1990 Dr. Ho had been named scientific director and chief executive officer of the Aaron Diamond AIDS Research Center, or ADARC, the largest independent nonprofit organization dedicated to basic research in HIV/AIDS.

His work has played a key role in what is now known about HIV. He helped elucidate the nature of HIV replication, developed a number of antiretroviral drugs, and at the 1996 International AIDS Conference presented his team's breakthrough study results that proved combination therapy could reduce HIV viral loads to undetectable levels for at least one year. "That was a turning point in the treatment efforts," says Dr. Ho.

"And I believe over the next five or 10 years, we are going to see tremendous progress in preventing HIV infection, not just with drugs like PrEP, but with antibodies and perhaps even with vaccines."

This year, Dr. Ho is bringing ADARC to Columbia. "The Aaron Diamond AIDS Research Center is a world-leading center for the study of HIV and AIDS," says Lee Goldman, MD, dean of the faculties of health sciences and medicine and chief executive of Columbia University Irving Medical Center. "Our faculty are excited about the new collaborations that will advance our understanding of HIV and how to treat and prevent this viral infection."

ADARC will move into a new, specially designed facility on two floors of the Hammer Health Sciences Center. Says Dr. Ho: "There is nothing like having a home at an academic medical center."

Much of ADARC's research focuses on antibodies to prevent HIV transmission. One antibody in particular, engineered by ADARC six years ago, obstructs viral entry into the host cell. "It turns out to be extremely powerful in blocking HIV infection in the lab and in laboratory animals," says Dr. Ho. He and his team have initiated a year-long, phase 1 trial of the antibody in infected patients and healthy volunteers. The trial is also being conducted at Columbia, led by Magdalena Sobieszczyk, MD, chief of the infectious diseases division.

If all goes well in this and subsequent human trials, Dr. Ho foresees the antibody being delivered every few months by subcutaneous injection to protect against HIV infection, much like a long-acting contraceptive prevents pregnancy.

Dr. Ho's antibody research is one vital endeavor amid a broader and urgent effort to prevent new HIV infections worldwide, and ADARC is joining existing Columbia research programs with the same goal. The goal announced by the U.S. president in early 2019—to end AIDS including decreasing the number of new HIV infections by 90% by 2030 in the United States—is a bold one, notes University Professor and global director for ICAP at Columbia University Wafaa El-Sadr, MD. "While there has been a huge scale-up in terms of treatment domestically and globally, we are not on track to reach the goal of HIV prevention in terms of the number of new infections. More than a million are still reported globally every year."


JÖRG MEYER

In May, the New England Journal of Medicine published a perspective on the 2030 target by Dr. El-Sadr and coauthored by Miriam Rabkin, MD, associate professor of medicine and of epidemiology (in Columbia's ICAP) with colleagues at the Fenway Institute and the University of West Virginia. "HIV affects the most vulnerable among us," they noted, highlighting the disproportionate number of new cases among people of color, transgender people, people in rural areas who use injectable drugs such as opioids, and those most affected by poverty and unstable housing.

The medical community already has the tools to overcome these challenges, says Dr. El-Sadr, who is co-principal investigator of the NIH-funded HIV Prevention Trials Network, or HPTN. In 2016, an HPTN study confirmed that HIV treatment is, itself, a highly effective form of prevention. "When you treat people living with HIV," she says, "not only does the person being treated benefit, but you also decrease the risk of transmission of HIV to others." Thus, the scale-up of HIV treatment has been a fundamental global priority championed as well by ICAP in the countries where it works.

David Ho

For individuals who are HIV-negative, several preventive options are now available. An important one is pre-exposure prophylaxis, or PrEP, an approach where persons can protect themselves by taking a daily pill. Post-exposure prophylaxis, on the other hand, offers protection by taking medications after a suspected sexual or occupational exposure to prevent infection.

As co-PI of HPTN, Dr. El-Sadr designs and implements HIV prevention research across the United States and in Latin America, Africa, and Asia. "Our goal is to design the best possible research to identify new prevention tools and determine how to use them. Then, importantly, we need to get what we know works to the people who need it so we can demonstrate the benefits at a population level." The same values infuse ICAP, the Columbia-based global health center that Dr. El-Sadr founded in 2003 to develop and deliver comprehensive, family-focused HIV services and evidence-based initiatives to bolster national health systems.

Despite more positive attitudes toward people living with HIV, Dr. El-Sadr notes that stigma still impedes testing, status disclosures, and access to prevention and treatment among many people in high-risk populations. "Keep in mind that some of these same populations, even without HIV, are stigmatized," she says. "If you are a young man having sex with men in a Southern rural community in the United States, if you are a transgender woman, even in New York City, your whole outlook on life is shaped by prevailing stigma and discrimination. Adding HIV makes it doubly difficult in so many ways."

To fight back, Dr. El-Sadr marshals creativity and engagement. Many of the ICAP-led projects she has created train and empower peer educators to share their own experiences, talk about how they overcame similar challenges, and encourage others to participate in research studies as well as programs. That approach has been the backbone of her work since the late 1980s, when she established the first HIV research unit at Harlem Hospital. "Peer educators are from the same communities as those we seek to serve. They know what is going to resonate. They also know how to model behaviors. They have been a huge part of our work, whether it be in Tanzania, Swaziland, Kazakhstan, or right here in New York."

Outreach has been central to the peer educators' roles, says Dr. El Sadr. For example, in Tanzania, the ICAP-supported teams work to reach those most disenfranchised, going wherever they are needed and doing whatever is needed. They organize festive campaigns in village centers, visit artisanal miners, brothels, drug dens, fishing villages where the population is transient. Carrying backpacks loaded with supplies, peer educators talk to people, gain their trust, set up mobile units and tents, or do whatever is needed to get them the prevention and treatment they need. "If you get out of the comfort zone of health facilities, clinics, hospitals, or research labs, get creative and collaborative, and sit with

COLLABORATING TO HASTEN THE END OF AIDS

The move of the Aaron Diamond AIDS Research Center to Columbia and appointment of its leader, David Ho, MD, as the Clyde'56 and Helen Wu Professor of Medicine will amplify the ongoing basic and clinical research in HIV/AIDS at VP&S.

The Division of Infectious Diseases in the Department of Medicine sees the move of ADARC to Columbia as a transformative event for both ADARC and infectious diseases faculty who have been at the forefront of the response to the HIV/AIDS pandemic since its onset in the 1980s. Under the leadership of the former chief, Scott Hammer, MD, the division's clinicians delivered state-of-the-art care to patients and pursued cutting-edge research to improve patient care. "Numerous individuals and groups across CUIMC have contributed to the impressive progress seen in managing and preventing HIV disease both domestically and internationally," says Dr. Hammer. "There isn't sufficient space in this article to give credit to those who have given of themselves so mightily over the past 35 years."

"Faculty members in the infectious diseases division have matching and complementary interests to those of ADARC," says the division's current chief, Magdalena Sobieszczyk, MD. Faculty have helped set standards of care for the treating community, led major clinical trials of antiretroviral agents resulting in changes in approach to effective treatment, demonstrated that measurement of plasma HIV-1 RNA (viral load) can be a surrogate for clinical disease progression thus eliminating the need to do clinical endpoint (AIDS or death) trials for registrational studies of antiretroviral agents in the United States, elucidated approaches to treatment of HIV-1 drug resistance, and studied new classes of antiretroviral agents.

Magdalena Sobieszczyk and Scott Hammer

JÖRG MEYER

In the past decade, Drs. Sobieszczyk and Hammer have intensified their focus on HIV-1 prevention, leading HIV-1 preventive vaccine trials (early phase through efficacy studies), and studying the safety and efficacy of broadly neutralizing monoclonal antibodies in prevention of HIV-1 acquisition. Division members have also developed and implemented one of the largest programs in New York City to provide pre-exposure prophylaxis (PrEP) and access to HIV prevention and sexual health services to individuals of all ages, genders, and sexualities. Much of this work has focused on building collaborations with local community-based organizations and city, state, and federal public health programs to provide this care to communities at high risk of HIV acquisition, including the Washington Heights and northern Manhattan neighborhoods.

Among the VP&S faculty who will collaborate with or join ADARC:

STEPHEN P. GOFF, PHD

The Higgins Professor of Biochemistry in the Departments of Biochemistry & Molecular Biophysics and Microbiology & Immunology conducts detailed genetic analysis of the replication cycle of the human immunodeficiency virus type 1 (HIV-1). In hundreds of peer-reviewed studies, Dr. Goff has defined the functions of many viral gene products, characterized host proteins that are exploited by the viruses, and identified cellular proteins that interact with and sabotage retroviral replication, laying the groundwork for today's HIV combination therapies. His current work focuses on the chromatin and histone modifications involved in silencing HIV-1 in the latent reservoir of infected cells.

SCOTT HAMMER, MD

The Harold C. Neu Professor of Medicine and former chief of the Division of Infectious Diseases focuses on the treatment and prevention of HIV. He is a co-PI of the NIH-funded HIV Vaccine Trials Network and an investigator in the NIH-sponsored AIDS Clinical Trials Group. He has partnered with ADARC on clinical trials since 2000. He is the current protocol chair of HVTN 505, an advanced phase 2 study of the preventive HIV vaccine regimen developed by the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases.

PETER KWONG, PHD

The longtime adjunct professor in the Department of Biochemistry & Molecular Biophysics and a 1995 Columbia PhD graduate is chief of the structural biology section of the Vaccine Research Center at the NIH. Early in his career, Dr. Kwong solved the structures of the HIVgp120 envelope glycoprotein and of CD4 (the human receptor to which HIV binds) along with a set of broadly neutralizing antibodies isolated from people infected with HIV. For the past several years, his group at the Vaccine Research Center has focused on applying the atomic-level tools of structural biology to the development of antibody-guided vaccines against HIV-1 and other viral pathogens; promising candidate vaccines are currently being developed against respiratory syncytial virus, human parainfluenza viruses types 1-4, and HIV-1. At Columbia, Dr. Kwong is working to extend his structure-based antibody-to-vaccine paradigm through Antibodyomics, the informatics of antibody recognition, development, and improvement.

LAWRENCE SHAPIRO, PHD

The professor of biochemistry & molecular biophysics and ophthalmic science

(in ophthalmology and in the Naomi Berrie Diabetes Center) is a principal investigator at Columbia's Zuckerman Institute. His work relating development of effective antibodies to their structural biology has revealed molecular mechanisms by which antibodies can achieve broad neutralization of HIV. These studies have characterized sites of vulnerability on the virus, identifying promising targets ripe for exploitation in the search for a vaccine.

MAGDALENA SOBIESZCZYK, MD

The clinician and associate professor of medicine is PI of the NIH-funded Columbia HVTN and ACTG Clinical Research site and chief of Columbia's Division of Infectious Diseases. Her research focuses on developing, testing, and implementing biomedical strategies to prevent HIV infection, specifically preventive HIV vaccines and pre-exposure prophylaxis (PrEP). Her particular interests include assessing combination biomedical prevention strategies such as vaccines and PrEP. This work also includes testing novel technologies to improve uptake of and adherence to biomedical prevention modalities. She is co-chair of a phase 2b HIV vaccine protocol to determine the safety and efficacy of the DNA prime-Ad5 boost vaccine regimen in individuals at risk of HIV infection (HVTN 505) and site PI for several studies evaluating broadly neutralizing antibodies for the prevention and treatment of HIV infection.

MICHAEL YIN, MD

The associate professor of medicine and co-director of the Biobehavioral Core of the HIV Center for Clinical and Behavioral Studies at the New York State Psychiatric Institute focuses on optimization of HIV treatment and care. In particular, his research focuses on evaluating and preventing metabolic complications associated with chronic inflammation and antiretroviral therapy throughout the lifespan, from children with perinatal HIV acquisition to older adults living with HIV. He is an active investigator in Women's Interagency HIV Study, ACTG, and HVTN and a co-investigator on the Columbia Partnership for Prevention and Control of HIV/AIDS Clinical Trials Unit.

Wafaa El-Sadr

the people, listen to their concerns, speak in their language and offer them prevention, offer them treatment, right where they need it, guess what? They are quite willing to engage."

With nearly four decades of experience in the field, Dr. El-Sadr counsels diligence to achieve the ambitious U.S. HIV goals. First, she says, adequate funding is critically important. Second, the affected communities must be fully engaged. Third, resources and actions must be focused on the populations and locations where they are needed, informed by evidence and data. And finally, hard science must drive policy. "We need to do what is supported by evidence," she says. "There should be no room for political expediency."

"We need to do what is supported by evidence. There should be no room for political expediency."

Dr. Ho takes a cautiously optimistic stance on the 2030 target. "It is possible, but a daunting task," he says. "It requires political leadership, political will, and making sure that resources are properly given to the effort."

Over the past decade, ADARC has received nearly $50 million collectively from the Gates Foundation and the NIH to advance its research, with more to come. "I think we could move the work we are doing with antibodies into the clinic and into at-risk communities to block HIV transmission even more effectively," says Dr. Ho. "And I believe over the next five or 10 years, we are going to see tremendous progress in preventing HIV infection, not just with drugs like PrEP, but with antibodies and perhaps even with vaccines."

Decades of innovations, action, and partnerships have ushered in a new era in the global HIV response—one that could mean the end of AIDS. "We are at a moment in history where we know enough to stem this epidemic, and we need to take what we know into action," says Dr. El-Sadr. "At the same time, we must continue to seek new discoveries through research in the laboratory, in the clinic, and in the community. Both discovery and action are needed as we move forward." ❖

THE FUTURE OF GENE EDITING

COLUMBIA SCIENTISTS USE AND REFINE CRISPR TO PROVIDE INSIGHTS TO HEALTH

BY SHARON TREGASKIS

In the 19th century, the Swiss military contracted for a multifunctional pocket knife for officers to carry in the field. In addition to having a short blade, the compact gadget featured a fold-out can opener and two implements vital for maintaining the standard-issue Swiss rifle: a screwdriver, essential for disassembling and reassembling the firearm for cleaning, and a reamer, used to smooth burrs in the gun's metal barrel. Today, the Swiss Army knife comes in dozens of models, each featuring tools curated for a particular audience—gardeners, hunters, locksmiths, even oenophiles.

The iconic tool also is an analogy for CRISPR. For 3 billion years, unicellular bacteria have deployed CRISPR—Clustered Regularly Interspaced Short Palindromic Repeats—to defend themselves against viral attacks. In 2012, scientists demonstrated that CRISPR could be reprogrammed to modify the DNA of eukaryotes. Think precision scalpel, gene silencer, gene amplifier, and—like the modern-day Swiss Army knife—an expanding inventory of additional tools.

At VP&S, CRISPR has become a mainstay of discovery, with basic scientists developing new CRISPR-based tools while translational researchers put those tools to use, revealing new insights into human disease and its management.

"There are so many variations on the core theme," says Sam Sternberg, PhD, assistant professor of biochemistry & molecular biophysics, who—with his PhD adviser,

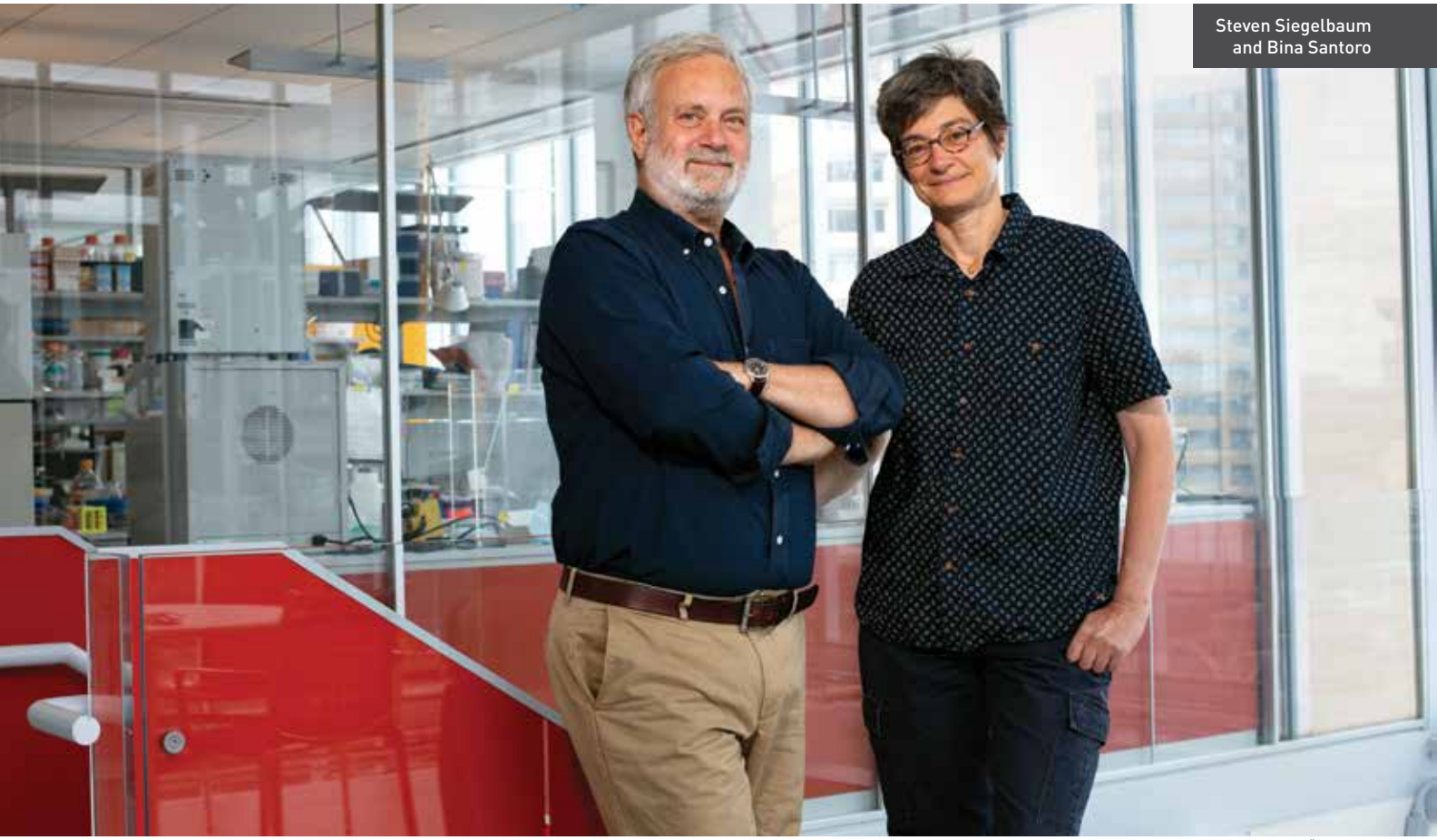
CRISPR pioneer Jennifer Doudna—advanced the Swiss Army knife analogy in "A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution," a 250-page book on the discovery of CRISPR and its implications for the life sciences.

