EINSTEIN

THE MAGAZINE FOR ALUMNI AND FRIENDS OF ALBERT EINSTEIN COLLEGE OF MEDICINE



A Message from the Dean

n 1949, the illustrious chemist Linus Pauling published a paper in *Science*: "Sickle Cell Anemia, a Molecular Disease." The paper reported that hemoglobin, the oxygen-carrying protein of red blood cells (RBCs), shows distinct physical-chemical properties when isolated from RBCs of subjects with sickle-cell disease (SCD) compared with normal hemoglobin. His work led to the discovery that SCD is caused by the misspelling of a single letter of DNA in both copies of the gene that codes for the beta subunit of hemoglobin.

Our cover story, "Overcoming Sickle-Cell Disease," tells the story of the Osouna family of Queens, NY. Daughter Aniyah, age 11, and son Tristan, age six, both have SCD. The article describes how research by Einstein and Montefiore scientists is changing that picture so that Aniyah, Tristan and other children with SCD may have better treatment options.

Paul Frenette, M.D., professor of medicine and of cell biology and director of the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research at Einstein, has teamed with Deepa Manwani, M.B.B.S., professor of pediatrics at Einstein and director of pediatric hematology at Children's Hospital at Montefiore, to conduct a phase 2 trial of intravenous immunoglobulin for treating SCD pain.

This issue also provides an overview of Einstein's strong viral research program, which is making strides against some of the world's major disease-causing viruses. Over just eight months, for example, Einstein scientists led by Kartik Chandran, Ph.D., professor of



microbiology & immunology and the Harold and Muriel Block Faculty Scholar in Virology, and Jonathan Lai, Ph.D., associate professor of biochemistry, published papers describing two promising but quite different approaches to treating all strains of the notorious Ebola virus.

Fittingly, this issue profiles an Einstein alumnus with an illustrious record of global health accomplishment: Sten Vermund, M.D., '77, who now serves as the dean of the Yale School of Public Health. Looking back on his long relationship with Einstein, Dr. Vermund calls it "a very special place."

I wholeheartedly agree.

ALLEN M. SPIEGEL, M.D.

The Marilyn and Stanley M. Katz Dean Albert Einstein College of Medicine Executive Vice President, Chief Academic Officer Montefiore Medicine

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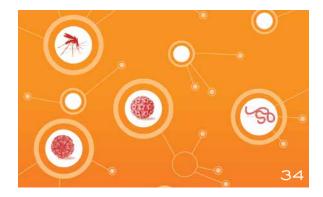
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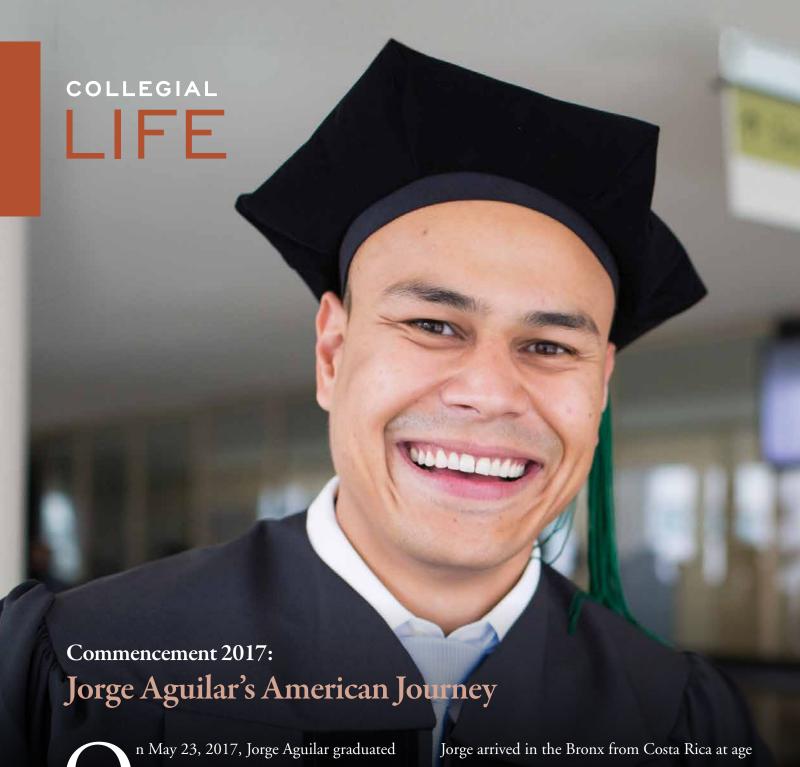








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n May 23, 2017, Jorge Aguilar graduated from Einstein along with 209 other students. "I felt like I'd won the lottery," he says, about receiving his M.D./Ph.D. degree. But his path to success wasn't easy.

Jorge arrived in the Bronx from Costa Rica at age seven with his divorced mother. She became a permanent U.S. resident when she remarried. But Jorge's application for a green card was turned down three times because the family's income was below the poverty line.

Slated for deportation while a junior in high school, Jorge turned to anyone who might be able to help: his teachers, his school principal, even his baseball coach. Fortunately, his coach's father—a retired judge—persuaded a lawyer to take Jorge's case pro bono, and his deportation was postponed. Meanwhile, Jorge graduated from St. Agnes Boys High School, landed a full scholarship to Swarthmore College and moved to Pennsylvania, where he was able to become a legal resident. He was later admitted to Einstein's M.D./Ph.D. program, also on scholarship.

As luck would have it, the first day of his Einstein orientation, July 3, 2010, coincided with Jorge's naturalization ceremony on Ellis Island—the final step in becoming a U.S. citizen. That morning, he and his family took the ferry to Ellis Island for what he describes as "a very emotional event," in which new citizens crossed the stage to receive their certificates.

Jorge headed to Einstein as soon as the ceremony ended, grabbing lunch just before getting on the subway. "My first act as a U.S. citizen was to

eat a McDonald's Big Mac," he recalls. He arrived for his group picture at the Belfer Building half an hour late, just as the photographer was putting his equipment away. "When I told him why I was late, he hugged me and congratulated me," says Jorge.

Looking back, Jorge credits his "angels"—people who helped him along the way-for much of his success. "Had any of them not been there," he says, "I would not be where I am today."

Jorge and his fiancée, Caitlin Proper, M.D., also an Einstein grad, are now serving residencies in pediatrics at Children's Hospital in Philadelphia. He is planning a career in pediatric cancer research. "I can't think of a more rewarding line of work than to help kids with cancer, in the hospital and in the laboratory," he says.

Jorge hopes his story will inspire other potential Einstein students from the Bronx. "There are so many invisible barriers to success," he explains. "I was never the smartest student—many other kids were smarter. But there were no angels to help them. It's our responsibility to identify these students and help them along the way."



As luck would have it, the first day of his Einstein orientation, July 3, 2010, coincided with Jorge's naturalization ceremony on Ellis Island—the final step in becoming a U.S. citizen.



"I felt like I'd won the lottery," said Jorge of the day he received his M.D./Ph.D. degree. Jorge is pictured here with his mother, Denia Ching, and his younger brother, Anthony.

COLLEGIAL LIFE

Getting Personal:

An Exclusive Interview with Dr. Tom Frieden



"There is a natural tendency to be comfortable in what we believe. It's difficult to keep in mind that we always need to question ourselves and improve."



Visit our video-enhanced online edition at magazine.einstein.yu.edu

On May 23, Tom Frieden, M.D., M.P.H., delivered the keynote address at Einstein's 2017 Commencement ceremony. The former director of the Centers for Disease Control and Prevention (CDC) talked about the personal quality—humility—essential for success in medicine. Shortly afterward, Dr. Frieden shared his views with Einstein magazine on humility, learning from one's mistakes, fixing the American healthcare system and other issues.

Do most physicians agree with you about humility's importance?

Remaining humble is a challenge we all face, and a constant challenge for virtually all physicians. There is a natural tendency to be comfortable in what we believe. It's difficult to keep in mind that we always need to question ourselves and improve.

In your speech, you shared an early experience caring for a patient with heart failure at a time when the consensus was that beta blockers were contraindicated in systolic heart failure, but some research was beginning to suggest that beta blockers could improve heartfailure outcomes. But you didn't feel confident enough to try this treatment, and the patient died. How did that affect you?

One of the hardest things to do is recognize you've made an error, but we have to—and we need to take our mistakes seriously. We also need to ask ourselves: "Did I get the result I wanted?" If we didn't, how can we do better next time?

You've worked with the World Health Organization in India, and served as New York City's health commissioner and most recently as director of the CDC. Which public health accomplishments are you most proud of?

My proudest accomplishment in each position I've held has been mining data and using it to drive progress. When New York City was in the midst of the largest outbreak of multidrug-resistant tuberculosis ever to occur in this country, we were able to document where and how TB was spreading and use that to rapidly control the disease. In India, working with the World Health Organization, we improved diagnosis, treatment and monitoring to expand effective TB control services to half a billion people.

Back in New York, I had the privilege of working under Mayor Michael Bloomberg. He really understood public health and supported what we were doing. For example, we were able to show that you can rapidly reduce tobacco use, and we eliminated artificial trans-fats from restaurants.

A lot was happening during your time at the CDC—the Ebola outbreak of 2013-16, the opioid epidemic and the controversy over vaccines. What public health problems deserve more attention than they are receiving today?

Heart attacks and strokes. They seem so common that we've become inured to them. But in fact, we are living in an epidemic of cardiovascular disease. And a lot of it is preventable with inexpensive, easily applied tools that we're neglecting such as lifestyle changes and medication. Even though heart attack rates have dropped in recent years, they are still a leading cause of death.