As a graduate student, Dr. Sternberg worked with Dr. Doudna to develop one of the earliest CRISPR-based tools. Since joining Columbia in 2018, Dr. Sternberg has broadened his search, looking for additional gene-editing systems found in nature's earliest life forms and detailing how they can be deployed to advance genomic discovery in the lab. "Bacteria have been fighting off viruses for a long time and the diversification of their immune systems is a treasure trove for building new technologies," he says. "We're not done discovering new biology, and the more we find, the more we can leverage for tool development."

The work emerges from the predominantly unicellular life forms known as prokaryotes, the organisms that lack a nucleus or other dedicated organelles. With DNA floating freely throughout their cytoplasm, prokaryotes can't afford to get sloppy about detecting and neutralizing foreign genes that could prove their undoing. Enter the innate DNA surveillance tool that serves as a protean adaptive immune system. Each time a bacterium vanquishes pathogenic DNA, it captures a few characteristic snippets—those clustered regularly interspaced short palindromic repeats—and creates an RNA copy, the genetic equivalent of a wanted poster. As the bacterium's adaptive immune system continues surveilling the prokaryotic cytoplasm, it peruses those sheaves of wanted posters. In the event of a positive ID, it uses a CRISPR-associated protein (Cas, for short) like a precision scalpel to mount a brisk and robust defense, snipping the offending DNA to pieces and stopping the invader in its tracks.

Eukaryotes—from fungi to humans—boast a nucleus to contain and protect DNA, making targeted gene modification a time-consuming and technically challenging enterprise. Using a combination of chemicals, electrical current, viruses, and micropipettes, technicians break through the cellular membrane and into the cell nucleus to induce breaks in the DNA—all without killing the cell. Then they rely on homologous repair, an innate quality control system that cells use to fix broken strands of DNA. (It's a lot like patching a pair of jeans: If the patch and the hole correspond around the edges, the splice will hold.)

Technological innovations in recent decades—gene sequencing, cell cloning, RNA interference, zinc finger nuclease technology, and transcription activator-like effector nucleases, for example—have given scientists greater control of their tinkering, allowing them to turn on or off target genes to create "knock-in" or "knockout" animals. CRISPR, however, has been transformative,



Steven Siegelbaum and Bina Santoro

PHOTOS BY JÖRG MEYER

allowing scientists to cut and paste strands of DNA at specific locations, all within the nucleus of living cells. First, they create a CRISPR RNA seeded with snippets of a target genetic sequence. Then they inject it, along with a Cas enzyme, into the nucleus of a eukaryote. Cas zeroes in on the location specified by the RNA and induces double-strand breaks.

"CRISPR-Cas immune systems have completely transformed the ways biologists study biology," says Dr. Sternberg. "It has given basic scientists a new and more powerful way of asking questions like, 'What genes are involved in cancer becoming metastatic?' and opened new avenues for drug development. Across campus, people are using CRISPR as a better way to design their experiments."

Neuroscientist Steven Siegelbaum, PhD, has spent decades digging into the mechanisms of HCN1, a gene that serves as an electrical pacemaker within the human cortex, the part of the brain responsible for higher thought processes. In recent years, genomewide association studies have implicated HCN1 mutations in forms of infantile and pediatric epilepsy that cannot be explained by a head injury, infection, metabolic disorder, or other clinical evidence. In some cases, seizures are so severe they lead to progressive brain dysfunction and developmental delays.

To develop the mouse models that could reveal how those mutations wreak such havoc, Dr. Siegelbaum and associate research scientist Bina Santoro, PhD, a longtime lead investigator in the Siegelbaum lab's HCN1 research, turned to CRISPR. "It's very fast, it's comparatively cheaper than the traditional way of introducing point mutations, and there are a lot of these mutations in human patients that affect different parts of the HCN1 gene,"

Lorraine Clark

One of the tools we spend a lot of time on is improving how we can use CRISPR to turn genes on and off.

says Dr. Santoro. "We wanted to generate not just one mouse line, but a collection of mutations in the HCN1 gene, which are also present in human patients, to see the extent to which the mice reproduce the human condition."

Using support from a Columbia Precision Medicine Initiative program and expertise in the Columbia transgenic mouse shared resource, Dr. Siegelbaum and Dr. Santoro have already developed four lines of mice with HCN1 mutations and seizure disorders and begun analyzing the morphology of their brains for preliminary clues about how the mutations affects brain anatomy and biochemistry. "In the best case, you save a year with CRISPR, maybe 12 to 18 months, depending on how lucky you are with the technique," says Dr. Siegelbaum. "The general proof of principle, that these mutations are causing the seizures, will happen pretty soon."

Deeper understanding—about the mechanisms by which proteins altered by the mutation affect electrical activity in the brain—will take considerably longer. "By using CRISPR we know that this one mutation to HCN1 is the only one in our experimental mice," he explains. "And if they also develop seizures, that's strong evidence that the mutation is a cause of the disease, not just associated. That's our goal: We want to demonstrate that it's the HCN1 mutations in the patients that are causing the disease."

By simultaneously exploring multiple HCN1 variants and their role in seizures, Dr. Siegelbaum and Dr. Santoro also hope to gain insights into a basic conundrum about epilepsy, that seizure disorders take myriad forms and the drugs that can ameliorate symptoms in some patients aggravate the condition in others. "If in the mouse we can tie different mutations to different kinds of epilepsy," says Dr. Santoro, "then we can see which mutations respond better to which drugs, or which drugs exacerbate which forms of the disease."

Like Dr. Siegelbaum and Dr. Santoro, Lorraine Clark, PhD, assistant medical director of the Laboratory of Personalized Genomic Medicine, mixes genomewide association studies, basic biochemistry and functional studies, and mouse models to reveal how gene variants affect brain function. Her research focuses on such neurodegenerative diseases as Parkinson's and essential tremor.

Scientists already know that p.E326K, a specific variant of the glucocerebrosidase (GBA) gene, has been implicated in the severity of Gaucher disease and is one of the most common risk factors for Parkinson's disease and dementia with Lewy bodies. Research suggests that the problem common to all three conditions has to do with how GBA encodes for the enzymes vital to the function of lysosomes, the organelles responsible for cellular digestion and waste removal. But scientists do not understand the specific mech-

anisms by which p.E326K disrupts enzyme production. Without that crucial insight, targeted therapies to ameliorate symptoms remain out of reach.

To learn more about how p.E326K alters lysosomal function, Dr. Clark is combining an award from the Columbia Precision Medicine Initiative with an R03 award from the NIH to generate a mouse model that has the gene variant so she can characterize the resulting brain pathology. "CRISPR is cost-effective, convenient, and easy to use," says Dr. Clark. "Determining the disease mechanism associated with p.E326K may open up new therapeutic targets and could have a major impact on treatment of Parkinson's disease and dementia with Lewy bodies."

Alex Chavez, MD, PhD, assistant professor of pathology & cell biology, spends roughly half of his time digging into how CRISPR works, trying to make it more effective and more efficient. He has been awarded a dozen patents; 10 of those feature CRISPR technology. This spring, Columbia filed the first patent application for his work to rapidly generate hundreds of cell lines, each with targeted mutations. "One of the tools we spend a lot of time on," he says, "is improving how we can use CRISPR to turn genes on and off."

When not developing new CRISPR-based tools, Dr. Chavez uses the tools to investigate cancer and neuropathology. By activating and silencing genes implicated in such conditions as Alzheimer's, he hopes to reveal the role of each gene in the disease process. In particular, he has homed in on the genes that help a neuronal cell tolerate proteins perturbed in Alzheimer's and some other neurodegenerative afflictions. Healthy neuronal cells have myriad ways to protect themselves against bad proteins, including apoptosis, or programmed cell death. Dr. Chavez wants to find both the genes that buffer the effect of misfolded proteins and those that amplify their effect. "We're looking for which levers to pull," he says. "Nothing works in isolation. You need to know the connections to pick apart the system."

The same holds true of the basic biology from which CRISPR derives. To boost the understanding of how best to leverage that biology to refine existing tools and build better ones, a cadre of junior faculty convenes regularly to review the projects underway in their laboratories and troubleshoot technical challenges. They call themselves SLCC (pronounced slick) for Sternberg, Lu, Chavez, and Ciccia. "Everyone comes from different angles," says Dr. Sternberg. Chao Lu, assistant professor of genetics & development, focuses on the epigenome—proteins that turn genes on and off. Alberto Ciccia, also assistant professor of genetics & development, investigates the mechanisms that repair DNA lesions and maintain genome integrity. Says Dr. Sternberg: "We're each thinking about the science from a unique angle—that's when you achieve intellectual synergy."

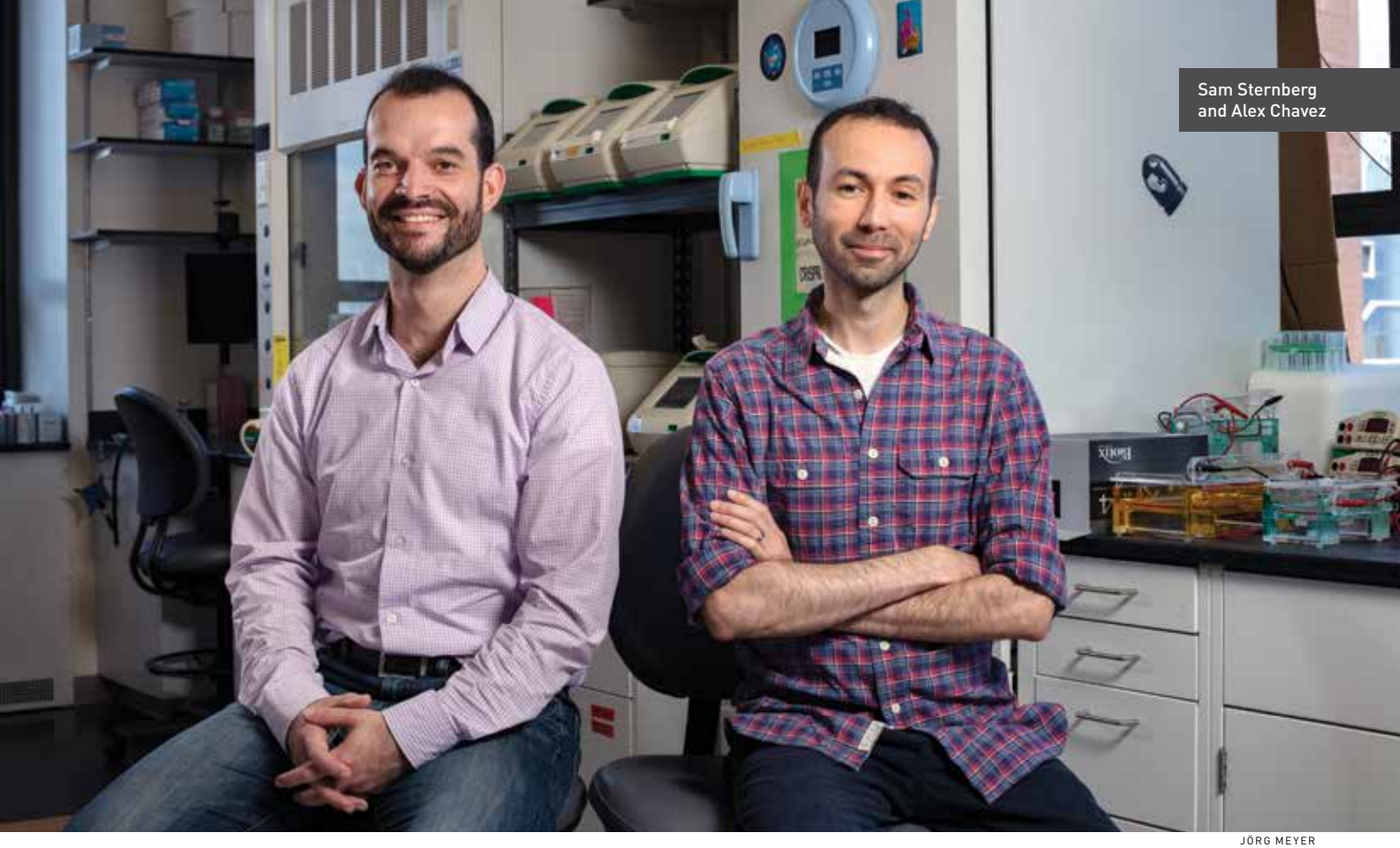
In June, Nature published the first paper from Dr. Sternberg's lab at Columbia—a report on how a CRISPR-like system found in the bacterium *Vibrio cholera* can be modified to insert genetic material at a precise location, without first blasting a hole in the target DNA. Dubbed "INTEGRATE," the new system relies on parasitic "jumping genes" known as transposons that can insert themselves into a strand of DNA, using an enzyme that works like molecular glue. "Rather than introduce DNA breaks and rely on the cell to repair the break," says Dr. Sternberg, "INTEGRATE directly inserts a user-defined DNA sequence at a precise location in the genome, a capability that molecular biologists have sought for decades."

Even as scientists develop more technically advanced CRISPR-based tools and use them to increase understanding of human disease and how to treat it, questions mount. "Scientists have been actively discussing the more technical issues," says Dr. Sternberg, "but on the societal and ethical side, we need a lot more people present, including members of the public who will be affected—disability rights activists, disease advocacy groups, people of all stripes who just want to understand this better."

To promote such conversations, Dr. Sternberg has made outreach to off-campus audiences a high priority. "Part of my role here is not just to train postdocs, grad students, and undergraduates in the laboratory," he says, "but to be involved in educating others too." To that end, he hosts visiting high school students from the metro New York area in his laboratory and participates in a program that uses web conferencing to connect scientists with classrooms across the country. This spring, he also participated in Taste of Science, a program that invites scientists to talk about their research in local watering holes. Together with a scientist from the New York Genome Center, Dr. Sternberg discussed CRISPR at a bar in the East Village. "There were people there who have definitely never set foot in a research lab, but they're curious," says Dr. Sternberg. "They want to know how CRISPR

Who's Who

- **Paul S. Appelbaum, MD,** the Dollard Professor of Psychiatry, Medicine, & Law and director of the Division of Law, Ethics, and Psychiatry
- **Alex Chavez, MD, PhD,** assistant professor of pathology & cell biology
- **Alberto Ciccia, PhD,** assistant professor of genetics & development and member of the Herbert Irving Comprehensive Cancer Center
- **Lorraine N. Clark, PhD,** associate professor of pathology & cell biology (in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain) at CUMC and assistant medical director of the Laboratory of Personalized Genomic Medicine
- **Chao Lu, PhD,** assistant professor of genetics & development
- **Bina Santoro, PhD,** associate research scientist in Steven Siegelbaum's lab
- **Steven Siegelbaum, PhD,** the Gerald D. Fischbach, MD, Professor of Neuroscience, professor of pharmacology, and chair of the Department of Neuroscience
- **Sam Sternberg, PhD,** assistant professor of biochemistry & molecular biophysics



Sam Sternberg and Alex Chavez

JÖRG MEYER

can be used and want to think about how companies are going to apply this technology, what's ethical, what's safe, and so on."

Ethicist Paul S. Appelbaum, MD, was exploring the ethics of gene modification long before CRISPR came on the scene. When he launched Columbia's Center for Research on Ethical, Legal & Social Implications of Psychiatric, Neurologic & Behavioral Genetics, CRISPR was still an obscure phenomenon observed among unicellular organisms. But in November 2018—just six years after the first paper detailing how CRISPR could be used to modify a eukaryotic cell—a Chinese scientist announced that the genomes of twin girls born earlier that month had been modified using the technology.

Are we treating individual patients or are we seeking interventions that will affect the next generation and future generations?

While the Chinese case brought to the fore myriad technical and ethical questions about human gene editing, Dr. Appelbaum sees the central issue raised by CRISPR as this: whether particular modifications die with the individual or can be passed to the next generation. "Are we treating individual patients on one hand," he asks, "or are we seeking interventions that will affect the next generation and subsequently future generations after that? They have very different ethical implications."

The current regulatory environment varies among nations, with the legality of human gene modification depending heavily on a clinician's geography, raising the possibility that scientists with ambitions curtailed in their home countries might move to more favorably regulated environs. And, no consensus has emerged on the mechanisms that might be used to impose international standards for how CRISPR is used. "There are a variety of possibilities," says Dr. Appelbaum. "You could have legislation that controls or proscribes use of CRISPR or other gene-editing technologies, you could have voluntary self-regulation by the research community, or rules imposed by funders, or a completely unregulated environment, in which researchers and clinicians are free to do what they want with technology that's available to them."

As the technology advances, Dr. Appelbaum anticipates that society will be forced to confront profound questions about what it means to be human. "The assumption that we can identify conditions that should be extirpated from the human gene pool—assuming that were possible, which given the heterogeneous bases for many conditions is extremely unlikely—makes the question of whether it would be desirable a real one." Consider, he suggests, the enormous creativity in mathematics demonstrated by some individuals on the autism spectrum or the cultural contributions of artists afflicted by mood disorders. "There are questions of neurodiversity," he says, "but also the reality that the same gene, the same variant may have multiple consequences, particularly when we're talking about complex traits." And, he notes, it may be impossible to fully comprehend the choices we confront. "As we begin to be able to edit the gene pool it may be the case that we can't anticipate some of the consequences of the changes we're making." ❖

HELP FROM OUR FRIENDS

THIS REPORT gives us an opportunity to recognize the many friends and partners who have helped us continue our extraordinary progress as a leader in medicine. Through this support, we continue to make tremendous advances in research, education, clinical care, and community service.

As part of this effort, we not only are recruiting and training the brightest young minds in medicine, we also are providing them with opportunities to make the greatest possible difference over the course of their careers and in the lives of patients. These opportunities begin from the very start of medical school. Contributions from Roy and Diana Vagelos and many other alumni, faculty, friends, and supporters have helped to eliminate loans for all VP&S students who have financial need and replace them entirely with scholarships. This new scholarship program, launched in Fall 2018, allows our graduates the opportunity to pursue careers they are passionate about without letting a burden of medical student debt impact their choices.

Roy and Diana Vagelos

These efforts have been recognized well beyond the borders of our campus: We have seen an increase in applicants, allowing us to bring in the most talented students and nurture them early in their careers, regardless of their current financial capacity.

Roy and Diana Vagelos also have been a driving force in another of our top priorities: precision medicine. Their commitment to Columbia's Precision Medicine Initiative and related programs at the medical school has made us a magnet for talent and the destination of choice for faculty recruits in this area. These experts are helping us to build on the accomplishments of leading faculty members, including our newest Nobel laureate, Joachim Frank.

Nowhere is the promise of precision medicine more evident than in our work in the field of cancer. We are expanding and advancing our cancer research and treatment programs thanks to the generosity of the late Herbert and Florence Irving. Their transformative estate gift allowed us to recruit Anil Rustgi, MD, the outstanding new director of the Herbert Irving Comprehensive Cancer Center, and will help to build upon the center's programs in immunotherapy, neuro-oncology, and genomics and expand our clinical trials, which translate the discoveries from our laboratories directly into improving the lives of patients.

At VP&S and across the medical center, our philanthropic partners have been vital to the success of our programs, which have one shared goal: to improve the lives of our patients, communities, and populations. We are grateful for this tremendous support and commitment, which have made us a leader in health care over the past 250 years, this past year, and into the next generation of teachers, scientists, and healers.

Cardiology Division Renamed in Recognition of Flanzer Philanthropic Trust Gift

The Louis and Gloria Flanzer Philanthropic Trust of Sarasota, Florida, made a gift of $32.5 million this year to benefit the Division of Cardiology in the Department of Medicine. The gift is in honor of Allan Schwartz, MD, chief of the division.

In recognition of the gift, the Columbia University Trustees renamed the division the Seymour, Paul and Gloria Milstein Division of Cardiology. This is the first named division in the history of VP&S. The naming reflects Gloria Flanzer's wish to recognize the contributions that her brothers, Seymour and Paul, and the entire Milstein family have made to Columbia University Irving Medical Center and NewYork-Presbyterian. The Milstein family's support has been integral to the success of both institutions and the medical center as a whole, says Lee Goldman, MD. With this portion of her legacy, Mrs. Flanzer honors her family and her association with Dr. Schwartz.

In addition to naming the division, the gift establishes the Seymour, Paul and Gloria Milstein Professorship of Cardiology. Upon Dr. Schwartz's retirement from the faculty of VP&S, the professorship will be renamed the Allan Schwartz, MD Professorship of Cardiology.

The gift creates an endowed fund of $30 million to support clinical, research, and educational activities in the Division of Cardiology. The remaining $2.5 million of the gift establishes an endowment to pay the salary and expenses related to the teaching and research of the faculty member occupying the Milstein Professorship of Cardiology.

Louis and Gloria Flanzer

Kenneth A. Forde'59 Teaching Scholar Fund

Before the recent death of Kenneth A. Forde'59, the Kenneth A. & Kareitha O. Forde Private Family Foundation committed $1 million to establish the Kenneth A. Forde, MD Teaching Scholar Fund in the Division of Cardiology in the Department of Medicine. This gift honors David I. Sahar, MD, professor of medicine at CUMC. The endowment payout from the fund will be used to support an annual award to clinical educators in the Division of Cardiology at the discretion of the chief of the division. Upon Dr. Sahar's retirement from the faculty of VP&S, the fund shall be renamed the David I. Sahar, MD VP&S'80 Teaching Scholar Fund, and award recipients will be known as David I. Sahar, MD VP&S'80 Clinical Educators.

Ken and Kareitha Forde

Berrie Foundation Gift Launches Diabetes Simulation Program

The Russell Berrie Foundation has pledged $1.1 million to support a new medical education initiative that will use simulation training to prepare physicians to improve clinical care for patients with diabetes. The program is a collaboration between Columbia's Michael and Mary Jaharis Simulation Center and the Naomi Berrie Diabetes Center and will be led by the Simulation Center's medical director, Arnold Advincula, MD, and the Berrie Center co-director, Robin Goland, MD. Currently, most simulation training focuses on fundamental, mandated skills rather than specialized care. This pilot program is a unique opportunity to develop simulation curricula tailored to a specific disease area. In the long term, Drs. Advincula and Goland believe the program could help develop a new paradigm for training medical professionals who treat patients with diabetes, both primary care providers and specialists.

Thompson Family Foundation Honored at Crown Awards

VP&S at its annual Crown Awards Gala honored the Thompson Family Foundation for its most recent gift of $12 million to support research at Columbia on neurodegenerative disorders, such as Alzheimer's disease, multiple sclerosis, and Parkinson's. Historically, these diseases have had a devastating impact, and progress in treating them has been modest.

With a universitywide commitment, the recruitment and retention of the brightest and most promising scientists and clinicians, and the support of the Thompson Family Foundation, all of that is changing. Meaningful improvements in the diagnosis and treatment of these diseases is already happening with the prospect of even more significant breakthroughs in sight.

The Thompson Family Foundation's first gift to Columbia was to support research into painful neuropathies, a frequently debilitating side effect of chemotherapy that can make cancer treatment not just difficult but intolerable, a tradeoff no patient should have to make. This support has brought together faculty from across departments, disciplines, and campuses to foster the collaboration that is necessary for change and better treatments for patients.

Since its inception in 1986, the Thompson Family Foundation has donated millions to medical, scientific, educational, and cultural organizations in the New York metropolitan area. The Thompson Family Foundation was established by Wade F.B. Thompson, co-founder of Thor Industries, the world's largest manufacturer of recreational vehicles. The president of the Thompson Family Foundation is Amanda J.T. Riegel, the late Mr. Thompson's daughter, who stewards her father's legacy and ensures the Thompson Family Foundation's continued leadership with wide-ranging philanthropy that impacts New York City and the entire nation.

Alan Siegel, Amanda J.T. Riegel, Richard Mayeux, and Lee Goldman at the December 2018 Crown Awards

Alan Siegel, Mr. Thompson's longtime friend and attorney and a visionary and dedicated director of the Thompson Family Foundation, died in March 2019. Columbia remains dedicated to collaborating with the Thompson Family Foundation to carry out the important projects Mr. Siegel helped establish, including the development of effective and much-needed new treatments for neurodegenerative diseases.

Stewart J. Rahr Foundation Supports Eating Disorders Research

Felicia Bersh, center, accepts the Gray Matters at Columbia Award on behalf of the Stewart J. Rahr Foundation. She is photographed with Jeffrey Lieberman, chair of psychiatry, and Evelyn Attia.

The Stewart J. Rahr Foundation, a longtime supporter of the Columbia Center for Eating Disorders in the Department of Psychiatry, amplified its generosity this year with a $2 million gift to enhance the work supported by the Rahr Eating Disorders Research Project Fund, which the foundation established in 2007. The newest gift brings the foundation's support of the center to over $7 million and will advance important research on eating disorders. "The Stewart J. Rahr Foundation has been transformational for the Eating Disorders Program at Columbia," said Evelyn Attia, MD, director of the center, at this year's Gray Matters at Columbia benefit luncheon, which honored the Rahr Foundation. "The foundation's generosity for more than 10 years, as well as its commitment to continued support over the next five years, is driving progress in the diagnosis, treatment, and prevention of eating disorders."

Walentas Gift Will Advance Glaucoma Genetics

David Walentas has donated $1 million to the Department of Ophthalmology's glaucoma division to help prevent unnecessary blindness from glaucoma. The division, under the direction of Jeffrey Liebmann, MD, will use the gift to lead new research emphasizing gene discovery and the development of new glaucoma treatments. Points of emphasis include the genetic causes of pigmentary glaucoma, a subtype of glaucoma affecting patients in their 20s and 30s, and the pursuit of a new treatment to reverse exfoliative glaucoma, a common form of glaucoma affecting older patients. Both conditions are causes of glaucoma-related blindness. Mr. Walentas is a New York City real estate developer.

Nearness of You

Volunteer leader Susan Brecker again helped to lead the biennial Nearness of You concert at Lincoln Center in January 2019 to support cancer research at Columbia University Irving Medical Center and specifically the work of Azra Raza, MD, and Siddhartha Mukherjee, MD, DPhil. The event, which is held in memory of Ms. Brecker's husband, 15-time Grammy Award-winning saxophonist Michael Brecker, featured performances by Patti Austin, Hugh Jackman, James Taylor, Harolyn Blackwell, and Bernie Williams among others and raised more than $1.3 million.

Azra Raza and Siddhartha Mukherjee

Faith Tenenbaum, Janet Carrus, Joseph Tenenbaum, and Cathey Romano.

Gerald and Janet Carrus Foundation Endows House Staff Fund

The Gerald and Janet Carrus Foundation has committed $1,250,000 to establish an endowed fund for medical house staff training in the Department of Medicine. The endowment payout from the fund will be used to support the educational and training activities of the training program at the discretion of the program's director. The gift honors Joseph Tenenbaum, MD, the Edgar M. Leifer Professor of Medicine at CUMC, for his many years of dedication and commitment to educating residents and physicians in humanistic patient care.

Marsal Family Fund to Support Junior Faculty's Cardiology Programs

The Marsal Family Foundation has committed $1 million to establish the Marsal Family Fund in the Division of Cardiology in the Department of Medicine. This current-use fund will provide support for junior faculty in research and activities related to heart disease, particularly focused on cardiac precision medicine. Awards from the fund will be determined by the chief of the Division of Cardiology, Allan Schwartz, MD.

Bryan and Kathleen Marsal with Dorette and Peter Sacripanti

Project ALS

Project ALS has made a gift of $1.5 million to the Project ALS Therapeutics Core in the Motor Neuron Center at Columbia University as part of a larger multiyear pledge of $6.3 million. An effort unlike any other, this core program takes a rational, evidence-based approach to the development of new therapies for ALS by utilizing the most predictive laboratory models of the disease and rapidly and thoroughly testing the most promising drug candidates for safety and potential efficacy before they reach clinical trials.

BRIGITTE LACOMBE

Jenifer Estess

Directed by Serge Przedborski, MD, PhD, Hynek Wichterle, PhD, and Neil Shneider, MD, PhD, the Project ALS Therapeutics Core leverages Columbia's many institutional resources and works with academic and industry partners to fast-track the best drug candidates to clinical trials in patients. Advancing the mission of Project ALS, this open and collaborative effort is a major resource for the ALS research community, filling a previously unmet need to evaluate new drugs and biological therapies for their potential to stop, slow, or prevent the onset and progression of ALS.

Project ALS, which recently marked its 20th anniversary, has a long history of visionary philanthropy at Columbia University, giving nearly $20 million for programs such as the Jenifer Estess Laboratory for Stem Cell Research and the ongoing ALS Families Project. "Columbia is proud to partner with Project ALS, which has advanced the field through its unique and trailblazing support of open, collaborative research and team-based science, as we continue to search together for effective treatments for this devastating disease," says Dr. Przedborski.

Lisa Baker's Rheumatology Pledge Will Advance Autoimmune Studies

A $1 million gift from Lisa Baker will advance autoimmune research led by the Division of Rheumatology. The gift established the Lisa Baker Autoimmunity Innovation Fund to be led by Joan Bathon, MD, chief of rheumatology. The fund will provide start-up support for new and innovative research. The fund has already contributed to Dr. Bathon's recruitment of Adam Mor, MD, PhD, a rheumatology investigator whose research focuses on T lymphocytes adhesion, a key cause of autoimmune inflammation. Ms. Baker is director and chief curator of the HBC Global Art Collection and a member of the medical center's Board of Advisors. She is a member of the New York State Council on the Arts, appointed by Gov. Andrew Cuomo, and serves on the boards of numerous art institutions, including the Herbert F. Johnson Museum of Art at Cornell University, the Solomon R. Guggenheim Photography Committee, and the Solomon R. Guggenheim International Director's Council Committee. Her philanthropic partnership with Columbia is inspired by a desire to expand the potential of science to improve human health. Autoimmunity is poorly understood and not well funded by the National Institutes of Health, yet it is the driving force behind diseases ranging from rheumatoid arthritis to lupus to type 1 diabetes that are a leading cause of death among young and middle-age U.S. women. The Lisa Baker Autoimmunity Innovation Fund will launch new studies to advance understanding of these and other disease areas.

Velocity Ride

More than 800 participants came out in 2018 for Velocity, Columbia's Ride to End Cancer, which raised more than $1.2 million. The goal of the ride is to raise money to support cancer research and care at Columbia's Herbert Irving Comprehensive Cancer Center. All funds raised support cancer research, patient services, and essential infrastructure to improve treatment outcomes for cancer patients. The ride each year begins in Pomona, New York, and continues south through the scenic Hudson Valley before all riders cross the George Washington Bridge and arrive at Columbia University Irving Medical Center for a Finish Line Festival.

Second Annual Joint Symposium of the Wu Family China Center for Health Initiatives

The legacy of the late Helen and Clyde'56 Wu is growing at Columbia. The Wu Family China Center for Health Initiatives held its second annual joint symposium in October 2018 to support collaboration in medical research and education between Columbia and Zhejiang University School of Medicine in China. The event featured 24 speakers, including 10 from Zhejiang University. The 2018 Dr. Clyde Y.C. Wu and Mrs. Helen Wu Award in International Understanding was presented to Stanley Chang, MD, the K.K. Tse and K.T. Ying Professor of Ophthalmology at Columbia, and Yi Sun, MD, PhD, dean of the Institute of Translational Medicine and vice dean of the School of Medicine at Zhejiang University.

In the front row at the 2018 joint symposium of the Wu Family China Center for Health Initiatives at Columbia VP&S are, from left, David Wu, MD; Yi Sun, MD, PhD; David Ho, MD; Roy Vagelos, MD; Anke Nolting, PhD; Roger Wu, MD; and Nancy Wexler, PhD.

Roger Wu, MD, and David Wu, MD, have continued to underline their parents' commitment to medicine, VP&S, and Columbia's historic ties with China with ongoing support of the Wu Family China Center, which is welcoming David Ho, MD, onto its faculty committee. A pilot visiting-scholar program was inaugurated with the visit of Junwei Su, MD, a physician from the Department of Infectious Diseases of the First Affiliated Hospital of Zhejiang University. He spent 2017-18 working with Columbia researchers Michael Yin, MD, and Utpal Pajvani, MD, PhD. Future exchanges are being planned.

The third annual Wu Family China Center joint symposium is scheduled for October 2019 in Zhejiang, Hangzhou, China.

Foley Commits $2.25 Million to Eye Research, Fellowship Training

David Foley

David Foley has pledged $2.25 million to the Department of Ophthalmology to support eye research and medical training for ophthalmologists. The gift will advance stem cell studies led by Tongalp Tezel, MD, director of the department's vitreoretinal division. This research seeks to restore sight to patients with macular degeneration, a retinal disease that is a leading cause of vision loss in older patients. The gift also includes an endowment to establish the Foley Clinical Retina Fellowship, which will provide training to young ophthalmologists specializing in retinal care and clinical research. Mr. Foley is a senior managing director of the Blackstone Group, a private equity firm, and CEO of Blackstone Energy Partners.

Moynihan Clinical Research Fellowship Program Established by the Leon Levy Foundation

The Leon Levy Fellowship Program in the Department of Psychiatry continues to recruit, nurture, and train the most promising young physician-scientists, providing them with the resources and mentorship to expand understanding of the workings of the brain and how they go awry in psychiatric illness. This year, the Leon Levy Foundation created an ambitious new program to focus on translational clinical research: Moynihan Clinical Research Fellowships. Named by the Leon Levy Foundation for U.S. Sen. Daniel Patrick Moynihan, Moynihan Fellows are MDs or MD-PhDs continuing their training with a particular interest in patient-oriented research who will work under the mentorship of leading investigators at Columbia. Their work will focus on translating pioneering science into clinical applications for patients, building bridges between laboratories and patient care.