Globalization has a huge impact on public health. What have you learned about addressing crossborder health risks?

That there is no way we can protect Americans without working globally. Our health is bound up with the health of others, and this means we have to engage with the world. That needs to be more widely understood.

The Trump administration recently released its 2018 budget recommendations. Are you concerned about their public health implications?

They would be devastating for public health. We would be vulnerable to diseases both within our country and around the world. The CDC is the first line of defense to protect Americans from health threats, and if the CDC budget gets cut, healthcare costs will increase and more people will die.

Other than being humble, what are the greatest challenges

physicians face today?

One challenge is to learn how to incorporate the vast amounts of data becoming available and apply those data to actual medical practice. These days, it would be malpractice not to give beta blockers to a patient with systolic heart failure. Science has advanced.

If you could change one thing about the American healthcare system, what would it be?

I would align the priorities of patients and the healthcare system overall. The problem is that what's optimal for patients is *not* profitable for the system.

Is that because we're still working largely within a fee-forservice system?

That's just part of the problem. We end up paying a lot for care that doesn't deliver anywhere near the health value it could. Some of our institutions are not structured to optimize care, and we do not have a healthcare system that looks at data to hold us accountable for how we are doing.

Your late father, Julian Frieden, served as chief of coronary care at Montefiore for many years. Did he influence you to become a doctor?

My father showed me how satisfying life as a physician could be, especially when it combines rigorous science and the opportunity to shape policy. He practiced evidence-based medicine before the term was even invented and knew that 80 percent of the diagnosis comes from a carefully taken history. He also made use of the latest literature and data to drive treatment decisions. I recall sitting at the breakfast table when I was in high school and learning the CDC had discovered the cause of Legionnaires' Disease. After that, I wanted to work there.

Do you have a final message for current Einstein students?

Yes. Einstein has a wonderful way of inspiring and humbling future physicians. Humility fosters optimismabout science, the excitement of learning and the opportunity to apply new knowledge.

Tom Frieden with, from left to right, Philip O. Ozuah, M.D., Ph.D., executive vice president and chief operating officer, Montefiore; Steven M. Safyer, M.D., president and CEO, Montefiore, and Dean Allen M. Spiegel, M.D., Albert Einstein College of Medicine.



COLLEGIAL LIFE

Addressing M.D. Students' Wellness Needs

BY DANNA R. LEVY



ragile self-esteem...self-doubt...
loneliness. All are familiar to
medical students facing four
years of intense pressure and
separation from family and friends. It's
no surprise that a recent *U.S. News & World Report* survey found that half of all
medical students show signs of burnout,
including emotional exhaustion, detachment and the feeling that their efforts
don't matter.

Fortunately, Einstein medical

students have WellMed, the student wellness program that helps them deal with issues that could derail their careers.

WellMed began in 2012 as the brainchild of Allison B. Ludwig, M.D., Einstein's associate dean for student affairs. Dr. Ludwig was concerned that many students have trouble balancing the demands of medical school with their own physical and emotional needs. She enlisted help from Benjamin E. Kligler, M.D., associate professor of

family and social medicine, to design a program combining new and existing initiatives under the WellMed umbrella. WellMed offers services that address eight key areas: physical health, emotional wellness, nutrition, intellectual challenges, social connectedness, physical fitness, spiritual soundness and financial stability. "We've tried to think of all the ways people become unbalanced," explains Dr. Ludwig. They're focusing on these three areas:



Counseling is a big part of WellMed's effort. One second-year student says, "I always feel behind in medical school. There's a lot to keep up with and you put a lot of pressure on yourself." Students under stress can seek counseling in study skills and time management from Mary S. Kelly, Ph.D., director of the office of academic support and counseling. Peer tutors are available and peer-mentoring networks match small groups of first-year students with upperclassmen for advice on academic, social and emotional concerns. The career advisory program can help ease anxiety about career decision-making.

Dr. Kelly also provides confidential support on a free and unlimited basis for students facing emotional issues, including mental health crises such as depression or thoughts of suicide. Dr. Kelly can refer students to a nearby network of providers who are sensitive to their specific concerns as medical students.



SOCIAL CONNECTEDNESS

To help students socialize on campus, WellMed sponsors activities including musical performances, residence hall happy hours, ice cream and study breaks and holiday parties. Tuition now includes free gym membership.

"Everyone in medical school has a complex that everyone else is smarter than they are, and that they just snuck in."

-EINSTEIN FOURTH-YEAR MEDICAL STUDENT

The third year can be especially challenging for med students, who can find the experience isolating. "Not everyone is on the same schedule, so for a long time you may not see people you know," recalls a fourth-year student. "You are coming home late, studying, going to bed and then doing it all over again the next day." To address the needs of third-year students, WellMed has added four required stress-management seminars to a course that all third-year students attend: the Patients, Doctors, Communities course. In addition, all students are offered training in mindfulness and "positive reappraisal."



PHYSICAL HEALTH

At Einstein's Student Health Service in the Block Building, students can get free walk-in urgent-care assessments as well as treatment and referrals to specialists. "One of our goals is to teach students that their own health comes first when they're ill," says health service director Jane Haimes, M.S.N., R.N., F.N.P. "It's the same message they will be giving to their patients."

Despite its success, WellMed faces challenges, including how to persuade medical school students-many of whom are uncomfortable seeking helpto get the assistance they need, says

Dr. Ludwig. "Those most in need may be the least likely to use these programs." A new initiative called "Me Too" gives fourth-year students the chance to chat informally with classmates about their personal mental health struggles and hear experts discuss issues such as loneliness, depression, anxiety and substance abuse.

Dr. Ludwig describes WellMed as "an ever-evolving program" that is responding to student feedback. Top priorities for the near future include creating an on-campus mental health center, expanding WellMed's offerings to graduate students and offering medical students built-in time off for self-care.

"By creating and constantly improving WellMed, we're telling students, 'We care about your well-being and you should care too," she says.

MORE INFORMATION AND LINKS TO WELLNESS RESOURCES ARE AVAILABLE AT

www.einstein.yu.edu/education/ student-affairs/student-wellness-wellmed





Actors Training Doctors

BY PAULA DRANOV

edical students probably don't expect actors to take part in evaluating the students' diagnostic and examination skills. But that's what's happening at Einstein and other medical schools throughout the nation. New York offers a huge pool of acting talent to draw from, and working as a "patient" for medical students has become a popular "between engagements" gig. Medical students encounter these actors, known as standardized patients (SPs), throughout their four-year education, applying what they've learned in class to their encounters with real people in exam rooms.

"It's a way to determine that students have needed clinical skills, which include communication, history taking and physical exams."

Didi Charney, a professional actor, plays female SPs age 40 through 65. Her non-SP acting career has included roles on TV's As the World Turns and Another World and in a number of plays. Her SP repertoire spans 25 different roles. One, whom we will call "Janet Jones," is her favorite.

Janet fainted while on the toilet. She chalked it up to not having eaten breakfast but sought treatment at her husband's urging. The diagnosis: vasovagal syncope, a harmless fainting spell usually triggered by emotional distress. Didi knows Janet well. Einstein's SPs play their characters up to 16 times a day, as one student after another interviews them about the health problem they're depicting.

Ms. Charney learned about standardized patients 10 years ago via a newspaper article, and took to the idea right away. She liked the extra income and the opportunity to help future doctors learn how to communicate with their patients.

A BRIGHT IDEA

The use of SPs dates to 1963, when Dr. Howard Barrows at the University of Southern California started using actors as a way to test medical students' skills. Today, SPs are a staple of medical education in this country and internationally. "It's a way to determine that students have needed clinical skills, which include communication, history

taking and physical exams," explains Felise Milan, M.D., professor of clinical medicine and director of the Ruth L. Gottesman Clinical Skills Center and the Introduction to Clinical Medicine Program at Einstein, and an internist at Montefiore.

"The folks we work with are not just actors; they're medical educators as well," says Dr. Milan. "They need to be the character they're playing, get the story right and keep track of what questions the student has asked and whether an exam was thorough. As soon as the encounter ends, they have to get on the computer and record what the student did and didn't do."

The actors help create a realistic environment in which students can practice their skills—but it is still a safe environment, where students can make mistakes.

Abigail Bergman, a second-year medical student, was nervous before her first SP interview even though she knew she would be dealing with an actor, not a real patient. Here, her patient had been instructed to resist questioning and to insist that she wanted to see a "real" doctor, not a student. "You have to learn how to calm patients down," Ms. Bergman says. The difference between interviewing a standardized patient and a real one is that "if you forget what to ask an SP next, you can stop and say so-something you can't do with a real patient."

THE BACKSTORY

For each new role, Ms. Charney receives information about her character and the medical problem she'll be enacting. Beyond that, she explains, "You need to develop a backstory to flesh out who the patient is, so that he or she is not just a

cipher with a bunch of symptoms."

Once, when playing a patient who owned a flower shop, Ms. Charney devised a backstory with numerous details, down to her character's favorite flower. She makes notes of each backstory for future reference, since she may play the same role every few months for new crops of students.

But there's no way to anticipate all the questions students will ask, so improvisational skills are vital. While Ms. Charney was playing the mother of a sick infant, a student asked how soon after birth her baby had his first bowel movement. Although a mother herself, she was momentarily stumped. Should I say I need to check my records or that I can't remember, she wondered, finally settling on, "I'm sorry, I don't remember."

Anna Lank, who recruits SPs for Einstein and other New York City-area medical schools, maintains a database of 1,600 people of varying ages, genders, sizes and ethnicities. She likens her job choosing the right person for the desired SP to that of a casting director. "We take great care to find exactly the right SP for each encounter," she says.