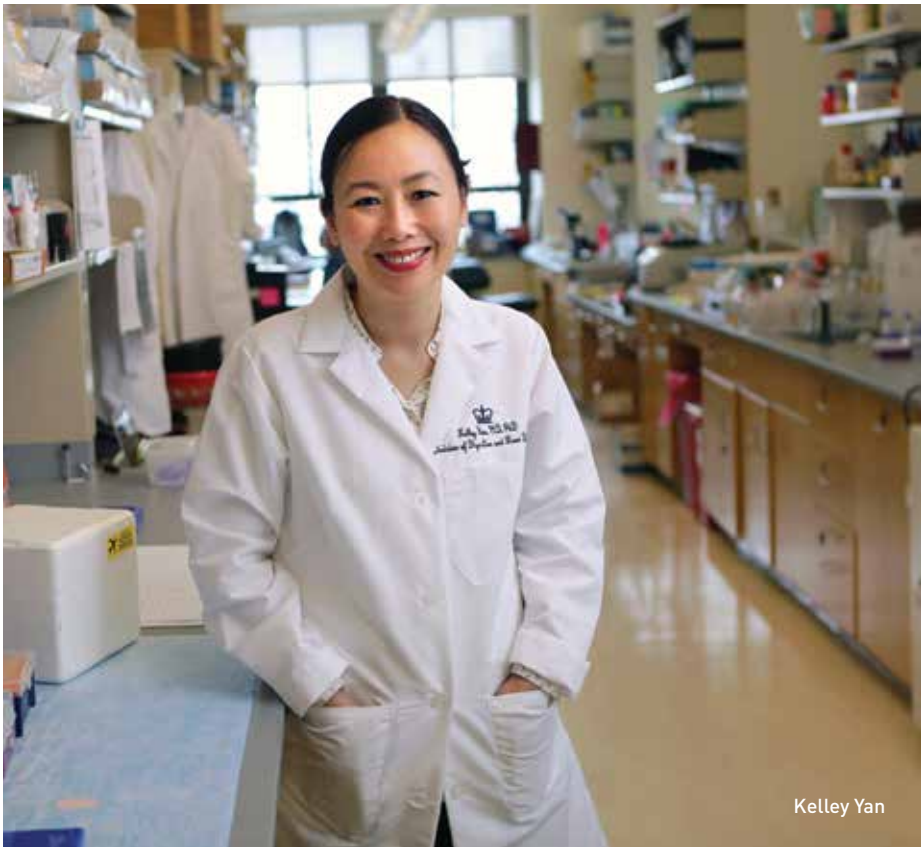
2019 **Research** Highlights

Revealing the Role of Stem Cells in Gut Regeneration

In the laboratory of Kelley Yan, MD, PhD, the Dorothy L. and Daniel H. Silberberg Assistant Professor of Medicine in the Division of Digestive and Liver Diseases, studies of intestinal stem cells are shedding light on the mechanisms of gut regeneration in normal circumstances and under conditions of injury. As a physician-scientist, Dr. Yan has set her sights on applying the discoveries made in her lab to improve tissue healing and treatment for the many diseases that can affect the gut.

"The intestinal epithelium is the most rapidly self-renewing tissue in the body and its vigorous regeneration is enabled by highly active intestinal stem cells," says Dr. Yan, whose interest in gastroenterology and training in basic science research began as a medical student in the MD-PhD program at the Icahn School of Medicine at Mount Sinai.

It was only a short time before Dr. Yan began her GI fellowship and a postdoctoral research fellowship conducting studies in intestinal stem cell biology at Stanford University that scientists, for the first time, had identified and isolated a stem cell in the gut. The timing was fortuitous, helping to solidify Dr. Yan's own scientific direction.



JOHN ABBOTT

Kelley Yan

Today, the Yan Laboratory at Columbia focuses on understanding tissue renewal in health and disease using the intestine as a model system to study adult stem cell biology.

To better understand the behavior of stem cells, Dr. Yan and her team use mouse models and human organoids derived from patient tissues that are grown as "mini-guts" in dishes to study intestinal stem cells as they divide to produce more cells to endlessly replenish or repair the intestinal epithelium.

"The intestine is remarkably dynamic," says Dr. Yan. "Cells that line the intestine get replaced every few days throughout life by new cells generated by intestinal stem cells. These stem cells are the mother of all other cells. They face the most decisions. Stem cells generate more stem cells but they also generate all the mature cell types that work in nutrient absorption, hormone secretion, and interfacing with the external world. So the main question that we had was, Given all its choices, how does a stem cell actually decide what it wants to do? Is a stem cell hardwired to act in a predictable fashion or can we alter its behavior?"

For Dr. Yan this is the most fundamental question in stem cell biology, with an answer that she and her team deciphered in the intestine itself. "It turns out that the intestinal stem cell takes instructional cues from its environment. In fact, it requires multiple types of signals from its surroundings," explains Dr. Yan. "It requires Wnts and R-spondins, which are signals released by other cells in the vicinity. Wnts convey a signal to the stem cells that they are in

the right location and prepares them to act. R-spondins then instruct them to divide and to generate more stem cells. Stem cells are so powerful that two separate signals are needed to activate their power. If either signal is lost, then 'stemness' is lost and a stem cell becomes just another typical cell destined to die after a few days.

"These signals not only control tissue regeneration, but they also are involved in the development of cancer," says Dr. Yan. "Colorectal cancer, for example, starts from mutations within the Wnt pathway, which is activated by the Wnts and R-spondins that control stem cell behavior. There is growing evidence that cancer originates from a runaway stem cell that no longer is reliant on environmental signals for its activity."

The results Dr. Yan and her colleagues published in Nature provided a major advance in identifying discrete and separate functions of the Wnt and R-spondin proteins. "We developed tools for manipulating levels of Wnts and R-spondins that enabled us to identify their function within an animal," says Dr. Yan. "Essentially, we revealed the external cues that a stem cell receives from its environment to enable it to act as a stem cell. We were very excited to discover that stem cell behavior is malleable. We were able to easily manipulate stem cells to make the choices we desired once we decoded and understood their signals. This has broad implications for precision control of tissue regeneration and for treatment of cancer."

The Yan Lab at Columbia is focused on bringing these findings into clinical practice. "My love for clinical gastroenterology drew me to the science, and my goal is to help patients through our discoveries," says Dr. Yan. "If we can understand the mechanisms for how the gut normally regenerates and how it regenerates under conditions of injury, then we will actually be able to promote and enhance the process of healing after injury.

"The gut is really interesting because it has so many different functions," says Dr. Yan. "It absorbs nutrients and it is our major interface with the outside world and with the immune system. The gut is also a powerful endocrine organ that regulates appetite and metabolism. I want to use stem cell biology to enhance all those functions."

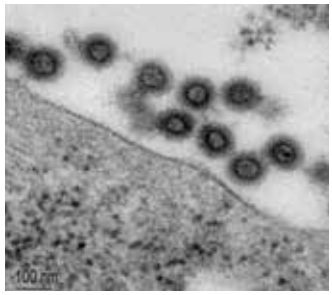
One of her long-term goals is to use stem cell biology to enhance the gut's endocrine function. "We have shown that we can manipulate stem cell behavior to influence the types of cells produced in the gut. I want to figure out how to make more of the types of cells that would optimize our metabolism to treat diseases like obesity and diabetes, which we normally think of as endocrine rather than GI diseases. My vision is to ultimately tailor your gut cells to your individual needs. A designer gut, if you will."

New Markers Could Improve Chemotherapy for Breast Cancer

In mouse models of breast cancer, tumor-associated macrophages (TAMs) promote the growth and spread of the tumor and suppress the immune system's attempts to fight back. A new study of human breast cancer shows that TAMs also promote human malignancy and has identified uniquely expressed genes in human TAMs that may provide new therapeutic targets and diagnostic/prognostic markers. The study was published in Cancer Cell. "Cancer is not just a group of cells, it is an evolving and ever changing landscape where many actors take the stage and play an important part," says co-author Lisa S. Wiechmann, MD. "The lead, of course, is the cancer cell, but the supporting actors can make or break the performance. By bolstering the players that interfere with cancer's success, and suppressing those who help, we may be able to create improved therapies."

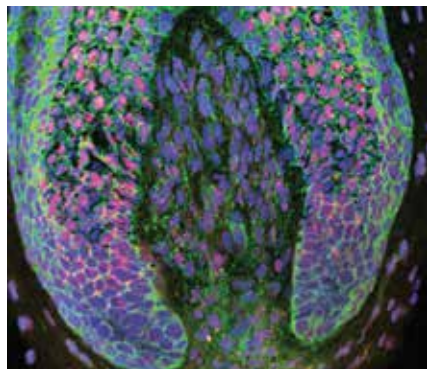
Possible Way to Improve Gene Therapy

An antivirus system that evolved eons ago in vertebrate cells helps to defend us against viruses. But it also vexes scientists. Whenever researchers try to insert foreign DNA into a cell's nucleus—to study the function of a gene or try to develop a gene therapy—the antivirus system silences the DNA. Now, scientists may be able to disable the antivirus system, based on new findings from research led by Stephen P. Goff, PhD. The researchers identified a molecule that inactivates the antiviral system in the cell nucleus, a finding that could have widespread impact, from more effective gene therapies to simpler laboratory techniques for scientists. The study was published in Nature.



Growing Hair

Two recent studies led by Angela Christiano, PhD, describe novel ways to combat pattern hair loss in men and women. In the first study, researchers discovered previously unknown cells that keep mouse hair follicles in a resting state and show that inhibiting the activity of these cells can reawaken dormant follicles. In another study, the team created a way to grow human hair in a dish, which could open up hair restoration surgery to more people, including women, and improve the way pharmaceutical companies search for new hair-growth drugs. The papers were published in Cell Stem Cell and Nature Communications.

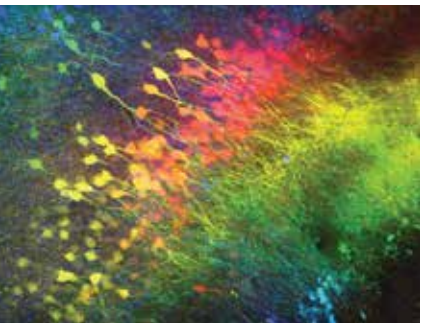


Open Hysterectomy for Early Cervical Cancer

A new study shows that women with early-stage cervical cancer who underwent minimally invasive hysterectomy had a 65% higher risk of death compared with those who had open surgery. The study, which contradicts the general assumption that minimally invasive surgery is safer than conventional open surgery, was published in the New England Journal of Medicine. "We suspected that there might be a difference in survival between the two approaches, but the extent of the difference was surprising," says co-principal investigator Jason D. Wright, MD.

The Brain and Social Aggression

Columbia scientists have identified a brain region that regulates social aggression. This brain area, called CA2, is part of the hippocampus, the brain structure known to be critical for our memory of people, places, things, and events. CA2 was already known to specialize in social memory, the ability to remember encounters with others. These new findings reveal that a single brain region can control both higher order cognition, such as social memory, and innate, instinctual behavior, such as social aggression. And because CA2 dysfunction has been implicated in psychiatric diseases, such as schizophrenia and bipolar disorder, these results provide further support that altered CA2 function may contribute to abnormal social behaviors associated with such illnesses. The research, published in Nature, was led by Steven Siegelbaum, PhD, and Eric Kandel, MD.



More Bad News for Couch Potatoes

Sitting for long periods of time has been linked to increased risk of cardiovascular disease and early death, but not all types of sitting are equally unhealthy. A study led by Keith Diaz, PhD, shows that leisure-time sitting—while watching TV—was associated with a greater risk of heart disease and death among the study's more than 3,500 participants. The good news: Moderate-to-vigorous exercise may reduce or eliminate the harmful effects of sedentary television watching. The study published in the Journal of the American Heart Association did not show the same danger for people who sit for long periods of time at work.

Hair Loss Gene and Cancer Immunotherapy

A gene associated with an autoimmune form of hair loss could be exploited to improve cancer immunotherapy, suggests a Columbia mouse study published in Cell Systems. "Most cancer patients do not benefit from immunotherapies because their tumors are able to evade the immune system," says study leader Angela M. Christiano, PhD. People with autoimmune diseases have the opposite problem—the affected tissues attract the immune system—suggesting that cancer immunotherapies could be improved by taking a page from the autoimmune playbook. The new study showed that a gene that recruits T cells to hair follicles in autoimmune hair loss is turned off in various types of cancer, protecting them from the immune system. If the gene could be turned back on, it could make those cancers vulnerable to the immune response.

New Home for Stem Cell Research

Scientists in the Columbia Stem Cell Initiative moved into new and enhanced facilities this year. The initiative provides support and expertise to more than 50 laboratories across the university that are engaged in stem cell research. The goal is to promote the use of stem cells to model human diseases, develop new diagnostics and therapies, and create new cells and tissues to replace damaged, aged, or diseased body parts. Says initiative director Emmanuelle Passegué, PhD: "Stem cells are everywhere and they are certainly at the heart of modern medicine. Incredible progress has already been made. We can take bone marrow stem cells and treat many hematological and other disorders with transplantation. We can harness the regenerative potential of skin's stem cells to replace the entire skin of children suffering from a genetic skin disorder, allowing them to live. We can also use the power of embryonic stem cells to regrow the retina and restore some level of vision in blind patients. All of these achievements have grown from excellent and rigorous scientific research like we are doing here at Columbia, but there are still many things to be done, and we need more basic, translational, and clinical research to develop more of these therapies of tomorrow."

Emmanuelle Passegué

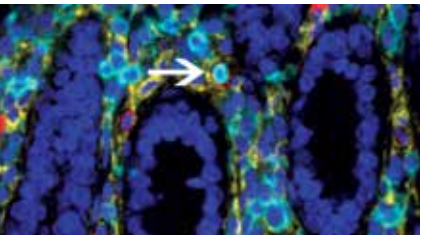
Autism Linked to Shape of Cerebellum

Structural differences in the cerebellum may be linked to some aspects of autism spectrum disorder, according to a Columbia neuroimaging study published in PLOS ONE. The researchers found that the boys with autism had significantly lower fractal dimension—indicating a flatter surface structure—in the right cerebellar cortex compared with the controls. Because the right side of the cerebellum supports language processing in typically developing individuals, this finding suggests that having a flatter cerebellar surface may be related to communication difficulties in those with autism. "Our findings suggest we may need to rethink the role of cerebellar function and structure in young individuals at risk for atypical brain development," says senior author Kristina Denisova, PhD. "Early life differences in perception, including timing, e.g., atypical

detection of pauses in conversation, could shape cerebellar development and account for the current structural findings in boys with autism."

Intestine's Role in Organ Transplantation

The human intestine may provide up to 10% of blood cells in circulation from its own reservoir of blood-forming stem cells, a Columbia study found. Scientists previously thought that blood cells are created exclusively in the bone marrow from a special population of hematopoietic stem cells, but the intestine's reservoir of blood-forming stem cells was discovered when researchers led by Megan Sykes, MD, noticed that patients who had received intestinal transplants also had the donor's blood cells. The researchers tracked the donor's



blood cells back to their source: hematopoietic stem cells in the donated intestine. The blood cells created from cells in the donor's intestine also may be beneficial to the transplant recipient. The more donor blood cells a patient had in circulation, the less likely that person was to reject the transplant. The research was published in Cell Stem Cell.

Genetic Mutations and Disease

Researchers at Columbia and the New York Genome Center have uncovered a molecular mechanism behind one of biology's long-standing mysteries: why individuals carrying identical gene mutations for a disease have varying severity or symptoms of the disease, a phenomenon called variable penetrance. Reporting in Nature Genetics, the researchers provide evidence for modified penetrance, in which genetic variants that regulate gene activity modify the disease risk caused by protein-coding gene variants. The study links modified penetrance to specific diseases at the genomewide level, which has implications for future prediction of the severity of serious diseases such as cancer and autism spectrum disorder. Tuuli Lappalainen, PhD, led the study.

Microglia and Alzheimer's in Elderly Brains

Microglia, the resident immune cells of the brain, have important roles in brain health, but little is known about the regulation and consequences of microglial activation in the aging human brain. Researchers, including Philip De Jager, MD, PhD, and other Columbia investigators, reported in Nature Communications that the proportion of morphologically activated microglia (PAM) in postmortem cortical tissue is strongly associated with β-amyloid, tau-related neuropathology, and the rate of cognitive decline. Effect sizes for PAM measures are substantial, comparable to that of APOE ε4, the strongest genetic risk factor for Alzheimer's disease, and mediation models support an upstream role for microglial activation in Alzheimer's disease via accumulation of tau.

Humanized Mice for Diabetes

Mice with human immune systems—dubbed personalized immune (PI) mice—are important tools in the study of type 1 diabetes. At Columbia, most of the bone marrow donors for PI mice are type 1 diabetes patients at the Naomi Berrie Diabetes Center. Each bone marrow aspiration creates up to 30 PI mice, giving researchers an opportunity to study everything from the genesis to the genetics of human type 1 diabetes and other autoimmune diseases, says Megan Sykes, MD. Her team, which described the PI mice in Science Translational Medicine, is working with the Berrie Center to recruit bone marrow donors both with and without type 1 diabetes to study the causes of autoimmunity using PI mice.

Alzheimer's Drug Not Effective in Depressed

Results from a clinical trial conducted at Columbia and Duke suggest that the Alzheimer's drug donepezil does not improve cognitive performance in people at risk for Alzheimer's disease who also have depression. The study's findings, published in the American Journal of Geriatric Psychiatry, run counter to the common practice of treating people who have both depression and cognitive impairment with cholinesterase inhibitors like donepezil. "It is critical to find effective therapies for this population," says study author D.P. Devanand, MD. "Both late-life depression and mild memory loss are established risk factors for dementia, and when they co-occur, the risk for future dementia is even higher."

Precision Medicine Pilot Awards

Three proposals were chosen from among 34 applications to receive awards during the second year of the Roy and Diana Vagelos Precision Medicine Pilot Awards. The awards provide seed money for research into new ideas in precision medicine. The three proposals cover epilepsy, neurooncology, and tissue engineering.

- "Development of novel therapies for STXBP1 encephalopathy," Michael Boland, PhD, Neurology and Institute for Genomic Medicine; Wayne Frankel, PhD, Genetics & Development; Sophie Colombo, PhD, associate research scientist in the Institute for Genomic Medicine; and Sabrina Petri, staff associate in the Institute for Genomic Medicine

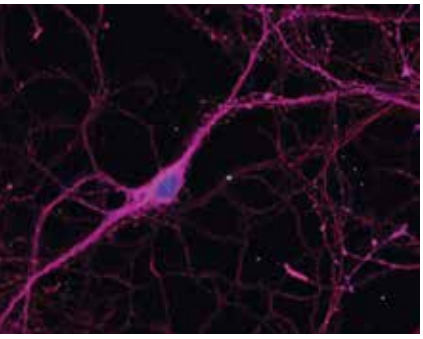
- "Molecular characterization of gliomas under immunotherapy," Raul Rabadan PhD, Biomedical Informatics and Systems Biology; Fabio Iwamoto, MD, Neurology; and Junfei Zhao, PhD, associate research scientist in Systems Biology

- "Exploiting the basic mechanism of Notch activation to develop new diagnostic, therapeutic, and tissue engineering tools for precision medicine," Gary Struhl, PhD, and Paul Langridge, PhD, Genetics & Development (in Neuroscience) and Zuckerman Mind Brain Behavior Institute

Neurons with Clean Habits Resist Alzheimer's

Some neurons in the brain protect themselves from Alzheim-

er's with a cellular cleaning system that sweeps away toxic tau proteins associated with the disease, according to a study published in Nature Neuroscience. The study was led by Columbia's Karen Duff, PhD, and coauthors from Ohio State University and the University of Cambridge. Dr. Duff and her colleagues also identified a protein, called BAG3, that



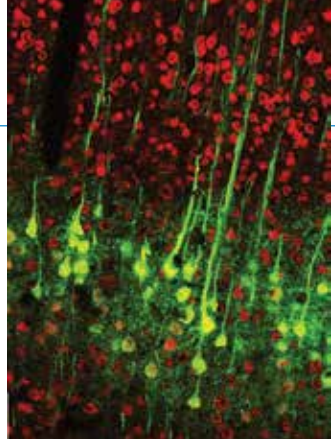
controls the cleaning system: "If we can develop therapies to support these natural defense mechanisms and stop tau from accumulating, we might be able to prevent, or at least slow, the development of Alzheimer's and other tau-related neurodegenerative diseases."

Fruit Fly Nerve Cells: Live!

Columbia neuroscientists and engineers have created 3D videos of individual nerve cells moving, stretching, and switching on inside fruit fly larvae. Data gleaned from the videos reveal how nerve cells called proprioceptive neurons work together to help the body sense where it is in space. The researchers harnessed SCAPE, a cutting-edge microscope developed at Columbia that images neurons at lightning fast speeds. Findings published in Current Biology from the labs of Elizabeth Hillman, PhD, and Wesley Grueber, PhD, illustrate SCAPE's ability to reveal the inner workings of the nervous system in unprecedented detail. By creating 3D, live-action images of nerve cells in larvae as the animals crawled, SCAPE allowed the researchers to see how those cells along the body wall reported movements back to the brain. "We know that the brain receives sensory signals though electrical pulses passed along neurons, but we didn't understand why some kinds of neurons are located in specific positions or how particular signaling patterns represented different movements," says Dr. Grueber, the paper's co-senior author. "To understand this process, we needed to know what signals the neurons are sending while the larva crawled around unconstrained."

Colliding Genomes Cause Transplant Failure

A genomic collision could explain why many kidney transplants fail, even when donors and recipients are thought to be well matched, according to a Columbia study published in the New England Journal of Medicine. The genomic collision is a genetic incompatibility between kidney donor and recipient, causing the recipient to mount an immune attack against a protein on the donated kidney. The findings could lead to more precise matching between donors and patients. The same genomic collision may potentially occur in heart, liver, and lung transplants. "This project illustrates how genetic analysis is empowering clinical care by enabling better matching," say senior authors Ali G. Gharavi, MD, and Krzysztof Kiryluk, MD.



Memory Storage

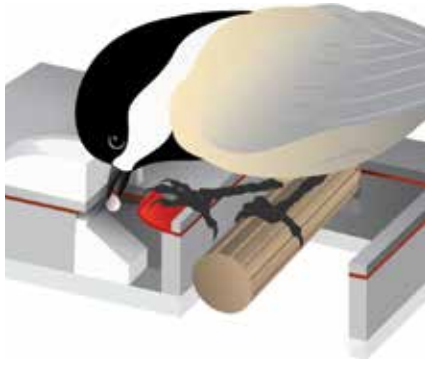
A new study by Columbia neuroscientists provides evidence that learning and memory are not relegated to a few select regions but instead may permeate the brain. The research, published in Cell Reports, reported that a primitive brain region known for processing basic sensory information also can guide complex feats of mental activity. In mice, the researchers found, the somatosensory cortex plays a key role in reward learning, a sophisticated type of learning that allows the brain to associate an action with a pleasurable outcome, such as connecting our work to a paycheck or an A+ to studying for a test. "Our brains are masterful at making connections, or associations, between seemingly disparate pieces of information, but where those associations are stored has remained an unresolved question," says Randy Bruno, PhD, the paper's senior author. The new research shows that these associations can be made in the primary sensory cortex, which has not previously been believed to have that capacity.

Diverse Motives for Human Curiosity

Neuroscientist Jacqueline Gottlieb, PhD, and a Columbia economics professor are working together to understand what motivates us to pay attention to certain pieces of information and invest in acquiring them. Neuroscience tells us that there are limits to our attention, says Dr. Gottlieb. Our brains bias us toward certain sources of information by releasing chemicals that reward us for focusing on certain things. By combining the mathematical models of economics and the brain-monitoring techniques of neuroscience, the professors hope to gain greater insights into both of their fields. They published the initial results of this work—revealing the diversity of motives that guide human curiosity—in Nature Human Behavior.

Studying Memory with the Help of Chickadees

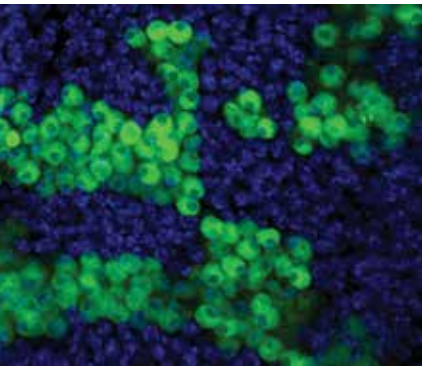
Chickadees have phenomenal memories: A single bird can, in one day, store as many as 7,000 bits of food—each in a different spot—and remember many of those locations for weeks. That natural ability caught the attention of Dmitriy Aronov, PhD, who thinks the birds will bring a fresh approach to studying how brains create memories. In many laboratory studies of memory, rats or mice are trained to perform certain tasks. "The kind of memory involved in learning these tasks is different from the kind of memories we form about our daily experiences, like remembering a time you



saw a shooting star or where you put your keys," says Dr. Aronov. As a result, in rodent models it is difficult to link the process of storing and recalling memories to specific, neural activity within the hippocampus itself. "By caching and then retrieving food items, the birds are effectively telling the observer what they remember and when," which may allow researchers to better understand how the hippocampus creates spontaneous memories.

Those Cheatin' Cells

During development, cells compete with each other for high stakes. Within a growing tissue, the stronger "winner" cells expand to take up



more space in the tissue and the weaker "loser" cells are eliminated. These interactions, known as cell competition, are thought to rid tissues of cells that are potentially dangerous to the tissue. Cells have to recognize differences among each other for competitive interactions to work. A study led by Laura Johnston, PhD, and published in Developmental Cell found that cells produce and emit "death signals" relative to their own ability to tolerate the signal. In a group of cells, some cells "win" because they release—and can tolerate—higher levels of the signal. Relatively weaker "loser" neighbors cannot tolerate the levels released by healthier cells and die. If a cell plays fair, it will produce only an amount of killing signal that it can tolerate. But some cells can cheat the system, the study found, by producing high levels of the death signal, while simultaneously shutting down its ability to respond to the death signal. These same mechanisms may help explain why emergent cancer cells get a foothold to establish territory within healthy tissues.

Gene Identification and Disease Discovery

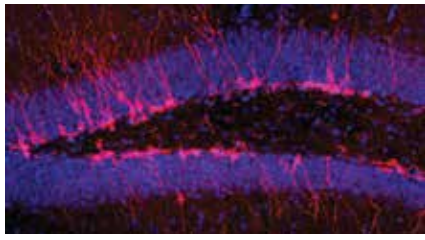
Wendy Chung, MD, PhD, and a team in Indiana published a landmark study identifying the first human mutations in the deoxyhypusine synthase (DHPS) gene. The study identified five children from four unrelated families who all developed similar if not identical symptoms of unknown cause, until the identification of common DHPS mutations. The research was published in the American Journal of Human Genetics. "The families affected by this disease have been so supportive of our work, which was essential to the success of the study," says Dr. Chung. "In the short time we've been working together, the DHPS Foundation has also been formed, which continues to help get the word out and support other families living with this disease."

ALS Drug Study

A phase 3 study led by Jinsy Andrews, MD, studied the efficacy of tirasemtiv, a new class of drug tested in ALS patients, on respiratory function. Results of the study of 744 ALS patients internationally were published in the journal Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. Although the study did not show a meaningful effect of tirasemtiv on slow vital capacity, subanalyses suggest that tirasemtiv had a biological effect and the drug class remains worthy of further study. Dr. Andrews led early phase studies that previously found that a similar-acting drug, reldesemtiv, has the potential to produce a larger pharmacodynamic effect than tirasemtiv. Results from a recent trial of reldesemtiv suggest that patients who received the drug declined less on all outcomes measured than patients receiving placebo with improved tolerability.

Young Neurons: Few but Mighty

Though few in number, neurons that are created in the brain during adulthood during neurogenesis have an outsized impact on mood and memory because of their unparalleled networking and communication abilities, according to a study by scientists at Columbia, Hunter College, and NYU. The study, conducted in adult mice, showed that unlike other neurons in the brain, young neurons can directly connect with their mature counterparts and send out tailored messages depending on the source of incoming information. "Without these cells, we would be incapable of distinguishing similar situations from each other, a process sometimes termed pattern separation, which is critical not only for forming novel memories but also for discriminating between safe and dangerous contexts," says study senior leader Rene Hen, PhD. The findings, published in Science, may help researchers develop new treatments for memory loss



and mood disorders and may explain why electroconvulsive therapy works for many patients with severe depression.

Dynamic Spatial Structure of Human Seizures

The increasing use of microelectrodes in epilepsy surgery has made it possible to apply principles derived from decades of laboratory research to the problem of mapping the spatiotemporal structure of human focal seizures and characterizing the corresponding EEG signatures. Catherine Schevon, MD, PhD, and colleagues have provided a comprehensive review of the key spatial and temporal properties of seizure activity in humans, at both the microscale and macroscale. The new framework, published in Neurobiology of Disease, is important for investigating open questions in ictogenesis and how this model can inform targeted epilepsy therapies.

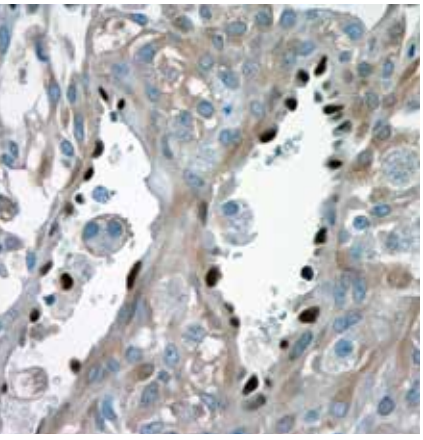
Sensing Brain Signals

Jennifer Gelinas, MD, PhD, and a Columbia engineering faculty member, Dion Khodagholy, PhD, developed the first biocompatible ion driven

transistor that is fast enough to enable real-time signal sensing and stimulation of brain signals. The internal-ion-gated organic electrochemical transistor—IGT—provides a miniaturized, soft, conformable interface with human skin, using local amplification to record high quality neural signals suitable for advanced data processing. This could lead to safer, smaller, and smarter bioelectronic devices that could be implanted in humans over long periods of time, the researchers reported in Science Advances.

Mice, Omega-3 Fatty Acids, and Miscarriages

A new study in mice reveals that omega-3s, a type of fat found in fish oil, reduce fetal and neonatal deaths. Accord-



ing to research led by Yiping Han, PhD, and published in JCI Insight, compounds found in fish oil prevent pregnancy complications, including preterm birth, neonatal death, and stillbirth, in mice when the complications are caused by a common oral bacteria, *F. nucleatum*. The experiments showed that supplements containing omega-3 fatty acids also inhibited inflammation and bacterial growth in pregnant mice. In another study published in EMBO Reports, Dr. Han found that the same bacterium can accelerate the growth of colon cancer and exacerbate cancer progression.

Statistics and What Your Brain Knows

Brains have a remarkable ability to spot new objects and figure out how to manipulate them. Scientists have long believed that the brain accomplishes this by methodically interpreting visual and textural cues, such as an object's edges or boundaries. But a Columbia study suggests that the human brain requires only a tiny bit of information, as well as previous experience, to calculate a complete mental representation of a new object. These results help to explain the mental mathematics that enable us to easily know what a novel object looks like simply by touching it or imagine the way an object feels from sight alone. The study, led by researchers at Columbia, the University of Cambridge, and Central European University and reported in the journal eLife, illustrates the brain's natural power to learn quickly and generalize. "Our brains' ability to single out one object from many by touch is a broadly used skill and key to our ability to interact with the world," says neuroscientist Daniel Wolpert, PhD, the study's co-senior author.

Moody Gut and Depression

For people with depression, gastrointestinal distress is common, and a Columbia study suggests that for some, the two conditions arise from the same glitch in neuron chemistry: low serotonin. The study, conducted in mice and published in Gastroenterology, shows that a shortage of serotonin in the neurons of the gut can cause constipation, just as a serotonin shortage in the brain can lead to depression. Led by Kara Gross Margolis, MD, at Columbia with researchers at Duke, the researchers also found an experimental drug treatment developed by two of the study's co-authors raised serotonin levels in the gut's neurons and alleviated constipation in the mice. The slow-release drug delivery of 5-HTP, a precursor of serotonin, works in part by increasing the number of GI neurons in adult mice. The study is one of the first to show that neurogenesis in the gut is possible.

Maternal Mortality Assessment

Maternal mortality has more than doubled in the United States since 1990, and the United States has the highest rate among wealthier nations. But the rate may be even higher if deaths from suicide and accidental overdoses are counted, according to a new report from Columbia researchers who say that rising rates of opioid use, depression, and maternal mortality are closely connected. "Most estimates of maternal mortality only report deaths caused by complications of childbirth, such as stroke, preeclampsia, or hemorrhage," says Kimberly Mangla, MD, who with Catherine Monk, PhD, coauthored the review published in the American Journal of Obstetrics and Gynecology. "Yet pregnancy does not protect against depression and substance abuse, and the postpartum period has been identified as a particularly vulnerable time. Some studies in other countries suggest maternal suicide is much more common than previously thought and even a leading cause of death."

Ciliates Help Us Understand Our Genome

A new study of a single-celled eukaryote with 16,000 tiny chromosomes may shed light on a recently discovered feature of the human genome. Methyladenine, or 6mA—a modification of DNA common in Oxytricha trifallax—has only recently been found in multicellular organisms, with some studies suggesting a role in human disease and development. Finding the enzymes that lay down the methyl marks will be critical to understanding what 6mA is doing in Oxytricha and other organisms, but the enzymes have been difficult to identify. The research published in Cell reveals how 6mA marks are made to the Oxytricha genome and suggests why the enzymes have been hard to find: Evolution recruited

two DNA-binding proteins to transform an enzyme that normally methylates RNA into a complex that methylates DNA. Except for the lack of centromeres, Oxytricha's chro-

mosomes have everything we have—including telomeres, histones, and base modifications—so they provide elegant models for the study of chromatin biology and how DNA is packaged," says the study's senior author Laura Landweber, PhD, who has been studying Oxytricha for two decades and previously uncovered Oxytricha's 16,000 chromosomes.

Clinical Trial for Progressive MS

Columbia is a clinical site for NeuroNEXT, the Network for Excellence in Neuroscience Clinical Trials, which was created to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations, and industry. Columbia's Claire S. Riley, MD, was coauthor of a New England Journal of Medicine paper about a phase 2 trial of ibudilast for progressive MS, which has limited treatment options. Ibudilast was associated with slower progression of brain atrophy than placebo, though with higher rates of gastrointestinal side effects, headache, and depression. About a dozen drugs have been approved for the treatment of relapsing-remitting MS, but few therapies are available for the progressive stage of the disease.

Late-Onset Alzheimer's and Ethnicity

Alzheimer's researchers at Columbia are using next-generation sequencing methods to uncover rare genetic variants that are hard to find but have a big impact on disease risk. Rare variants tend to be ethnicity specific, so lack of diversity in genetic studies can cause some genes to be overlooked. In their latest study, the researchers analyzed data from 15,030 people, including many Caribbean Hispanic participants in the Washington Heights, Hamilton Heights, Inwood Community Aging Project. Their work, published in JAMA Neurology, identified PINX1, a gene involved in telomere integrity, and TREM2, a gene that codes for an immune receptor found in microglia, associated with the late-onset form of the disease in both Caribbean Hispanics and non-Hispanic whites. The finding could help researchers develop genetic tests that better predict Alzheimer's risk and identify potential new treatments. The research team was led by Richard Mayeux, MD.