Not all SPs are actors—"I have a writer, a retired nurse, students, a graphic designer," says Ms. Lank—but actors do have an edge. "To become an SP you have to listen and observe well, and those are skills actors are trained in," she notes. "You also need to be comfortable in imaginary circumstances and have the discipline to recreate your role over and over."

Just like on stage.

COLLEGIAL LIFE

REMEMBERING Isabelle Rapin

sabelle Rapin, M.D., who advanced our understanding of autism through her rigorous studies and who popularized the term "autism spectrum disorders," died on May 24 at age 89. Dr. Rapin joined the Einstein faculty in 1958 and taught and conducted research at the College of Medicine for more than 50 years.

Her interest in autism stemmed from her study of communications disorders that impair children's ability to function in the world. Although she officially retired in 2012, she was Skyping with colleagues and finishing a paper about congenital blindness and autism just days before her death.

In 2012, Einstein honored Dr. Rapin by creating the annual Isabelle Rapin Conference on Communication Disorders. Topics to date have included advances in research on Williams syndrome, dyslexia, Rett syndrome and tuberous sclerosis.

FASCINATED BY SCIENCE

Isabelle Martha Juliette Rapin was born on December 4, 1927, in Lausanne, Switzerland. When she began medical school in 1946 at the University of Lausanne, she was one of about a dozen women in a class of some 100 students.

In an autobiographical article published in the Journal of Child Neurology, she wrote, "By my first rotation, I noted that I lavished more effort on neurologic cases than others." An experience in 1951 set the course for her career.

"I spent 6 weeks in neurology at la Salpêtrière and another 6 at the Hôpital des Enfants Malades in Paris where I attended the . . . public consultations of Professor Stéphane Thieffry, my first encounter with a child neurologist," she wrote in the article. "I came back from Paris with my mind made up: I was to become a neurologist for children."

"Consider every patient a potential source of knowledge, pursue your interests vigorously, find a good mentor, enjoy what you do, and be lucky."

Dr. Rapin immigrated in 1953 to the United States, where her first job involved working in pediatrics at Bellevue Hospital in Manhattan. A year later, she began a residency at the New York Neurological Institute at Columbia-Presbyterian Hospital, and in 1958 she was hired by Saul Korey, M.D., Einstein's founding chair of neurology.

The neurologist and author Oliver Sacks, M.D., was a close friend and colleague of Dr. Rapin's and called her his "scientific conscience." In his book On the Move: A Life, Dr. Sacks wrote: "Isabelle would never permit me, any more than she permitted herself, any loose, exaggerated, uncorroborated statements. 'Give me the evidence,' she always says."



ON HAVING IT ALL

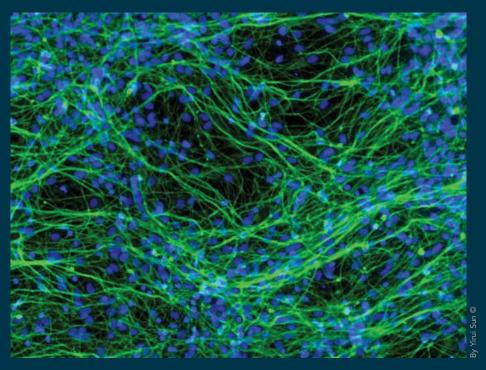
In her autobiographical article, Dr. Rapin had this advice for young women interested in entering her field: "Child neurology is a wonderful field, intellectually and personally, because of the families you will meet. In order to have it all, that is, be married, have children, and have a great job, you need a supportive and generous mate. Consider every patient a potential source of knowledge, pursue your interests vigorously, find a good mentor, enjoy what you do, and be lucky."

Dr. Rapin is survived by her husband, Harold Oaklander, Ph.D., and their four adult children and four grandchildren.

Dr. Rapin with her close friend and colleague Dr. Oliver Sacks.



RESEARCH NOTES



Brain Cells Control Aging

instein scientists have found that stem cells in the brain's hypothalamus govern how fast aging occurs in the body. The finding, made in studies with mice and reported last July in Nature, could lead to new strategies for warding off agerelated diseases and extending life spans.

The hypothalamus was known to regulate such important processes as growth, development, reproduction and metabolism. In a 2013 Nature paper, Einstein researchers reported the surprising finding that the hypothalamus also regulates aging throughout the body. Now the scientists have pinpointed the cells in the hypothalamus that control aging: a tiny population of adult neural stem cells, known to be responsible for forming new brain neurons.

"Our research shows that the number of hypothalamic neural stem cells naturally declines over the life of the animal, and this decline accelerates aging," says senior author Dongsheng Cai, M.D., Ph.D., a professor of molecular pharmacology at Einstein. "But we also found that the effects of this loss are not irreversible. By replenishing these stem cells or the molecules they produce, it's possible to slow and even reverse various aspects of aging throughout the body."

In studying whether stem cells in the hypothalamus held the key to aging, the researchers first looked at the fate of those cells as healthy mice got older. The number of hypothalamic stem cells began to diminish when the animals reached about 10 months, which is several months before the usual signs of aging start appearing. "By old age about two years of age in mice-most of those cells were gone," says Dr. Cai.

The researchers next wanted to learn if this progressive loss of stem cells actually caused aging and wasn't merely associated with it, so they observed what happened when they selectively disrupted hypothalamic stem cells in middle-aged mice. "This disruption greatly accelerated aging compared with control mice, and those animals with disrupted stem cells died earlier than normal," says Dr. Cai.

The hypothalamic stem cells appear to exert their anti-aging effects by releasing molecules called microRNAs (miRNAs), which play key roles in regulating gene expression. They are packaged inside tiny membranebound vesicles called exosomes, which hypothalamic stem cells release into the cerebrospinal fluid of mice.

Could adding stem cells to the hypothalamus counteract aging? To find out, the researchers extracted miRNA-containing exosomes from hypothalamic stem cells and injected them into the cerebrospinal fluid of two groups of middle-aged mice: those whose hypothalamic stem cells had been destroyed and normal mice. This treatment significantly slowed or even reversed aging in both groups of animals, as measured by tissue analysis and behavior testing.

Efforts are under way to identify the particular populations of miRNAs and perhaps other factors secreted by these stem cells that are responsible for the anti-aging effects—a first step toward possibly slowing the aging process in humans.

Stifling Virulent Viruses

he National Institutes of
Health (NIH) has awarded
Einstein researchers three
grants totaling more than \$12
million to protect against three deadly
viruses—Ebola, Marburg and hantavirus.

A five-year, \$6 million grant will support the development of broadly active monoclonal antibody (mAb) therapies against Ebola viruses. These therapies, which bind to and neutralize specific pathogens and toxins, have emerged as the most promising treatments for Ebola patients. A critical problem, however, is that three types of Ebola virus sicken and kill people, but most mAb therapies being developed are specific to just one

type. Einstein researchers hope to develop one or more broadly neutralizing antibodies that work against all three types of Ebola. The co-principal investigators are Kartik Chandran, Ph.D., professor of microbiology & immunology and the Harold and Muriel Block Faculty Scholar in Virology, and Jonathan Lai, Ph.D., associate professor of biochemistry.

The second grant, for \$2.9 million over four years, will further support Dr. Lai's efforts to develop a broadly neutralizing antibody therapy for Ebola and extend that strategy to Marburg virus, a deadly virus distantly related to Ebola.

Research into how hantaviruses (deadly pathogens transmitted by

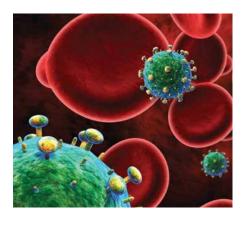
rodents) enter the human body will be supported by the third NIH grant, for \$3.2 million over five years. Hantaviruses cause a highly fatal cardiopulmonary syndrome in the Americas and a less fatal but more prevalent hemorrhagic fever with renal complications in Europe and Asia. Hantavirus infections are not common, but population growth and climate change are predicted to increase the size and frequency of outbreaks in coming decades. There are no approved anti-hantavirus vaccines and no drugs for treating the infections. Dr. Chandran is the principal investigator on the grant.

Focusing on HIV-Related Neurological Problems

hanks to antiretroviral drugs, many fewer HIVinfected people experience frank dementia anymore. Nevertheless, more than half of HIVpositive patients treated with antiretrovirals suffer from milder, lifelong HIV-associated neurocognitive disorders, or HAND, caused when HIVinfected white blood cells cross the blood-brain barrier. Joan W. Berman, Ph.D., professor of pathology and of microbiology & immunology, recently received three NIH grants totaling \$11 million to conduct research aimed at preventing HAND. She also holds the Irving D. Karpas, M.D., Chair for Excellence in Medical Research.

Dr. Berman and Susan Morgello, M.D., of the Icahn School of Medicine at Mount Sinai, received a five-year, \$3.6 million grant to study certain white cells known to be responsible for HAND. They will follow the cells' migration in HIV-positive patients and study the proteins that regulate their transit across the blood-brain barrier.

Dr. Berman and co-principal investigator Harris Goldstein, M.D., will use a five-year, \$3.8 million grant to study interactions among methamphetamines and other drugs of abuse, antiretroviral therapeutics and HIV. Dr. Goldstein is a professor of pediatrics and of microbiology & immunology and directs the Einstein-Rockefeller-CUNY Center for



AIDS Research. Such drugs may weaken the blood-brain barrier, enabling HIVinfected white cells to cross it.

Under a five-year, \$3.8 million grant, Dr. Berman and David Volsky, Ph.D., of the Icahn School of Medicine will study whether buprenorphine—an antiaddiction drug that works by binding to the brain's opioid receptors—can prevent or reduce HAND by binding to the opioid receptors of white cells.

Lab Chat

arle C. Chambers, Ph.D., studies racial and ethnic disparities in chronic diseases such as type 2 diabetes and cardiovascular disease. His research focuses on the link between people's health and their social and physical milieu, including family size, type of housing, income and education level, access to green spaces, neighborhood safety and exposure to noise. Dr. Chambers has been at Einstein since 2007 and is an associate professor of family and social medicine.

What is the main goal of your research?

The behaviors that people adopt and prioritize are crucial for determining their health outcomes. Getting enough exercise, eating "well" and other healthy behaviors depend not just on willpower, but also on whether your environment is conducive to those behaviors. More importantly, in countries including the United States, where racial and ethnic minorities were segregated and relegated to underserved neighborhoods based on racist policies, we must work to undo the damage that living under these conditions has inflicted on segments of our population. My goal is to improve people's environments to maximize their potential for attaining good health—an opportunity that, in my view, everyone in society deserves.

What prompted your interest in this area?

I grew up in Maryland, outside DC, and went to a Jesuit high school, where social justice is part of the education and where I started thinking about using science to advocate for social justice.

What do you like best about Einstein?

I'm in the department of family and social medicine, so I didn't need to sell anyone here on the need to investigate the social determinants of health. That was huge for me.

What's piquing your research interest these days?

Gentrification is in full swing in New York City and is causing many people in low-income neighborhoods to be displaced. I'd like to know how the most vulnerable people of our communities particularly our patients—are affected.

What kinds of books do you read?

The book I'm reading now, Evicted: Poverty and Profit in the American City [by Matthew Desmond], is amazing! It won the Pulitzer Prize for nonfiction but reads like a novel.

Activities outside of work?

I'm an outdoor enthusiast! For the last three years my brother and I have hiked sections of the Appalachian Trail, starting in Shenandoah National Park in Virginia. We just finished a section from Harper's Ferry, VA, into central Pennsylvania—about 60 miles over three days. We'll do another 60-mile stretch next year.

Any other interests?

I've been training in Brazilian jiu-jitsu since moving to New York City 13 years



ago and usually practice two to three times a week. I just received my black belt, which is a big deal. It's an activity I can share with my kids.

Are your other family members into jiu-jitsu?

My wife and I have two boys, ages 10 and eight, who both love soccer. But when I take them with me to jiu-jitsu practice, they'll sometimes humor me by working out with me a bit.

What's your favorite cuisine?

My family is from Jamaica, so that's my go-to cuisine when I have a craving for comfort food. My wife's family is from Vietnam, and there are definitely some Vietnamese dishes that I like a lot. A Vietnamese sandwich called bánh mì is among my favorites. It's delicious!



Einstein received \$174 million in grants from the National Institutes of Health in fiscal year 2017 the highest annual total in the College of Medicine's history.*

* This excludes supplemental stimulus funding distributed as part of the American Recovery and Reinvestment Act of 2009. Several other fiscal year

2017 grants are described on page 12.

Seeking Anti-Aging Therapies

Scientists now believe that the Fountain of Youth flows from our genes, or at least from the genes of people who live healthy lives to age 100 or later. To discover what's special about the genes of these centenarians—and apply that knowledge to extend the healthy lives of the rest of us-the NIH has awarded Einstein and the Scripps Research Institute a five-year, \$9 million grant. Rather than study age-related diseases, researchers will focus on genetic differences between healthy centenarians and people with no family history of extreme longevity, looking for rare genetic variants that account for the centenarians' long lives. After pinpointing beneficial effects caused by these variants, researchers can then develop drugs that mimic those effects. The study's principal investigator is Jan Vijg, Ph.D., professor and chair of genetics and the Lola and Saul Kramer Chair in Molecular Genetics at Einstein.

New AIDS Research Center

The NIH has awarded researchers at Einstein, the Rockefeller University, and the City University of New York Graduate School of Public Health and Health Policy a \$7.5 million grant for the Center for AIDS Research. The new center, known as ERC-CFAR, is one of 19 CFARs nationwide that are funded as part of an NIH-coordinated effort to support multidisciplinary research to reduce the burden of HIV in the United States and abroad. ERC-CFAR brings together more than 150 investigators from the three New York City institutions and is directed by Harris Goldstein, M.D., professor of pediatrics and of microbiology & immunology at Einstein. New York City is considered an epicenter of HIV infection. More than 114,000 New Yorkers are living with HIV/AIDS, which is the third leading cause of death for NYC residents ages 35 to 54.



Detecting a Breast Cancer Precursor

Ductal carcinoma in situ (DCIS) increasingly detected thanks to widespread use of screening mammography—is a precursor of invasive breast cancer (IBC). When untreated DCIS patients are followed for up to 30 years, between 14 and 53 percent of them develop IBC. Einstein researchers have received a five-year, \$6.4 million NIH grant to identify molecular markers that can be used for early detection of those DCIS patients at risk for developing IBC. Such markers might also improve treatment for women found to be at high risk for IBC-by leading, for example, to novel agents that target molecular changes associated with invasive-disease development. The principal investigators are Thomas Rohan, M.B.B.S., Ph.D., D.H.Sc., professor and chair of epidemiology & population health and the Harold and Muriel Block Chair in Epidemiology and Population Health, and Olivier Loudig, Ph.D., of Hackensack University Medical Center.

Gene Networks against Alzheimer's

In an effort to find effective drugs against Alzheimer's, Einstein researchers received a five-year, \$6.3 million NIH grant to identify networks of genes in healthy centenarians that protect them against dementia. Co-principal investigators Nir Barzilai, M.D., and Zhengdong Zhang, Ph.D., will tap into the wealth of genomic data generated from Einstein's two existing longitudinal cohorts on aging, the Longevity Genes Project and the LonGenity research study. The researchers will look for networks of genes in these individuals that may combine to protect against genetic variants that would otherwise cause disease. Finding how these gene networks protect against Alzheimer's may lead to drugs that duplicate their effects. Dr. Barzilai is professor of medicine and of genetics and Rennert Chair in Aging Research at Einstein and attending physician in endocrinology, diabetes & metabolism at Montefiore. Dr. Zhang is an associate professor of genetics.

Fighting Alzheimer's with Diet

Inflammation overactivates the immune system and contributes to various diseases, including diabetes, cancer and Alzheimer's disease. Research suggests that the "Western diet"—high in fat, sugar and processed foods—may promote inflammation. The NIH has awarded Einstein nutrition scientist Yasmin Mossavar-Rahmani, Ph.D., R.D., associate professor of epidemiology & population health, a five-year, \$4 million grant to see if a diet rich in foods with anti-inflammatory properties can reduce cognitive decline and risk for developing Alzheimer's. More than 300 Bronx residents ages 40 to 65 will be divided into two groups; half will follow the anti-inflammatory diet, the other half their regular diet. Researchers will periodically assess participants' cognitive function during the 27-month study. The anti-inflammatory diet will include whole grains, fish, lentils, nuts, beans, herbs and spices and was designed to appeal to a multicultural population.

MAJOR NIH RESEARCH AWARDS



RESEARCH NOTES





Marijuana vs. Opioids for **Chronic Pain**

The NIH has awarded researchers at Albert Einstein College of Medicine and Montefiore Health System a fiveyear, \$3.8 million grant to conduct the first long-term trial assessing whether medical marijuana reduces opioid use among adults with chronic pain, including those who are infected with HIV. Chronic pain and resulting opioid use are common among people who have HIV. Given the dangers of opioid use and misuse, both doctors and patients are seeking safe and effective alternatives. The researchers will enroll 250 HIV-positive and HIV-negative adults with chronic pain who use opioids and who have received certification from their physicians to use medical marijuana. The principal investigator on the grant is Chinazo Cunningham, M.D., M.S., associate chief of general internal medicine in the department of medicine at Einstein and Montefiore.

Better Cognitive-Impairment Detection

Cognitive impairment related to dementia is underdiagnosed, even though tests are available for assessing it. The missed diagnoses—especially common among African Americans and Hispanics—cause delays in providing vital support services. Now, the NIH has awarded Joe Verghese, M.B.B.S., a five-year, \$3.8 million grant to develop and validate a low-cost, five-minute cognitive screening test that can be readily administered by nonclinicians after minimal training. The test will be accompanied by a decision tree aimed at helping providers identify and care for multi-ethnic primary care populations at high risk for developing dementia. It will be assessed at Montefiore primary care clinics. Dr. Verghese is a professor in the Saul R. Korey Department of Neurology, the Murray D. Gross Memorial Faculty Scholar in Gerontology and director of the Montefiore Einstein Center for the Aging Brain.

Roundworms and Alzheimer's

Humans aren't the only organisms faced with age-related declines in thinking ability and memory. The same problems afflict the roundworm C. elegans. The NIH has awarded Einstein scientists a five-year, \$3.7 million grant to seek new Alzheimer's treatments by combining roundworm and human research. Using tools for studying memory in worms and identifying gene-expression changes in worm neurons, the researchers will identify genes that change with age and are risk factors for Alzheimer's. They'll combine those results with findings from human genome-wide association studies, which indicate that changes in gene regulation cause cases of heightened genetic risk for Alzheimer's. This approach will identify gene regulatory networks shared by humans and worms and may provide new targets for Alzheimer's drugs. The co-principal investigators are Yousin Suh, Ph.D., professor of genetics at Einstein, and Coleen Murphy, Ph.D., of Princeton University.