Milestones in Children with MS

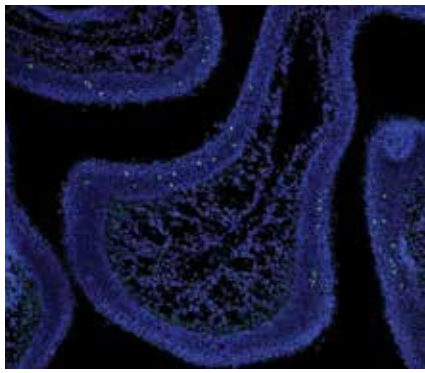
Research published in the Journal of Child Neurology has shown that children who develop pediatric multiple sclerosis are not delayed, relative to healthy controls, in acquisition of the early motor and verbal developmental milestones of walking independently and using two-word phrases, and children with MS were less likely to be delayed in walking independently. Results suggest that in patients with multiple sclerosis diagnosed in childhood, the disease might not have extended into the infancy and toddler period. It is possible, say the researchers, including Wendy Vargas, MD, that time to walking independently and using two-word phrases are not sensitive enough measures to detect subtle changes in toddlers. These data are in contrast with reports that some patients who go on to develop multiple sclerosis-like demyelination have genetic predispositions to abnormal white matter development.

Albuminuria and Respiratory Diseases

A large-scale, prospective study led by Elizabeth Oelsner, MD, provides strong support for the endothelial hypothesis of chronic obstructive pulmonary disease (COPD). Preliminary studies suggested that albuminuria, an indicator of endothelial damage, is associated with COPD development, but the studies were small and inconclusive. The new study followed 14,213 people over time and found that greater albuminuria was associated with accelerated decline in lung function and increased rates of respiratory disease events. Current medical therapies for COPD and other chronic lower respiratory disease target the airways. The new study suggests that endothelial and microvascular mechanisms may be promising targets for COPD prevention and treatment. The study was published in the American Journal of Respiratory and Critical Care Medicine.

How the Nose Knows

The human olfactory system can distinguish 1 trillion different scents, a feat it accomplishes with just several hundred different odor receptors. To make such fine distinctions with so few receptors, each of the 10 million olfactory neurons in the nose chooses—at random—just one receptor to express. How each neuron makes the choice has perplexed scientists, because the receptor genes are spread throughout the genome on different chromosomes: It seemed impossible that genes separated by great distances could be regulated in coordination. A study led by Stavros Lomvardas, PhD, found the answer. When a neuron makes the receptor choice, its genome rearranges itself into a multichromosomal hub that brings the receptor genes



together. The findings were published in Nature, and in a commentary that accompanied the article, an expert said, "These exciting findings show that interchromosomal interactions can have a determinant role in regulating gene expression." Dr. Lomvardas speculates that such interactions may cause the genomic translocations that are known to cause cancer.

Southern Diet Helps Fuel Hypertension Disparity

The high prevalence of hypertension among African American adults is a major contributor to disparities in life expectancy, but the causes for higher incidence of hypertension are unknown. A new analysis, published in JAMA, found that adherence to a Southern diet was the biggest factor in explaining the difference in hypertension between black and white participants for both men and women, accounting for 52% of the excess risk among black men and 29% of the excess risk among black

women. Other factors included the dietary ratio of sodium to potassium and education level and, among women, waist circumference and BMI. Understanding the reasons behind the disparity could guide efforts to prevent hypertension and reduce the difference in mortality between black and white populations. The research team included Columbia's Jennifer J. Manly, PhD.

Beyond the Science of Genetics

Medical anthropologist Sandra Soo-Jin Lee, PhD, is co-PI on a $7.1 million grant from the National Human Genome Research Institute to develop a national center on ethical, legal, and social implications (ELSI) of genetics. Dr. Lee will co-lead the center with a colleague at Stanford University, where Dr. Lee spent nearly two decades before being recruited to VP&S this year to lead the Division of Ethics in the new Department of Medical Humanities & Ethics. The new Center for ELSI Resources and Analysis will be the first of its kind and build on Columbia's foundation of ELSI research, including work by Paul Appelbaum, MD, Wendy Chung, MD, PhD, and George Hripcsak, MD. Dr. Lee's work focuses on the sociocultural and ethical dimensions of emerging genomic technologies, and she has published widely in genomics, medical, bioethics, and social science literature on patient consent, governance of data and biological samples, and commercialization of biotechnology and academic entrepreneurship. Recent publications have focused on ethics in precision medicine research and the importance of increasing diversity in research.

2019 **Education** Highlights

Community Service Formalized with New Office

A VP&S Office of Community Service Programs has been created to expand the commitment of VP&S to community service, with a focus on the Washington Heights/Inwood community, Upper Manhattan, and parts of the Bronx.

The new office will build upon the school's many ongoing efforts to improve the health and education of adults and children through a range of community engagement and health promotion activities, in part by developing new opportunities made possible by the creation of Haven Plaza, which opened during the summer of 2019.

The founding director of the Office of Community Service Programs is Rafael Lantigua, MD, professor of medicine at CUMC, who will have the additional title of associate dean for community service in VP&S. A native of the Dominican Republic and faculty member at Columbia since 1980, Dr. Lantigua has been a dean's special adviser for community health affairs since 2011. His clinical and research interest has focused on promoting the health of the diverse community in upper Manhattan and improving access to care for the community's growing aging population.

The recently established Service-Learning Program, which was created as part of the VP&S strategic plan, will function within the Office of Community Service Programs to develop and coordinate community service-learning opportunities for faculty, students, and staff.

Dr. Lantigua also will facilitate the creation of a new VP&S Academy of Community and Public Service to recognize medical school faculty who make substantial contributions to community and public health. The academy will be modeled after two other VP&S academies, the Virginia Apgar Academy of Medical Educators and the Academy of Clinical Excellence.

Rafael Lantigua

The new VP&S Office of Community Service Programs will be housed in the medical school within the Office of Government and Community Affairs, but it will be closely aligned with community programs at the Mailman School of Public Health, School of Nursing, College of Dental Medicine, and the New York State Psychiatric Institute. Programming for the office will include health fairs and student learning opportunities.

Mentoring Pregnant Teens

In a cozy space near 174th Street, a small group of female medical students and teenage mothers-to-be gather to share information, hopes and dreams, and looming fears regarding a soon to be life-changing event.

The gathering is part of APOYO, an adolescent pregnancy program in Washington Heights run by VP&S medical students. The program began in 2012 as a project by a VP&S student in the Daniel Noyes Brown Primary Care Scholars Program and became a student-run outreach program within the P&S Club in 2015. APOYO, a Spanish word for "support," is exactly its mission: to empower, educate, and offer emotional support specifically tailored to teenage motherhood.

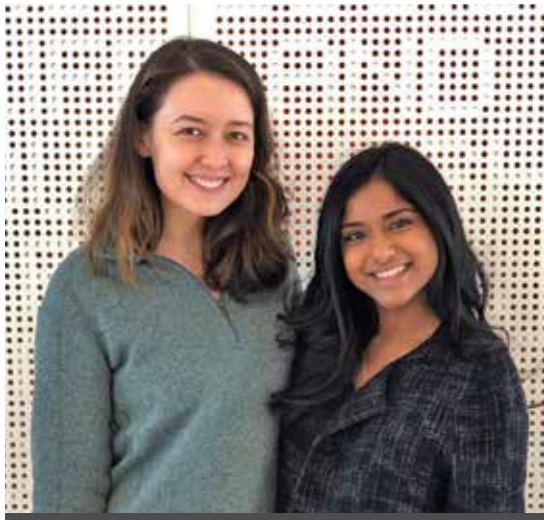
Natasha Natarajan'22 and Elena Wadden'22 co-chair the organization. "We pair each teenager with a student mentor to keep it intimate," says Ms. Wadden. The number of mentors accepted each year depends on how many adolescents are interested. Last year the organization mentored six pregnant adolescents. Language barriers are taken into consideration; a mentee is always paired with a mentor who speaks her language.

"Mentor" may be a misnomer, says Ms. Wadden. "We have never been in their situation. One of the first questions the girls ask us is if we have ever been pregnant."

On Wednesday evenings in the fall, the group gathers to discuss specific topics with an expert. The discussion is informal and gives the adolescents space to ask questions and voice concerns. Topics include everything from what bodily changes one can expect during pregnancy, nutritional advice, and delivery options to inter-relationship and/or domestic violence, birth control choices, breastfeeding, and baby care. "We even have a psychiatrist who comes in to discuss postpartum depression," says Ms. Wadden.

Many of the teenagers face a lack of financial resources, and APOYO connects the mothers-to-be with programs available to them. For instance, the girls qualify for a doula companion after delivery, and another organization provides free cribs.

"Participating in APOYO has changed the way I look at patient care," says Ms. Natarajan. "In medical school, patient contact is very brief. You'll see the patient maybe once. Through this program, I am able to witness a young woman go through many transitions: pregnancy, delivery, and followup after delivery. It makes me aware that she has a home life separate from when we see her—I see her more holistically."



Elena Wadden'22 and Natasha Natarajan'22

STAR-U

The Summer of Translational Aging Research for Undergraduates—STAR U—welcomed its first students during the summer of 2019. The program is funded by an R25 grant from the National Institute on Aging and housed within the Taub Institute for Research on Alzheimer's Disease and the Aging Brain. The program strives to increase diversity in the field of neuroscience and aging by providing mentorship and training for young scientists who have unique experiences and perspectives.

Alumni Auditorium Renovation

An Alumni Auditorium renovation has reimagined the shared learning and assembly space. The first phase of the renovation updated the 6,464-square-foot auditorium with 648 new seats that feature table arms, charging stations, and USB ports. The second phase enhanced the auditorium with a soaring ceiling, LED lights, high-end acoustic integrated walls, and a new audiovisual system. The second phase also unveiled the three-story glass façade and the 3,000-square-foot lobby, now known as the Schaefer Awards Gallery.

Integrated Spine Fellowship

A new integrated orthopedic and neurosurgery spine fellowship program offers orthopedic and neurosurgery fellows formal rotations with both orthopedic surgeons and neurological surgery spine surgeons. The one-year fellowship offers training in all aspects of the cervical, thoracic, and lumbar spine, from degenerative diseases and deformity to trauma injuries and tumors. Fellows perform surgical cases that include complex scoliosis and kyphosis

corrections with three-column osteotomies and minimally invasive procedures for cervical and lumbar disc disease.

White Coat Anniversary

The Class of 2022 was welcomed to VP&S in August 2018 at the 25th anniversary of the White Coat Ceremony.

Members of the class were cloaked in white coats and recited the Hippocratic Oath for the first time in the presence of families and friends, just as more than 4,000 new students have done every year since the ceremony began in 1993. The late Arnold P. Gold, MD, created the ceremony to reinforce a commitment to humanistic practice. He also founded the Arnold P. Gold Foundation, which has developed programs that support the education and training of humanistic health care professionals. The speaker at the 2019 ceremony, Emeritus Professor Gerald E. Thomson, MD, urged the Class of 2023 to put patients first, calling the values of medical ethics and medical professionalism "superior guides for physicians."

Gerald Thomson

A New "New" Curriculum

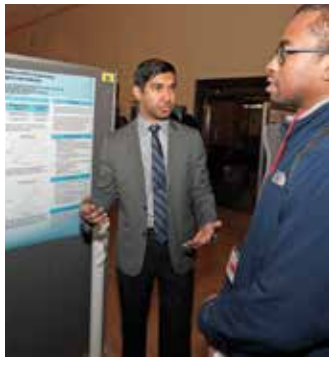
Even though the current MD curriculum, unveiled in 2009 for the incoming Class of 2013, is now 10 years old, it is still referred to as "the new curriculum" because of its sweeping changes for VP&S students. The curriculum, which other schools have emulated, is strong but changes in educational resources and health care delivery over the past decade have prompted the need for a review. The Vagelos Education Center and its simulation center did not exist when the current curriculum was conceived, and new educational priorities, such as integrated curricula, interprofessional education, programmatic assessment, and competency-based education, provide opportunities that were inaccessible a decade ago. The comprehensive reassessment of the curriculum as a whole will focus primarily on the first 18 months of medical school. Priorities for curriculum renewal will be identified by faculty working groups during the 2019-20 academic year with a prototype for discussion with the new incoming dean ready by late spring of next year.

Conference for Student-Run Clinics

Columbia's student-run clinics hosted this year's New York Student-Run Free Clinics Regional Conference for more than 120 students from 10 medical schools. The annual conference gives participating students an opportunity to network, learn about free clinics at other schools, and address unique or shared challenges. Columbia has five student-run clinics: the Human Rights Initiative Asylum Clinic, Columbia-Harlem Homeless Medical Partnership, Columbia Student Medical Outreach, Columbia University Harm Reduction Clinic, and Q Clinic: Primary Care for the LGBTQ Community. Keynote speaker at this year's conference was 2011 VP&S graduate Danny Neghassi, who urged students to become advocates for underserved communities. Dr. Neghassi volunteered with a clinic as a medical student and is now a family physician at Hudson River HealthCare and instructor in clinical medicine in the Center for Family and Community Medicine at Columbia.

Student Research

With topics ranging from epilepsy to electronic health records to Alzheimer's disease, 76 VP&S students shared their research with faculty, colleagues, and fellow students at the annual Student Research Day. They described their findings to judges, and awards were given for top work in four categories: research year, scholarly projects, summer research, and MD-PhD research.



Learning to be Education Researchers

Faculty members from throughout the medical center participated in the first year of the Medical Education Research Intensive Training (MERIT) program. A graduation event in June 2019 allowed the 22 faculty graduates to display and present the research proposals developed in the program. The MERIT program helps participants hone their core skills in hypothesis generation, research design, methods, data analysis, program evaluation, and scholarly writing to earn a Medical Education Research Certificate from the Association of American Medical Colleges.

MD-PhD Student Research

Research posters presented at the 14th annual MD-PhD Student Research Symposium covered topics ranging from neurological diseases to stem cells. The symposium featured the work of 34 aspiring physician-scientists. A 2013 MD-PhD graduate, Priya Rajasethupathy,

gave a lecture titled "The Evolving Memory Trace." Dr. Rajasethupathy is the Jonathan M. Nelson Family Assistant Professor and head of the Laboratory of Neural Dynamics and Cognition at Rockefeller University. Columbia's MD-PhD program prepares students to become biomedical leaders by combining clinical and scientific education and offering faculty-student collaboration in research laboratories across the University.

Master's Degree in Genetic Counseling

VP&S welcomed its first students into a two-year program that will earn them master of science degrees in genetic counseling. The 12 students in the class of 2021 come from across the United States, Canada, and Israel. Only one of the students is starting the program directly from undergraduate school; the others are coming from diverse work experiences. The VP&S program was one of 49 programs that participated in a match process during the spring. VP&S received an above average number of applications for a new program and interviewed approximately 60 applicants. The program has a broad faculty who will teach in the classroom and the clinics, with the majority being genetic counselors from a variety of departments who are full-time VP&S faculty. The program is led by Amanda Bergner, MS, CGC, associate professor of genetic counseling (in genetics & development).

Interprofessionalism

Classes at VP&S and other medical center schools were cancelled April 2 and replaced with workshops designed to foster teamwork and respect among all health care professionals. Nearly 1,400 students participated in the second annual Interprofessional Education Day of Action, which included more than 75 workshops and lectures led by close to 200 faculty members, students, and community organizations. This year's event—organized around the theme of social justice—was more closely integrated with the curricula of each school and program. Last year's IPE Day of Action led to the creation of IPE Nights, a monthly interprofessional forum where students organize workshops. "Based on that experience, we included student-led workshops in this year's event, and I think they were some of the most successful," says Rita Charon, MD, PhD, chair of medical humanities & ethics at VP&S, who started Columbia Commons IPE, the Columbiawide unit that sponsors the annual Day of Action.

About the MD Class of 2019

Members of the VP&S Class of 2019—the largest number of graduates since 1992—received MD and PhD degrees in a May ceremony attended by families and friends. The ceremony honored 172 students who received MD degrees and 60 students who received biomedical sciences PhD degrees from Columbia's Graduate School of Arts and Sciences. A few months earlier, at the annual residency match, 166 students matched to residencies in internal medicine, pediatrics, psychiatry, obstetrics & gynecology, ophthalmology, dermatology, and other specialties.

MORE ABOUT THE MD CLASS OF 2019:

50% women

20 MD-PhD graduates

3 graduates in the three-year PhD to MD program

1 graduate from the MD/MPH dual degree program

5 received degrees in the master of science in biomedical science program

4 received MD/MBA degrees

2 received MD/DDS degrees in the oral and maxillofacial surgery program

1 student received a master's degree in biostatistics

1 student received a master of education degree

1 student received a master of fine arts degree in creative writing

23 students did an additional year of research

34% of the class took extra time for research or for a dual degree

More than a third of the class volunteered as a senior student adviser for the class below them

Eight couples participated in the match, **six** of them in-house couples

24% of the graduates went abroad for their first-year summer experience, global health electives, scholarly project, or for master's degrees, mostly to developing countries

23% matched at Columbia for part or all of their postgraduate training

47% will remain in New York City

Six babies were born during medical school

11 graduates were married during medical school, including two in-house couples, and several more students are engaged

Many students ran full or half marathons and participated in triathlons

2019 **Clinical** Highlights

A Better Prenatal Test

Whole exome sequencing may be the next improvement in prenatal testing, a Lancet study by VP&S researchers suggests.