Mapping a Viral Infection Highway

Herpes simplex virus 1 (HSV-1), the virus responsible for oral herpes, infects about half the world's population. HSV-1 infects neurons of cranial nerves, traveling up their axons to multiply in their nerve bodies. Newly made HSV-1 then travels back down the axon to be released into the synapse. HSV-1 is thought to hijack the cell's microtubule network to travel back and forth in the axon, but how it does so is unclear. The National Institute of Allergy and Infectious Diseases has awarded Duncan W. Wilson, Ph.D., a five-year, \$3.5 million grant to study UL36p, an HSV-1 protein that appears to attach the virus to microtubules via the motor proteins kinesin and dynein. He will explore how UL36p helps HSV-1 move through axons during infection. Dr. Wilson is a professor of developmental and molecular biology. E



MORE ONLINE:

For information about additional major NIH grants and other research news, visit: www.einstein.yu.edu/research

TENURE FOR **NINE EINSTEIN PROFESSORS**

Hannes Buelow, Ph.D.

professor of genetics and in the Dominick P. Purpura Department of Neuroscience

Kartik Chandran, Ph.D.

professor of microbiology & immunology

Antonio Di Cristofano, Ph.D.

professor of developmental and molecular biology

Ganjam Kalpana, Ph.D.

professor of microbiology & immunology and of genetics

José Peña, M.D., Ph.D.

professor in the Dominick P. Purpura Department of Neuroscience

Michael J. Ross, M.D.

chief of the division of nephrology and professor of developmental and molecular biology

Ulrich Steidl, M.D., Ph.D.

professor of cell biology and of medicine

Yousin Suh, Ph.D.

professor of genetics, of ophthalmology and visual sciences and of medicine

Bin Zhou, M.D, Ph.D.

professor of genetics, of pediatrics and of medicine



OVERCOMING SICKLE-CELL DISEASE BY GARY GOLDENBERG

Einstein-Montefiore scientists seek better treatments for a debilitating blood disorder

n 2006, when Lindsy Osouna was on the cusp of her third trimester, prenatal testing showed that her daughter would be born with sickle-cell disease (SCD).

"It was devastating," she says, "but we decided that we have to face this." After an intensive search, she and her husband, Kwasi, decided to entrust daughter Aniyah's care to the SCD specialists at Children's Hospital at Montefiore (CHAM), who collaborate with Einstein's SCD researchers. These experts are focused on gaining insight into SCD and developing new therapies to transform the way the disease is treated.





Today, Aniyah is a charming and vivacious 11-year-old, healthy enough to attend school and even participate in gym class. But as with virtually all kids with SCD, her childhood has been far from easy, despite significant improvements in the care of children with the disease over the past few decades.

Kids with SCD now receive penicillin as standard treatment to prevent blood infections, a common and potentially fatal complication. Repeated blood transfusions can help keep anemia in check. And the drug hydroxyurea reduces the frequency of debilitating pain crises. As a result, the vast majority of children with SCD survive into their 40s—a significant improvement compared with the life spans of children born with SCD just a generation ago. But more advances are needed.

"For kids born with SCD, a minor cold or infection can turn into a major health crisis, and a case of the flu can be deadly," says Henny Billett, M.D., professor of medicine and of pathology at Einstein and chief of the division of hematology at Einstein and Montefiore. "We've clearly got work to do to prevent these crises and to further extend the lives of SCD patients."

Aniyah's first crisis occurred when she was two and began gasping for breath. The Osounas rushed her from their home in Queens to CHAM, where they learned that her lungs were filling with fluid and verging on collapse due to acute chest syndrome, a potentially fatal pneumonia-like condition.

Her health stabilized after nine days, thanks to expert care from CHAM doctors and nurses—the type of care that should be available to all SCD patients but all too often is not. (See "Efforts to Increase Access," page 23.)

Deepa Manwani, M.B.B.S., with Lindsy Osouna and her children, Aniyah and Tristan.

Aniyah would experience the same emergency just a year later. Over the ensuing years came headaches, stomach cramps, gallstones, fevers, painfully swollen joints, an enlarged liver and early signs of retinal disease. In her short life, Aniyah has faced more health issues than many a frail octogenarian.

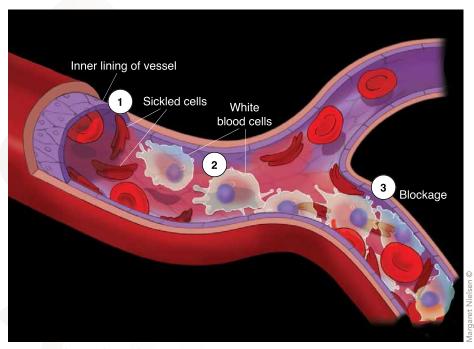
The sickle-cell center at CHAM is helping Aniyah and some 650 other children and adolescents with SCD overcome such challenges. It focuses on offering the best evidence-based treatments, recognizing preventable complications as early as possible, providing support for affected families and teaching its young patients how to manage their disease.

SICKLE-CELL DISEASE **EXPLAINED**

Sickle-cell disease is a debilitating condition that affects approximately 100,000 Americans and occurs in about one in 365 African American births. The disease affects millions of people throughout the world, particularly those with ancestors from sub-Saharan Africa and Spanish-speaking regions of the Western Hemisphere (South America, the Caribbean and Central America).

People with SCD typically have inherited two mutated copies of the gene that codes for the beta subunit of hemoglobin, the protein in red blood cells that acquires oxygen from the lungs and carries it to tissues throughout the body. As a result, their hemoglobin differs by a single amino acid from "normal" hemoglobin. Individuals with a single errant copy of the gene carry the sickle-cell trait but do not develop SCD.

Blood cells normally are disc shaped, like a doughnut without a hole, which provides flexibility to the cells as they glide through blood vessels large and small. But in SCD, abnormal hemoglobin molecules aggregate to form filaments that distort red cells into their characteristic sickle shape.



How vessels get clogged in SCD: Sickled cells irritate and inflame a blood vessel's inner lining (1), which responds by producing cell-surface receptors called E-selectins that entrap white cells (2). Trapped white cells express activated Mac-1 adhesion molecules that bind sickled red cells, culminating in white cell/red cell clumps that hinder blood flow (3).

"THERE IS A DIRE **NEED FOR NEW** THERAPIES FOR SICKLE-CELL CRISES."



Sickled red cells are fragile and often burst, leading to anemia that reduces oxygen delivery to tissues. Even more important, their distorted shape makes the sickled cells sticky, causing vasoocclusion—the clogging of small blood vessels that impairs oxygen delivery. Indeed, SCD is primarily a disease of oxygen starvation.

A chronic lack of oxygen causes organ damage that contributes to shorter life spans. Starting in early childhood, for example, SCD patients face a high risk of stroke due to faulty blood flow in the brain. (See "Silence of the Strokes," page 30.) But long before such problems occur, oxygen deficits caused by SCD can cause excruciating pain.

NO STRANGER TO PAIN

"I get a lot of headaches and stomach pain," says Aniyah matter-of-factly. "Sometimes my left arm hurts a little bit when I bend it." If she is like most other SCD patients, the pain from too little oxygen nourishing her tissues is much worse than Aniyah lets on.

The scientific term for a painful redcell clogging episode is a "vaso-occlusive crisis," more commonly known as a

sickle-cell crisis. It's characterized by pain in the limbs, chest, stomach or lower back that can last from hours to weeks. Sickle-cell crises are the main reason that SCD patients require hospitalization. And over time, the crises contribute to the tissue and organ damage that impair quality of life and increase the risk of death for patients.

Patients experiencing sickle-cell crises must make do with supportive measures such as over-the-counter pain medications, heat compresses or massage, with a significant number of patients turning to potent painkillers such as opioids, putting them at risk for addiction. Pain that becomes chronic, as it often does in adulthood, is even harder to treat.

"There's a dire need for new therapies for sickle-cell crises," says Deepa Manwani, M.B.B.S., who is Aniyah's physician as well as a professor of pediatrics at Einstein and the director of pediatric hematology at CHAM. The program's research arm is aimed at developing such therapies. One is a promising treatment for sickle-cell pain from the work of Einstein scientist Paul Frenette, M.D., professor of medicine and of cell biology and director of the Gottesman Institute for Stem Cell and Regenerative Medicine Research. Unlike opioid therapy used to dull pain, this approach instead blocks the underlying cause, which is vaso-occlusion.

In a 2002 PNAS paper, Dr. Frenette showed that sickled cells sticking to white cells and white cells sticking to the lining of blood vessels play a key role in vaso-occlusion. The process starts when sickled cells irritate and inflame the inner wall, or endothelial lining, of blood vessels, stimulating endothelial cells to produce cell-surface receptors called E-selectins. They entrap white cells, which in turn express adhesion molecules called activated Mac-1 that bind sickled red cells. The result: white cell/red cell clumps that cling to the

lining of vessels and hinder blood flow (see illustration on the facing page).

To identify the specific adhesion molecules that cause cell clumping, Dr. Frenette added antibodies to blood to inactivate adhesion molecules one at a time and observe if vaso-occlusion occurred. Then he made an unexpected discovery: Unrelated antibodies he'd added for comparison purposes were preventing vaso-occlusion from occurring—suggesting that a widely available product rich in antibodies might help relieve sickle-cell crises.

The product, intravenous immunoglobulin (IVIG), is used to treat autoimmune diseases and has antiinflammatory effects. Dr. Frenette's research group gave IVIG to an SCD mouse model experiencing potentially fatal sickle-cell crises. A 2004 paper in Blood reported that IVIG dramatically inhibited interactions between red and white cells, increased microcirculatory blood flow and extended animals' lives.

A phase 1 IVIG clinical trial directed by Dr. Manwani was completed in 2013. Children and adults admitted to CHAM and Mount Sinai for acute-pain crises were infused with varying doses of IVIG or a placebo solution. The trial yielded an IVIG dose that seemed well tolerated and effectively reduced activated Mac-1 adhesion molecules on white cells, making the cells less sticky.

In 2015, the National Institutes of Health (NIH) awarded Drs. Manwani, Frenette and colleagues a \$1.6 million grant to conduct a phase 2 clinical trial assessing IVIG for treating sickle-cell patients eight to 21 years old admitted to CHAM with sickle-cell crises. The trial is assessing how well and how rapidly IVIG resolves pain crises and whether it helps reduce opioid use and the length of hospitalization.

Dr. Frenette's cell-adhesion findings contributed to another promising therapy for SCD crises. In the 2002

EFFORTS TO INCREASE ACCESS

"Outside New York City and other major metropolitan areas, experts in sickle cell are hard to find," says Suzette Oyeku, M.D., M.P.H., associate professor of pediatrics at Einstein and chief of the division of academic general pediatrics at CHAM. "Many primary care providers have never even seen a child with SCD. This is a travesty. Access to proper care shouldn't be limited by your zip code." Dr. Oyeku recently participated in the Hemoglobinopathy Learning Collaborative, a group of 15 institutions around the country that was formed to reduce disparities in SCD care. The collaborative is part of the Sickle Cell Disease Treatment Demonstration Program, funded by the federal Health Resources and Services Administration. "Clinical trials tell us what therapies are effective," she says. "Our collaborative shows healthcare practitioners how they can implement these therapies in real-world settings."

As an example, Dr. Oyeku cites the underused drug hydroxyurea, which, among other things, reduces the number of pain crises experienced by SCD patients. It works by reactivating the body's production of fetal hemoglobin, which has an even higher affinity for oxygen than normal hemoglobin does. "But we've learned that many patients don't take hydroxyurea because of misconceptions about the risks and benefits or because it wasn't even offered to them," she says. "In response, we've developed decision-making tools that encourage families and providers to have conversations about hydroxyurea. This approach, along with other strategies, has increased the proportion of patients who are taking the drug." Other collaborative efforts include encouraging the use of telemedicine to bring hematology expertise to the hinterlands and developing expedited treatment protocols in emergency rooms to reduce the time that SCD patients must wait for pain relief.



PNAS study cited above, Dr. Frenette used a mouse model of SCD to show that P-selectin (a cell-adhesion molecule on endothelial cells) promotes vessel clogging by binding to white blood cells. Moreover, disrupting the expression of P-selectin on endothelial cells prevented binding from occurring and also prevented lethal vaso-occlusion.

Earlier this year, the New England Journal of Medicine published results of a multicenter, double-blind, placebocontrolled phase 2 trial in which 198 SCD patients received periodic infusions (14 per year) of a monoclonal antibody that neutralizes P-selectin. The treatment significantly reduced the number of pain crises compared with those reported by patients taking a placebo. Dr. Billett led the Montefiore portion of the study. A phase 3 clinical trial assessing anti-P-selectin antibodies (and again involving SCD patients cared for at Montefiore) is now under way.

In other sickle-cell adhesion work, Dr. Manwani is collaborating with Case Western Reserve University engineers to develop a way to measure the "stickiness" of red and white cells. "Our hypothesis is that acute vaso-occlusive pain is different from other types of pain commonly seen in SCD, such as neuropathy [nerve pain] and chronic pain," explains Dr. Manwani. "If so, a marker for blood-cell adhesion would help us identify which patients would benefit from IVIG and other novel therapies, and perhaps allow us to predict and even prevent pain crises." The researchers on this project are studying pediatric SCD patients being treated at Einstein-Montefiore.

THE MICROBIOME AND SICKLE-CELL DISEASE

Another Einstein-CHAM collaboration involves the surprising connection between the gut microbiome and the risk for a sickle-cell crisis.

Early in his career, Dr. Frenette discovered that vessel blockages in SCD occur when sickled red cells bind to white cells called neutrophils that have adhered to the vessel walls. He also noted that not all neutrophils were the same; some seemed inert, while others actively promoted inflammation which is useful for attacking microbes but causes neutrophils to capture sickled red cells inside vessels.

In a 2015 paper in Nature, Dr. Frenette's group reported that neutrophils become more pro-inflammatory as they age, in response to signals from the gut's microbiome—the diverse populations of microorganisms in the intestines. Chemicals produced by the microbiome cross the intestinal barrier and enter the bloodstream, where they generate the old, overly active neutrophils that contribute to SCD crises.

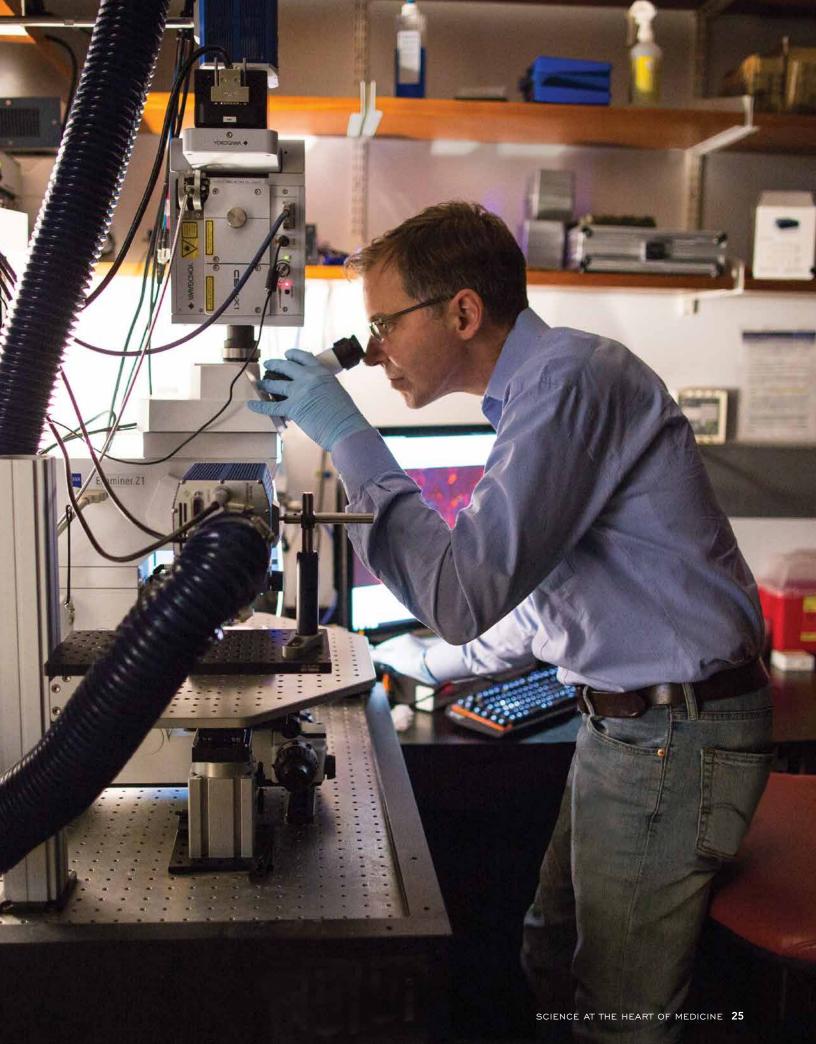
"Since the body's microbiota seems to 'educate' neutrophils to age," says Dr. Frenette, "we realized that purging those microbes with antibiotics might help against SCD." As it turned out, administering antibiotics to SCD mice did appear to prevent sickle-cell crises; it markedly reduced interactions between neutrophils and red cells, resulting in increased blood flow and greatly improved survival of the mice.

"What was most exciting to us was the antibiotics' beneficial effects on chronic tissue damage," says Dr. Frenette. "Spleen enlargement in SCD mice was significantly reduced in the microbiota-depleted animals, and we also saw major reductions in liver damage. This is the first time that any drug therapy has been found to have an impact on the organ damage that can be so devastating in SCD."

Were the findings in mice relevant to people? To find out, Drs. Frenette and Manwani obtained blood samples from SCD children being treated at CHAM and found that children taking "THIS IS THE FIRST TIME THAT ANY DRUG THERAPY HAS BEEN **FOUND TO HAVE** AN IMPACT ON THE ORGAN DAMAGE THAT CAN BE SO **DEVASTATING IN SCD.**"







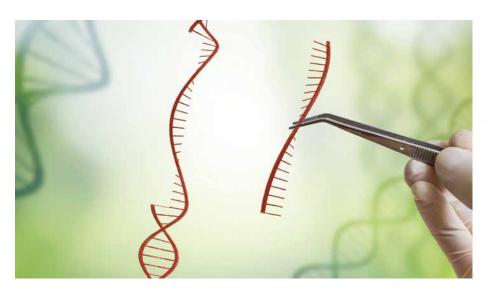
penicillin had significantly fewer aged neutrophils than those not taking the antibiotic. "Daily penicillin for patients with SCD younger than five works really well in preventing infections," says Dr. Frenette. "Our study suggests that antibiotics could potentially play an even broader role in benefiting older patients."