The new kind of prenatal genetic testing can improve obstetricians' ability to diagnose the underlying causes of fetal anomalies found during prenatal ultrasounds, but the results require expert interpretation. The new test would be important for the approximately 3% of pregnancies that have an ultrasound that reveals a significant fetal physical anomaly. Knowing the cause of the anomaly can help doctors and parents be better prepared, both during the pregnancy and after delivery, but doctors sometimes cannot identify the underlying cause. Standard genetic tests are able to identify the cause in fewer than half of such anomalies.

When a cause cannot be identified, families often embark on a diagnostic odyssey that can last for years until the exact cause can be determined, leaving them without information about whether future pregnancies could be similarly affected.

To address this, some clinicians have begun offering whole exome sequencing, a technique that reads the smallest details of all protein-coding genes in the genome, to obtain a genetic diagnosis of undiagnosed abnormalities. However, only a few studies have looked at the utility of the technique as a prenatal diagnostic tool, and much of the science connecting gene variants to fetal anomalies remains unsettled.

The Columbia researchers enrolled 234 pregnant women who had abnormal ultrasound findings but whose standard genetic tests were negative. "If an anomaly is detected at ultrasound, the current standard of care is to obtain a sample of amniotic fluid and perform karyotyping to determine if the fetus has the right number of chromosomes and if small regions are missing," says Vimla Aggarwal, MBBS, director of Columbia's precision genomics laboratory and an author of the study. But this test can only pinpoint the underlying cause for about 40% of anomalies found on ultrasound.

By sequencing the genomes of the parents and fetuses in the 234 pregnancies, the researchers were able to diagnose an additional 10% of the fetuses with a known genetic disorder. Another 20% of the fetuses had gene sequence signatures that were suggestive, though not definitive, of a genetic disorder.

The study was led by Ronald Wapner, MD, director of reproductive genetics at Columbia's Institute for Genomic Medicine (IGM) and vice chair of research in obstetrics & gynecology, and David Goldstein, PhD, director of the IGM.

"Based on our findings, whole exome sequencing could serve as a valuable addition to standard prenatal genetic tests, with the potential to improve perinatal care for infants with genetic conditions and ease parents' fears by offering a clear diagnosis," says Dr. Wapner, a maternal-fetal medicine expert.

Since the science surrounding genomic analysis is still developing, some of the gene sequence patterns had been associ-


Vimla Aggarwal


Ronald Wapner

David Goldstein

PHOTOS BY JÖRG MEYER

ated—but not definitively linked—to a specific developmental abnormality. Clinicians need to balance their desire to give patients definitive answers against the sometimes murky state of genomic science. A team of multidisciplinary experts—clinical and molecular geneticists, genetic counselors, developmental biologists, and maternal-fetal medicine specialists—is needed to ensure an accurate interpretation of the test results.

"Future studies are needed to determine whether performing whole exome sequencing on fetuses during pregnancy will lead to improved care and reproductive counseling," Dr. Wapner adds. Columbia researchers are conducting further studies.

The researchers predict that the diagnostic yield of whole exome sequencing, in combination with other genetic tests, could increase to more than 20% of cases as more information about the genetics of fetal anomalies comes to light. Sequencing data also may be used to develop better tools to offer treatment before and after delivery.

Ketamine and Other Next Generation Brain Therapeutics

Columbia Psychiatry opened a Next Generation Brain Therapeutics Program at ColumbiaDoctors Midtown in Fall 2018 to provide innovative and experimental treatments for mental and substance use disorders. The program provides the newest leading-edge treatments that are scientifically justified but may not yet be FDA-approved for people for whom standard treatments have been ineffective. Among the first treatments offered was ketamine for treatment-resistant depression and mood disturbances.

The program offers medical and psychiatric evaluations, diagnostic procedures, and treatments. "The Next Generation Brain Therapeutics Program is urgently needed because patients who are suffering can't always wait for the prolonged time it takes for the FDA to review and approve novel treatments," says Jeffrey Lieberman, MD, the Lawrence C. Kolb Professor and Chair of Psychiatry. "It is important that Columbia Psychiatry offer the newest, most innovative treatments to ensure their safe and competent administration."

Columbia Psychiatry has pioneered research into ketamine's benefits for people suffering from depression and suicidal thoughts and carried out two large NIH-funded studies. The principal investigator of the studies, John Mann, MD, the Paul Janssen Professor of Translational Neuroscience in Psychiatry and Radiology, says, "Our psychiatrists have many years of experience both evaluating patients for ketamine treatment and safely and successfully administering the treatments."

Ketamine program leaders Joshua Berman, MD, PhD, and J. John Mann, MD

JÖRG MEYER

"Depression affects more than 16 million Americans every year," says Lourival Baptista, MD, vice chair of clinical services in the Department of Psychiatry. "This program brings together the knowledge and resources of our entire department to offer an exciting new option to those who have suffered so much from this condition."

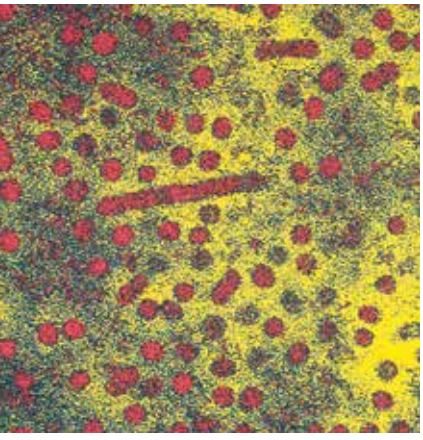
A few months after Columbia's program opened, the FDA approved a nasal spray form of ketamine, resulting in a bump in interest. From January to June 2019 alone, Columbia fielded more than 300 requests for this service and performed more than 100 infusions of ketamine.

Helping Kids with Congenital Heart Problems

Columbia surgeons have expanded surgical treatments to help children born with a vascular ring, which occurs when certain parts of the aorta develop abnormally, resulting in compression of the trachea and the esophagus. Minimally invasive video-assisted thoracoscopic surgery (VATS) vascular ring repair has advantages over traditional open surgery, including quicker recovery time and less pain. Some vascular rings are more severe than others. When a vascular ring causes a child to have trouble breathing or swallowing, surgical repair is required. The VATS minimally invasive approach allows surgeons to make repairs through three small incisions, avoiding a larger open approach between the ribs.

Hepatitis in Cancer

Many newly diagnosed cancer patients also are infected with hepatitis B or C virus and are unaware of their viral status,



reported a study published in JAMA Oncology. Dawn L. Hershman, MD, was a senior leader of the study, which was run by the SWOG Cancer Research Network. Cancer therapies can reactivate viral infections, and because patients with viral infections are usually excluded from clinical trials, it is not known how cancer treatments affect the clinical outcomes of people with hepatitis or HIV. Cancer patients are rarely screened for viral infections, a missed clinical opportunity, says Dr. Hershman. "We have effective treatments for HIV and hepatitis B, and hepatitis C can be cured." Experts disagree over the value of routine screening for hepatitis B and C and HIV in new cancer patients, partly because screening is expensive. "This study is a first step toward determining the prevalence of viral infections among newly diagnosed cancer patients and establishing new screening and treatment guidelines."

Epilepsy Database Used for Ongoing Sequencing

The Epilepsy Genetics Initiative funded by Citizens United for Research in Epilepsy was formed to create a centrally managed database of clinically generated exome sequence data. Investigators from Columbia's Institute for Genomic Medicine performed a systematic research-based reanalysis to identify new molecular diagnoses that were not possible at the time of initial sequencing. This database also is used to aid in novel gene discovery. Researchers reported on the first three years of the initiative's work, during which 139 individuals with epilepsy underwent diagnostic whole exome sequencing but had not received a genetic diagnosis. Eight new diagnoses were made as a result of updated annotations or the discovery of novel epilepsy genes. In five other cases, the investigators provided new evidence to support or contradict the likelihood of variant pathogenicity that had been reported. One novel epilepsy gene was discovered through dual interrogation of research and clinically generated whole exome sequencing.

COPD Diagnosis

Using data from the National Heart, Lung, and Blood Institute Pooled Cohorts Study, a resource developed at Columbia to combine numerous existing multiethnic cohort studies to support large-scale studies of chronic obstructive pulmonary disease (COPD), researchers have identified the optimal spirometry threshold to predict COPD-related hospitalizations and deaths. A study team led by Elizabeth Oelsner, MD, looked at the records of 24,207 adults and confirmed the prognostic significance of the diagnostic threshold for COPD that is recommended by current guidelines. The research published in JAMA now standardizes the diagnosis of COPD, which has the potential to improve diagnosis, clinical care, and clinical research.

ECMO for Patients with ARDS

During the flu pandemic of 2009–when large numbers of patients were hospitalized with severe respiratory failure due to acute respiratory distress syndrome or ARDS–many doctors turned to ECMO, or extracorporeal membrane oxygenation. ECMO can act as an artificial lung but is more invasive than mechanical respirators and more complicated to administer. Despite the extra risk and effort, many believed ECMO in 2009 saved the lives of people struggling with

ARDS, which is associated with a mortality rate that can exceed 50% in more severe cases, although at the time the benefits of ECMO were unproved and it remained a controversial therapy for years. Daniel Brodie, MD, director of the Adult ECMO Program at Columbia and NYP, was a senior author of a clinical trial that was reported in the New England Journal of Medicine in 2018 and an author on a subsequent analysis of the study in JAMA. Together, these studies demonstrated that ECMO saves lives in patients with the most severe forms of ARDS. "While we've come a long way in recent years, there is still a lot to learn about how best to manage patients during ECMO support," says Dr. Brodie. "A lot more research needs to be done."

Assessing Brain Injury Using EEG

Close analysis of EEG data reveals that nearly one in seven brain-injured ICU patients shows evidence of hidden consciousness just days after injury, and these

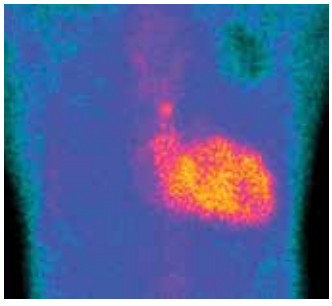
patients are more likely to recover, Columbia neurologists found. The researchers used a machine learning technique to analyze standard EEG data collected from 104 unresponsive patients hospitalized at NewYork-Presbyterian/Columbia to look for patient-specific brain activity indicating that they could understand instructions to move their hands. If the findings are confirmed in larger studies, the technique could help physicians better predict which patients will likely regain consciousness. The study, led by Jan Claassen, MD, was published in the New England Journal of Medicine.

Promising Sickle Cell Treatment Being Tested

A team of Columbia experts is studying a potential new way to treat sickle cell disease. "Patients who are born with sickle cell disease, depending on the severity, have a reduced life expectancy, and so far the only way of curing this disease is through a bone marrow or stem cell transplant," says Markus Mapara, MD, PhD, director of bone marrow transplantation and cell therapy. "Unfortunately, the chances of having a matched sibling donor, which provides the best outcomes, are only 25%." A new approach is being tested in a clinical trial at Columbia as part of a larger multicenter trial to use gene therapy. "Because sickle cell disease is caused by only one errant gene, it ranks high on the list of diseases that potentially could be cured with gene therapy. If you could fix that one defective gene, you could potentially cure the disease and reverse the genetic malfunction." The participants in the trial are getting new and genetically engineered hemoglobin through a stem cell transplant using the patient's own stem cells. Stem cells are removed from a patient's blood and sent to a laboratory where they are mixed together with a new, corrected gene. The genetically engineered cells are then returned to the patient's bloodstream, and the hope is that the stem cells with the modified DNA will start producing healthy red blood cells. The new gene is delivered to the patient's stem cells through a deactivated virus that is especially good at inserting the new gene into the stem cell. Early participants have been followed for more than three years, and so far they have increased healthy hemoglobin levels and reduced pain episodes.

Reducing Deaths from Heart Failure

A phase 3 clinical trial has shown that a drug called



tafamidis significantly reduces deaths and hospitalization in patients with transthyretin amyloid cardiomyopathy, a progressive form of heart failure that may be more common than doctors realize. The findings were published in the New England Journal of Medicine by the trial's co-chair Mathew S. Maurer, MD, a heart failure specialist, and colleagues.

Plastic Electronics May Improve Epilepsy Surgery

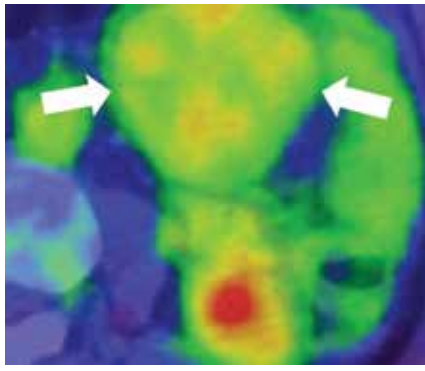
After nearly a century of status quo, the hardware for electrophysiology is evolving and enabling a new wave of research into epileptic disorders. Jennifer Gelinas, MD, PhD, and Dion Khodagholy, PhD, at Columbia are collaborating with multiple institutions to develop and test biocompatible polymer electrodes known as NeuroGrids, which offer the potential of improved signal recording and less morbidity compared with conventional metal electrodes. The polymer in the new device conducts both ions and electrons, which is ideal for brain-machine interaction. The device could help surgeons more precisely locate the origin of seizures to make surgery resection more efficient.

Routine Genetic Testing for Kidney Disease

A new study has found that genes cause about one in 10 cases of chronic kidney disease in adults, and identifying the responsible genes has a direct impact on treatment for most patients. The study showed that genetic testing can be used to personalize the diagnosis and management of kidney disease, says Ali Gharavi, MD, chief of nephrology and a co-senior author of the study, which was published in the New England Journal of Medicine.

Treating Rare Connective Tissue Tumor

In a phase 3 clinical trial, a drug called sorafenib stopped progression of desmoid tumors for two years in 80% of patients who completed treatment, a significant increase in progression-free survival compared with placebo. Results of the multicenter trial were published in the New England Journal of Medicine. "In general, desmoids are locally aggressive and often painful tumors for which there are



no effective therapies," says Gary K. Schwartz, MD, chief of hematology/oncology and a senior author of the paper. "Sorafenib is an oral agent that provides a new means to directly target the ability of desmoid tumors to grow and represents a new standard of care."

Improving Home Blood Pressure Monitoring

Obtaining out-of-clinic blood pressure measurements to confirm a diagnosis of hypertension is recommended before initiating treatment, but few studies have shown the number of measurements needed to reliably estimate blood pressure in home monitoring. In a paper published in the Journal of the American Heart Association, Natalie A. Bello, MD, and others described a community-based study of adults who were not receiving any antihypertensive treatment. The study showed that

using the average of morning and evening readings over at least three days is needed to reliably estimate out-of-office blood pressure and confirm a diagnosis of hypertension.

New IVF Center, Lab Open

The Columbia University Fertility Center features a new state-of-the-art IVF lab. "Our division of reproductive endocrinology and infertility cares for patients at a deeply sensitive time in their lives, and it is critical for us to have a facility that offers the highest degree of comfort and convenience as well as the most cutting edge technology possible,"

says Mary E. D'Alton, MD, chair of obstetrics & gynecology. The fertility center is led by Zev Williams, MD, PhD, chief of reproductive endocrinology and infertility, and Eric Forman, MD, the medical and laboratory director.

Launch of ALS Families Project

By closely following the relatives of some individuals with familial amyotrophic lateral sclerosis (ALS), researchers at Columbia's Eleanor and Lou Gehrig ALS Center hope to find ways to detect the disease before symptoms arise to allow for early therapeutic intervention. Columbia's ALS Families Project identifies asymptomatic relatives and will follow them. Since its launch in October, the project has enrolled more than 12 presymptomatic carriers and plans to expand. Participants will come to Columbia once or twice a year for examination and testing. The ALS Families Project will share data with other academic and industry researchers who are looking for ALS biomarkers and developing new therapies, including gene therapies.

Microlearning Videos on Insulin Management

A company specializing in patient education has partnered with a pharmaceutical company and Columbia's Naomi Berrie Diabetes Center and other diabetes programs to offer "microlearning," bite-sized (from 30 seconds to three minutes) digital information. Available in Spanish and English, the videos target patients who are new to using insulin, including the fastest growing populations with type 2 diabetes—African Americans, South Asians, and Hispanics.

Sugar-Sweetened Beverages in Early Life

Sugar-sweetened beverage consumption during the first year of life is linked to sugar-sweetened beverage consumption later in childhood. An article in the American Journal of Public Health, authored by Jennifer Woo Baidal, MD, and others, discusses the need to curb sugar-sweetened beverages during pregnancy and avoid introduction during infancy. Better understanding of the drivers of parental attitudes will inform the development of policy interventions such as the modification of beverage attributes (e.g., taste and cost) or shifts in marketing and advertising of infant and toddler products to reduce consumption in the first 1,000 days of life.

Getting Smarter About Brain Cancer Trials

Columbia will be among the first to enroll patients with glioblastoma, the most common primary brain cancer in adults, in a new type of clinical trial that could speed the identification and development of the most promising therapies for the disease, reports Andrew Lassman, MD. Instead of evaluating each therapy in its own separate clinical trial, the program is designed to evaluate several drug candidates at once.

Better Preparation for Childhood Epilepsy Surgery

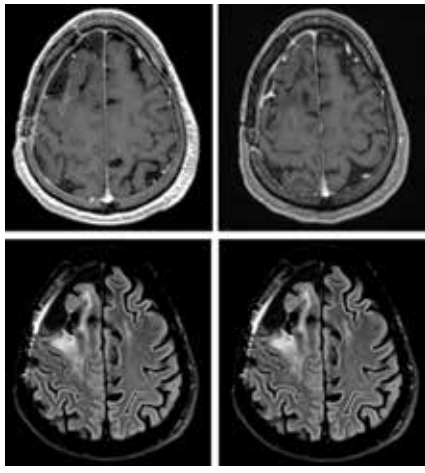
It has long been believed that cognitive tasks cannot be used to lateralize seizure onset in children. A prospective, observational study published in Neurology by Marla J. Hamberger, PhD, found that language tasks she developed specifically for children can reliably identify the hemisphere of seizure onset in pediatric epilepsy. Poorer auditory naming predicted left hemisphere epilepsy in both group and individual analyses, whereas no significant laterality differences were found on measures of visual naming, general intelligence, or other cognitive functions. Lateralizing the hemisphere of seizure onset in children with epilepsy can assist in the preoperative workup for pediatric epilepsy surgery.