Drs. Frenette and Manwani are planning a clinical trial to see if antibiotics can help SCD patients by preventing vaso-occlusive crises and the related long-term organ damage that shortens the lives of patients. Dr. Frenette is also working to identify

Umbilical cord blood is rich in blood-forming, or hematopoietic, stem cells. Transplanting those stem cells into someone with SCD can provide a healthy blood supply, if the recipient's marrow is first wiped out with chemotherapy. Such transplants are the only cure for SCD but are used sparingly because recipients and their donors typically siblings—usually must have closely matching blood antigens, and risks for fatal complications are high.

Unfortunately, prenatal testing revealed that their new baby would also have SCD. "It was a big blow," says Lindsy. "But again, we decided that we





CRISPR CAN CUT OUT UNDESIRABLE GENES, OR SPECIFIC DNA **SEQUENCES WITHIN GENES, AND SPLICE** IN "NORMAL" DNA-**MAKING IT IDEALLY** SUITED FOR SICKLE-**CELL DISEASE**

which gut microbiome bacteria in particular are responsible for driving neutrophils to age.

LIGHTNING STRIKES TWICE

When two SCD "carriers" like Lindsy and her husband Kwasi conceive, they have a three in four chance of having a baby free of the disease. The Osounas were counting on these odds when they decided to have a second child. "We also thought that if we had a healthy baby, we could bank the child's cord blood and have a cure for Aniyah," says Lindsy, referring to a stem-cell transplant.

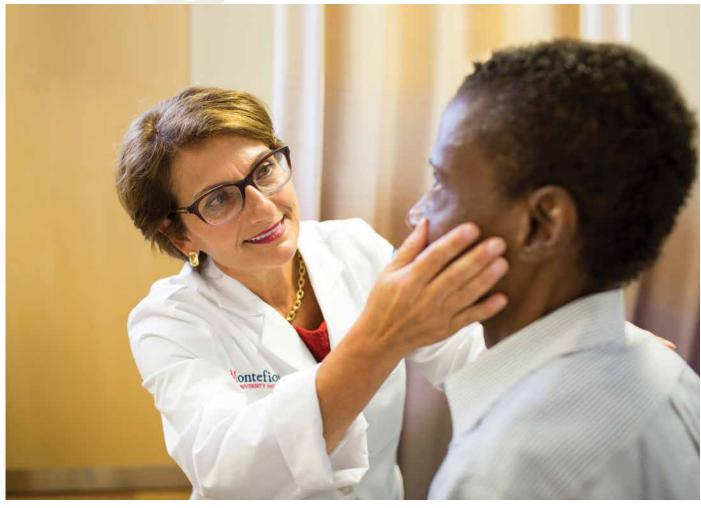
could deal with this." The Osounas are not unusual in this regard. "Maybe 10 percent of parents will opt to terminate an SCD pregnancy based on genetic testing," says Dr. Manwani. "It's a very personal decision, guided by complex social and spiritual beliefs."

Although Tristan, now six, has had fewer health problems than his sister, he struggles with severe asthma. "I'm sorry he's not well," says his mom, "but I'm happy he's here."

The Osounas take their children regularly to the CHAM sickle-cell center, despite the long drive from Queens. The family had considered moving

Ken Chen, Ph.D. (left), and Marc Vargas, B.S., use the CRISPR gene-editing technique in Einstein's Transgenic Mouse Facility.





Caterina Minniti, M.D., with a patient, Joseph Peay.

DEPENDING ON THE PERCENTAGE OF NORMAL BLOOD CELLS PRODUCED, CRISPR **COULD REDUCE A** PATIENT'S SYMPTOMS OR EVEN PROVIDE A CURE.



to Nassau County, but didn't want to change doctors. "I'm not sure I want to move farther away from CHAM," says Lindsy. "It's like a family there."

Doctors are hoping that a stem-cell transplant may still be an option for both Aniyah and Tristan, even without a healthy sibling who can serve as a donor. CHAM's bone marrow transplant program—one of the country's largest—provides "haplo-identical" transplants that use partially matched family members (usually the mothers or fathers) as donors. Such transplants do involve serious risks, including infection and graft-versus-host disease. But they make cures at least theoretically possible for the majority of SCD patients.

Scientists recently developed a gene-editing technology called CRISPR that may offer a safer and more reliable

SCD cure. CRISPR can cut out undesirable genes, or specific DNA sequences within genes, and splice in "normal" DNA—making it ideally suited for SCD, which results from a mutation involving a single nucleotide. Researchers have already used CRISPR to correct SCD mutations in animal models of the disease. A grant awarded to a Montefiore clinician and an Einstein basic scientist may bring CRISPR for SCD patients closer to reality.

Caterina Minniti, M.D., professor of medicine and of pediatrics at Einstein and director of the Sickle-Cell Center for Adults at Montefiore, and Eric Bouhassira, Ph.D., professor of cell biology and of medicine and the Ingeborg and Ira Leon Rennert Professor of Stem Cell Biology and Regenerative Medicine, received a \$1 million grant

from the Doris Duke Foundation's Sickle Cell Disease/Advancing Cures program. Using blood and bone marrow samples from SCD patients, they'll work to perfect CRISPR for editing the mutated hemoglobin gene in hematopoietic (blood-forming) stem cells. The ultimate goal: harvest an SCD patient's hematopoietic stem cells, correct the defective hemoglobin gene and reinfuse the blood-producing cells into the patient. Depending on the percentage of normal blood cells produced, the procedure could reduce a patient's symptoms or even provide a cure.

THE STARK TRANSITION TO ADULTHOOD

In caring for children who have SCD, the Osounas seek a healthy middle ground between helicopter and latchkey parenting. "We try to stress the importance of getting rest, staying hydrated, eating properly and taking their meds," says Lindsy. As if on cue, Aniyah runs to the kitchen to retrieve her weekly pill organizer for an impromptu show-and-tell.

"We imagine there will be rough times ahead," says their mom. "But we hope we've laid the foundation so that they will be able to take care of themselves later in life."

When they turn 18, SCD patients "age out" of the nurturing world of pediatric care and must deal with the disease on their own. "For many young adults, it's the first time they've had to make their own doctors' appointments, and they have to get used to a whole new team of doctors and nurses," says Dr. Minniti. "It's a perilous time, when emergency room visits, hospital admissions and readmissions and even mortality rates increase greatly."

Adult SCD patients may actually fare worse now than in the past. In a study published in 2013 in *Public Health Reports*, researchers used National

HEALTHCARE DISPARITY BY THE NUMBERS

SICKLE-CELL DISEASE

CYSTIC FIBROSIS

NUMBER OF AMERICANS AFFECTED





BABIES WITH CONDITION



One in every 365
African American babies



One in every 3,200 Caucasian American babies

NIH RESEARCH SUPPORT*



\$75 MILLION



FOUNDATION SUPPORT*

(Sickle Cell Disease Association of America, Inc. and Cystic Fibrosis Foundation)





NIH PLUS FOUNDATION SUPPORT PER PERSON WITH DISEASE

\$768



LIFETIME HEALTHCARE COSTS PER PERSON WITH DISEASE



\$8.75 MILLION

Assuming 50-year life expectancy

* Numbers apply to 2015



\$638,000

Assuming 47-year life expectancy

Center for Health Statistics data to calculate SCD mortality rates (deaths per 100,000 African Americans) between 1979 and 2005. As expected, the mortality rate for children with SCD declined significantly over that time interval. But for adult SCD patients 19 and older, the mortality rate increased by one percent each year from 1979 to 2005. The authors, led by Einstein alum Sophie Lanzkron, M.D., '91, M.H.S., attributed that rising mortality rate to "the lack of comprehensive care for adults with SCD."

CARE OVER THE LIFE SPAN

At Montefiore, Dr. Minniti is working to eliminate the artificial transition from pediatric to adult care. "I'm a proponent of life-span care, with one group of physicians caring for patients throughout their lives," she says. She worries that adult SCD patients in many parts of the country receive only episodic care, usually prompted by a sickle-cell crisis—a far cry from the care available to children.

"Visit pediatric clinics with their happy kids and then see how much worse the care is for adults with SCD,"



SILENCE OF THE STROKES

trokes—both silent and overt—are extremely common among SCD patients, affecting between 25 and 40 percent of them. But why are SCD patients so susceptible to strokes?

Over the past four years Craig Branch, Ph.D., associate professor of radiology and of physiology & biophysics and director of the Gruss Magnetic Resonance Research Center at Einstein, has sought the answer through in-depth research on the biological mechanisms that underlie strokes in SCD. He is one of the only researchers to have used animal models of SCD

SCD-associated strokes are assumed to result from sickled cells clogging brain arteries and restricting blood flow, as occurs elsewhere in the body. But by studying mouse models of SCD, Dr. Branch found that brain blood flow associated with SCD strokes is actually unusually high—a finding recently confirmed in SCD patients studied in his laboratory and in others. Dr. Branch attributes this high blood-flow rate in the SCD brain to anemia and oxidative stress. But he has also observed a related alteration in brain metabolism never before seen, possibly in response to mild but chronic oxygen deficits in the brain.

"In SCD, the brain may be changing the way it manages its energy needs to reduce the likelihood of a major hypoxic event [a sudden loss of oxygen]," says Dr. Branch. "This compensation may unfortunately lead to increased blood flow in the brain, along with inflammation and a reduction in the brain's ability to

respond to conditions requiring increased oxygen—a combination that raises the risk of stroke."

Today, physicians caring for SCD patients regularly assess their stroke risk by measuring blood-flow rate in the carotid artery; if the flow rate is abnormally high, they consider giving blood transfusions or treatment with hydroxyurea to increase the amount of oxygen reaching the brain. But confirmation of Dr. Branch's studies could lead to other treatments—to reduce oxidative stress or improve oxygen delivery—that might ward off strokes among SCD patients.