How Exercise May Protect Against Alzheimer's

Evidence shows that exercise produces a hormone that may improve memory and protect against Alzheimer's disease, according to a study co-led by Ottavio Arancio, MD, PhD. The study, published in Nature Medicine, looked for a link between irisin, a hormone that is released during physical activity, and Alzheimer's. Using tissue samples from brain banks, the team found that irisin is present in the human hippocampus and that hippocampal levels of the hormone are reduced in individuals with Alzheimer's. The findings suggest that irisin could be exploited to find a novel therapy for preventing or treating dementia in humans.

Why Some Brain Tumors Respond to Immunotherapy

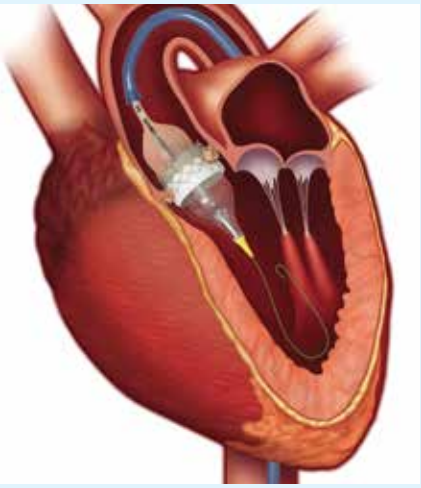
Columbia researchers have learned why some glioblastomas—the most common type



of brain cancer—respond to immunotherapy. The findings could help identify patients

TAVR: The Future of Treatment for Heart Valve Disease

Research led by Columbia and conducted in clinical trials at multiple centers showed that transcatheter aortic valve replacement, or TAVR, performed better than open-heart surgery in low-risk patients with severe aortic stenosis (AS). The study, published in the New England Journal of Medicine, found that one year after the procedure, the rate of death, stroke, or rehospitalization was significantly lower with TAVR than with surgery. The U.S. Food and Drug Administration has since approved the procedure for patients with severe AS who are at low risk for death or major complications associated with open-heart surgery to replace a damaged valve.



Earlier research led to approval of TAVR for patients at intermediate or higher risk for death or major complications during open-heart surgery. In low-risk patients, open-heart surgery has been the standard-of-care for aortic valve replacement. However, the procedure to insert a transcatheter heart valve is less invasive and involves a smaller incision and shorter recovery time than open-heart surgery.

As many as 400,000 patients around the world with aortic stenosis have had TAVR. TAVR was first introduced as an alternative for patients who were too sick to undergo open-heart surgery, but clinical trials over the years have shown that it may be superior to surgery even for patients with low operative risk. In TAVR, doctors thread a catheter through an artery in the groin and into the heart so that a new aortic valve can be fitted inside the diseased valve without surgically opening the chest.

The first PARTNER (Placement of AoRtic TraNscathetER) trial, published in 2010, found that the procedure dramatically reduced the risk of death among inoperable patients compared with those managed medically; in subsequent PARTNER trials, published in 2011 and 2016, TAVR was also found to be effective for patients with high- and intermediate-risk of death or serious complications from surgery.

Patients in the study published this year will be followed for at least 10 years to assess the long-term durability of the replacement valve and to measure their long-term outcomes.

who are most likely to benefit from treatment with immunotherapy drugs and lead to the development of more broadly effective treatments. The study, led by Raul Rabadan, PhD, was published in the journal Nature Medicine.

Finding the Best Drugs for Schizophrenia

Patients with schizophrenia are often treated with more than one type of psychiatric medication, but a new study led by T. Scott Stroup, MD, suggests that some combinations may be more effective than others. The findings, published in JAMA Psychiatry, found that individuals with schizophrenia who were taking an antipsychotic and added an antidepressant were less likely to use the emergency room or hospital for a mental health issue than those who started another antipsychotic or a benzodiazepine. Antidepressants reduced the risk of hospitalization by 16% compared with antipsychotics and by 22% compared with benzodiazepines. Antidepressants reduced the risk of emergency room visits by 8% compared with antipsychotics and by 18% compared with benzodiazepines.

Progressive Pancreatic Disease

The challenges of managing acute and chronic pancreatitis are being met with a new pancreatitis program at Columbia and NewYork-Presbyterian. The program's medical director, John M. Poneros, MD, and surgical director, Beth A. Schrope, MD, PhD, say Columbia's experience and large volume of patients led to the formalization of the treatment of patients with pancreatic disease. The program offers medical management, endoscopic interventions, nutritional support, and genetic testing. The program offers minimally invasive treatment approaches for patients who previously would have undergone open surgery. Traditional surgery is available when nonsurgical therapies have been exhausted. Dr. Schrope is among a small group of surgeons in the country who can perform total pancreatectomy with autologous islet cell transplantation.

Joint Pain and Breast Cancer Treatment

Researchers found acupuncture is associated with a statistically significant drop in joint pain among women taking aromatase inhibitors, a type of hormonal therapy, for breast cancer. Columbia oncologist Dawn Hershman, MD, coauthor Katherine Crew, MD, and colleagues conducted a multicenter clinical trial of 226 early-stage breast cancer patients, all of whom had moderate to severe joint pain. The women were randomly assigned to get acupuncture, sham acupuncture, or no acupuncture over six weeks. The differences in average pain, pain interference, and pain severity scores between the acupuncture group and both control groups were statistically significant, with nearly 60% of women in the acupuncture group experiencing at least a two-point reduction in pain on a scale of 0 to 10. The research was published in JAMA.

New Salvage System for Lungs

A multidisciplinary team from Columbia and Vanderbilt University has demonstrated in a clinically relevant model that severely damaged lungs can be regenerated to meet

transplantation criteria. In a study published in Nature Communications, the researchers describe the cross-circulation platform that maintained the viability and function of the donor lung and the stability of the recipient for 36 to 56 hours. Current methodologies of lung support are limited to only six to eight hours, too short a time for therapeutic interventions that could regenerate the injured lung and improve its function. The research team was co-led by Columbia's Gordana Vunjak-Novakovic, PhD. The collaborators hope their advance will lead to an increase in the number of lungs available for transplantation.

Hands-Only CPR

A new patient safety initiative launched by ColumbiaDoctors teaches hands-only CPR and automated external defibrillator awareness. Hands-only CPR has been shown to be as effective as conventional CPR in saving organs and lives, and providing hands-only intervention immediately following a cardiac arrest can make the difference between life and death.

Clinical Application of a New Test for CNS Infections

To optimize patient care, presumed central nervous system infections need to be rapidly and accurately diagnosed. Major advances have been made recently, including the FDA-approved FilmArray Meningitis/Encephalitis multiplex polymerase chain reaction panel for CNS infections, but significant concerns related to costs and how to use and interpret these tests effectively in clinical practice remain. Kiran Thakur, MD, and colleagues sought to assess the clinical utilization and performance of the ME/PCR assay among 705 inpatients who underwent testing at Columbia over the course of nearly a year. Their results, published in Frontiers in Neurology, found that the ME panel had rapid turnaround results, but routine availability led to overutilization of diagnostic tests; more than a third of ME panel tests performed were ordered for patients with little or no suspicion for CNS infection. Overall, agreement between the ME panel results and clinicolaboratory assessment was 98.2%. Of the 45 patients who tested positive, 26.6% were determined likely to be clinically insignificant. Researchers suggest that further studies are needed to gain insight into the bedside implementation of the ME panel in the diagnostic evaluation and management of CNS infections.

Reducing Stroke Risk During Pregnancy

The United States has experienced a significant rise in maternal mortality since 2000, as compared with a decrease in many countries throughout the world. Hypertensive disorders during pregnancy constitute a disproportionate share of preventable maternal mortality and morbidity in the United States, wrote Lynn Simpson, MD, Mary D'Alton, MD, and others in a report published in the American Journal of Perinatology Reports. To improve maternal outcomes and reduce risk of stroke and other complications, District II of the American College of Obstetricians and Gynecologists began the New York State Safe Motherhood Initiative in 2013. Co-chaired by Dr. D'Alton, this initiative is a quality improvement program to reduce preventable pregnancy-related deaths from causes such as hypertension. During the early implementation phase of the hypertension program, reports showed more timely treatment of severe hypertension in the majority of participating New York state obstetric hospitals. The long-term success of the program will depend on continued participation and commitment of the required resources in hospital settings.

New "Smart Drug" for a Breast Cancer

A new "smart drug" has shown promise for women with metastatic triple-negative breast cancer, based on data from a clinical trial at the Herbert Irving Comprehensive Cancer Center and other centers. Data on the drug, sacituzumab govitecan, were published in the New England Journal of Medicine. The drug is part of an emerging class of "smart drugs" designed to deliver a toxic payload directly to tumor cells by fusing an antibody that recognizes a protein expressed by breast cancer cells known as trop2 and the metabolite of an established chemotherapy drug (irinotecan), SN-38. "I think this drug has the potential to change practice, because the data look so compelling, even with the relatively small number of patients in the trial," says Columbia's Kevin Kalinsky, MD, the paper's senior author.

Ace Clinicians

The third class of clinicians was inducted into Columbia's Academy of Clinical Excellence this year in recognition of the clinicians' commitment to patient care and to training future generations of clinicians. This year's 46 new members—all full professors with at least five years at Columbia who devote more than half their time to patient care and training the next generation—join 154 clinicians who were among the first two ACE classes.

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Chief Financial Officer and Chief Business Development Officer for ColumbiaDoctors

Research

Michael L. Shelanski, MD, PhD
Senior Vice Dean for Research

Jennifer Williamson Catania, MS, MPH
Associate Vice Dean for Research Policy & Scientific Strategy

Muredach Reilly, MBBCh
Associate Dean for Clinical and Translational Research

Anil K. Rustgi, MD
Associate Dean for Oncology

Alumni Relations and Development

Anke Nolting, PhD
Associate Dean and Executive Director

Executive Committee of the Faculty Council, 2018-2019

Cigdem I. Akman, MD
Professor of Neurology at CUMC

Spencer Amory, MD
Jose M. Ferrer Professor of Surgery at CUMC

Joshua E. Hyman, MD
Professor of Orthopedic Surgery at CUMC

Gerard Karsenty, MD, PhD
Paul A. Marks Professor of Genetics & Development; Professor of Medicine; and Chair, Department of Genetics & Development

Stavroula Kousteni, PhD
Associate Professor of Physiology & Cellular Biophysics

Usha Krishnan, MD
Professor of Pediatrics at CUMC

Andrew R. Marks, MD
Professor of Physiology & Cellular Biophysics; Clyde'56 and Helen Wu Professor of Molecular Cardiology (in Medicine); and Chair, Department of Physiology & Cellular Biophysics

Edward Owusu-Ansah, PhD
Assistant Professor of Physiology & Cellular Biophysics

Amanda J. Powers, MD
Assistant Professor of Surgery (in Anesthesiology) at CUMC

Carrie B. Ruzal-Shapiro, MD
Professor of Radiology at CUMC

Karen Soren, MD
Professor of Pediatrics at CUMC

Jessica L. Spellman, MD
Associate Professor of Anesthesiology at CUMC

Department Chairs

(as of Sept. 1, 2019)

Anesthesiology
Ansgar Brambrink, MD, PhD

Biochemistry & Molecular Biophysics
Arthur G. Palmer III, PhD *(interim)*

Biomedical Informatics
George Hripcsak, MD *(on sabbatical)*
Noémie Elhadad, PhD *(co-interim)*
Soumitra Sengupta, PhD *(co-interim)*

Dermatology
David R. Bickers, MD

Emergency Medicine
Angela M. Mills, MD

Genetics & Development
Gerard Karsenty, MD, PhD

Medical Humanities & Ethics
Rita Charon, MD, PhD

Medicine
Donald W. Landry, MD, PhD

Microbiology & Immunology
Sankar Ghosh, PhD

Neurological Surgery
Robert A. Solomon, MD

Neurology
Richard Mayeux, MD

Neuroscience
Steven A. Siegelbaum, PhD

Obstetrics & Gynecology
Mary E. D'Alton, MD

Ophthalmology
George A. Cioffi, MD

Orthopedic Surgery
William N. Levine, MD

Otolaryngology/ Head & Neck Surgery
Lawrence Lustig, MD

Pathology & Cell Biology
Kevin Roth, MD, PhD

Pediatrics
Jordan Orange, MD, PhD

Pharmacology
Cory Abate-Shen, PhD

Physiology & Cellular Biophysics
Andrew R. Marks, MD

Psychiatry
Jeffrey A. Lieberman, MD

Radiation Oncology
Lisa Kachnic, MD

Radiology
Lawrence H. Schwartz, MD

Rehabilitation & Regenerative Medicine
Joel Stein, MD

– Programs in Occupational Therapy
Glen Gillen, EdD, *Director*

– Programs in Physical Therapy
Debra Krasinski, PhD, *Director*

Surgery
Craig R. Smith, MD

Systems Biology
Andrea Califano, PhD

Urology
James M. McKiernan, MD

Institutes, Centers, and VP&S Schoolwide Initiatives and Their Directors

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

Center for Family and Community Medicine
Richard Younge, MD

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

Center for Radiological Research
David Brenner, PhD, DSc

Columbia Stem Cell Initiative
Emmanuelle Passegué, PhD

Columbia Translational Neuroscience Initiative
Serge E. Przedborski, MD, PhD

Institute for Cancer Genetics
Riccardo Dalla-Favera, MD

Institute of Comparative Medicine
Brian Karolewski, VMD, PhD

Institute for Genomic Medicine
David B. Goldstein, PhD

Institute of Human Nutrition
Richard J. Deckelbaum, MD

Herbert Irving Comprehensive Cancer Center
Anil K. Rustgi, MD

Irving Institute for Clinical and Translational Research
Muredach P. Reilly, MBBCh

Kavli Institute for Brain Science
Eric Kandel, MD

Gertrude H. Sergievsky Center
Richard Mayeux, MD

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

Transplant Initiative
Jean C. Emond, MD

Weinberg Family Cerebral Palsy Center
David P. Roye Jr., MD

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

Wu Family China Center for Health Initiatives
David Ho, MD
(effective January 2020)

VP&S Hospital Affiliations

NewYork-Presbyterian Hospital
New York, NY

New York State Psychiatric Institute
New York, NY

Harlem Hospital
New York, NY

James J. Peters Veterans Administration Hospital
Bronx, NY

Mary Imogene Bassett Hospital
Cooperstown, NY

Stamford Hospital
Stamford, CT

Helen Hayes Hospital
West Haverstraw, NY

Lawrence Hospital
Bronxville, NY

FACTS & STATISTICS, FY19

MEDICAL SCHOOL ENROLLMENT, FALL 2018

Total medical school enrollment	620
Enrollment of in-state residents	176
Enrollment of international/nonresident students	24
Enrollment of men	315
Enrollment of women	305

ENROLLMENT BY YEAR

	MALE	FEMALE
First-year class	75	63
Second-year class	72	82
Third-year class	95	85
Fourth-year class	73	75
Total enrollment	315	305

MEDICAL SCHOOL ETHNICITIES

Hispanic/Latino	73
Black or African American, non-Hispanic/Latino	63
White, non-Hispanic/Latino	277
American Indian or Alaskan Native, non-Hispanic/Latino	2
Asian, non-Hispanic/Latino	129
Native Hawaiian or other Pacific Islander, non-Hispanic/Latino	1
Two or more races, non-Hispanic/Latino	15
Race and/or ethnicity unknown	36

OTHER STUDENTS

MD-PhD students	113
PhD students	424
Other students (PT, OT, Nutrition, Informatics)	460

DEGREES GRANTED, FY19

MD	171
PhD	80
Doctor of physical therapy	68
MS in nutrition	81
MS in occupational therapy	57
Certificate in psychoanalysis	1

APPLICATIONS (ENTERING CLASS 2018)

Number of applicants	7,537
Number of applications considered	6,796
Number of applicants interviewed	1,007
Number of acceptance letters issued	258
Bassett Program applicants	534

FACULTY, 2018-2019 ACADEMIC YEAR

Full-time faculty	2,189

FACULTY HONORS

Nobel Prize in Medicine	3
National Academy of Sciences	21
National Academy of Medicine	49
American Academy of Arts and Sciences	25
Howard Hughes Medical Institute	6

FINANCIALS, FY19 (EXCEPT WHERE NOTED)

Budget	$2.1 billion
Philanthropic support	$305 million
Endowment	$1.9 billion
Endowed chairs/professorships	295
NIH research support (FY 2018)	$501 million

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PHOTOS BY PAVEL BENDOV

Sharing a Bit of Haven with Our Neighbors

A pedestrian plaza has transformed approximately 60,000 square feet of an area on Haven Avenue and around nearby medical center buildings from West 169th Street to Fort Washington Avenue at 168th Street. Haven Plaza is now a public outdoor plaza shared by the medical center community and our Washington Heights neighbors. The project has transformed both public land (streets and sidewalks that make up about 40% of the area) and green space on medical center property (about 60% of the plaza). It is part of the New York City Department of Transportation Plaza Program, which has created neighborhood plazas throughout the city in an effort to ensure that all New Yorkers live within a 10-minute walk of quality open space.