Studies by Dr. Branch and Dr. Billett suggest that many SCD patients are experiencing silent, or subclinical, strokes that cause no obvious signs or symptoms. But silent does not mean harmless. "When we examine these SCD patients more closely," he says, "we see clear evidence of cognitive deficits and brain pathology even though they've never been diagnosed as having stroke. Some of these findings may also be due to impaired metabolic brain processes."

In a paper now under review for publication, Drs. Branch and Billett and a former Einstein medical student, Nicholas Farris, M.D., recruited adult sickle-cell patients who had no known history of stroke and an equivalent cohort of control individuals. All subjects underwent MRI brain scans as well as cognitive tests. The testing revealed that eight of 15 SCD patients had evidence of possible silent strokes and that all 15 SCD patients had significantly elevated brain blood flow and inflammation compared with the control subjects.



says Dr. Minitti. "I encourage every pediatric hematologist to go to hospitals in their area to see what happens when their beautiful young patients become adults."

When crises send SCD adult patients to the emergency room, "the focus is mainly on pain relief," says Dr. Minniti. "But the pain, as bad as it may be, isn't going to kill the patient. He is going to die because his kidneys are crashing or his heart is failing. Adult care must be multidisciplinary, because SCD causes complications that can damage all areas of the body, from the brain to the heart to the kidneys to the extremities."

One of her own research interests is finding treatments for leg ulcers-painful and often disabling complications of SCD that affect 5 to 10 percent of all SCD patients and often take months or even years to heal. In July, the U.S. Food and Drug Administration awarded her a four-year, \$1.9 million grant to carry out a phase 2 trial of a promising sodium-nitrite cream for treating leg ulcers in SCD patients.

In earlier work at the NIH, Dr. Minniti carried out a phase 1 trial of sodium-nitrite cream that found it was safe and well tolerated, and significantly reduced ulcer size and pain in the small number of patients treated. Applying the cream to the wound converts sodium nitrite into nitric oxide gas, which dilates vessels by relaxing their smooth muscle cells. This aids healing by increasing the amount of oxygenated blood that reaches the wound.

"We hope our phase 2 trial will confirm the promising results of our phase 1 study," says Dr. Minniti. "No approved treatments for leg ulcers in SCD are available, and many patients with leg ulcers must now rely on chronic use of opioid drugs to relieve the excruciating pain that ulcers can cause."

SCD-related problems tend to multiply and worsen with age. For example, years of working overtime to oxygenate the blood cause heart muscles to weaken and stiffen, setting the stage for heart failure and arrhythmias. Other chronic stresses compromise the joints, lungs, kidneys, gallbladder, spleen and brain.

"In treating SCD, we see all of the usual diseases of aging decades before they typically appear," says Dr. Minniti. "Unfortunately, there's only so much we can offer those patients. It's hard to believe, more than a century after the disease was first characterized, that we have just two FDA-approved drugs. (Hydroxyurea and L-glutamine [approved in July 2017] both reduce the frequency of pain crises and the number of hospital visits needed to treat them.) In contrast, we have perhaps 25 drugs for HIV and 15 for cystic fibrosis."

Nevertheless, Dr. Minniti is optimistic that things are heading in the right direction. "A number of drugs are now in clinical testing, including several at Einstein-Montefiore," she says. "I think that in a few years we'll have several therapeutic options. Then, perhaps, we'll be able to move to the sort of combination therapy that transformed HIV from a deadly illness to a chronic one. If we can develop a cocktail of drugs that attack the different pathways leading to sickling, adhesion and vaso-occlusionand if we can implement therapy early in life, before organ damage occurs—we will be able to extend and improve the lives of adults with sickle-cell disease."

Tristan Osouna has high hopes that Dr. Minniti is correct. In a recent school assignment, he wrote: "The one thing in the world I would change is sickle-cell disease. I would change it by donating money to help hospitals get a cure. I have sickle-cell disease and I wish it would go away."

Researchers at Montefiore and Einstein hope to make Tristan's wish come true.

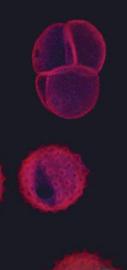
"IT'S HARD TO BELIEVE. MORE THAN A **CENTURY AFTER THE DISEASE WAS FIRST** CHARACTERIZED, THAT WE HAVE JUST TWO FDA-APPROVED **DRUGS.**"

PASSIONATE PURSUITS

HILLARY GUZIK:

Picturing Worlds, Inside and Out





Above: Pollen grains, as seen through a confocal microscope.

Upper right: "Small world" photo of high-rise buildings on Brooklyn's waterfront.

illary Guzik grew up in Syracuse, NY, loving photography and science the reason her early photos tended to exclude friends and family and instead featured insects, strands of human hair and even playground jungle gyms. "I've always liked things with repetitive patterns in them," she explains.

A research technician in Einstein's Analytical Imaging Facility (AIF), Ms. Guzik earned a B.S. degree in biomedical photographic communications from the Rochester Institute of Technology. "When I found that major at RIT," she says, "it was

like, 'That's what I'm going to do for the rest of my life!" She learned theoretical and practical microscopy applications—everything from sample preparation to imaging

acquisition to creating scientific posters. "So when I came here in 2009," she adds, "I had many of the skills I needed."

One of Ms. Guzik's tasks in the AIF

involves teaching people at Einstein how to use light microscopes, including epi-fluorescence, super-resolution, brightfield and confocal models the latter a specialized type of light microscope that uses lasers to scan across specimens to form images. She and her AIF colleagues also offer image analysis—for example, quantifying fluorescent intensities to see whether certain tumor-cell proteins are over- or underexpressed.

"Most of the work in the AIF is medically oriented," explains Ms. Guzik. "Researchers might use the facility to compare breast cancer treatments by viewing tumor cells that have been exposed to different therapies. Or researchers studying multiple sclerosis might assess various drugs to see if they help grow or regrow axons in nerves."

Ms. Guzik particularly likes applying her Photoshop skills to color scanning and transmission electron microscope images, both those she takes herself and those on which she collaborates. In 2014, her work colorizing originally black-and-white images garnered kudos

when she partnered with postdoctoral fellow Sabriya Stukes. They won first prize in the annual BioArt photography contest held by the Federation of American Societies for Experimental Biology to showcase "the beauty and excitement of biological research." Their vibrant image (at right) depicts a tugof-war between a fungal cell and two macrophages in a mouse.

"When I'm coloring these images, there are not many rules," she says. "A cell's nucleus is generally colored blue, but I basically use whatever colors I like!"

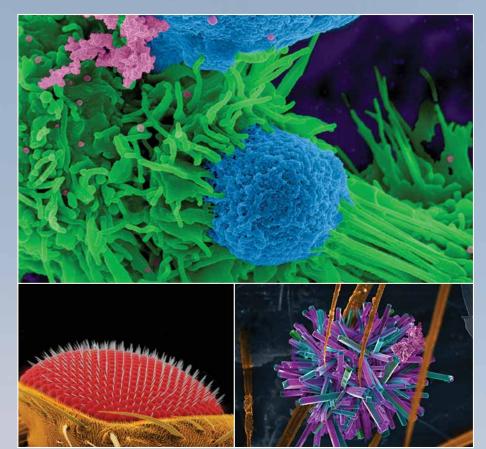
SMALL-WORLD PHOTOS

When not at work, Ms. Guzik likes being outdoors, hiking or rock climbing with her husband, Paul Jung-and still thinking in pictures. She especially enjoys creating 360-degree panoramic views of landscapes, towns and other scenes that she calls "small worlds." Rather than lugging around a tripod, she simply takes her Nikon digital camera to a location and, standing in a central spot, turns slowly while taking 20 to 40 photos, being careful to overlap the images. She then uses Photoshop to "stitch" the images together and connect the left and right ends. "Technically," she says, "it's pretty easy to do, but finding the perfect spot is tough."

Harking back to her early interest in insects, Ms. Guzik has a master's degree in entomology from the University of Nebraska. Many insects are vectors for disease, and she'd like to study mosquitoes that transmit viral diseases such as West Nile, Zika and yellow fever.

Clockwise, above: Award-winning photo of macrophages; debris on a termite setae; up-close view of a *Drosophila* eye.

At right: "Small world" photo of a state fair amusement park.







GOIG VIRAL

NEW INSIGHTS INTO NATURE'S TINIEST KILLERS

GOLDENBERG

he British biologist Sir Peter Medawar described a virus as "a piece of bad news wrapped in protein." There's surely not much good to say about these strange, neither-living-nor-dead particles, which multiply with abandon after infecting cells and often sicken or kill their hosts, be they bacteria, plants or mammals.

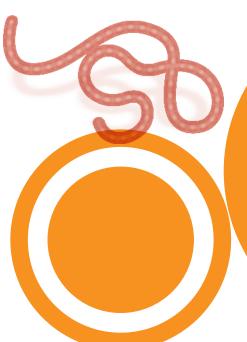
Throughout history, viruses have profoundly affected human health—the smallpox epidemic of the 1600s devastated Native Americans, the "Spanish flu" of 1918 sickened or killed one-third of the world's population, the HIV epidemic of the late 20th century killed some 35 million. Today, HIV and many other viruses still exact a deadly toll.

Einstein has long maintained research programs aimed at developing vaccines, treatments and cures for viral diseases, with emphasis on viruses that affect people in the developing world. This article describes the latest Einstein research into herpes simplex, chikungunya, Ebola and dengue, which together affect hundreds of millions of people worldwide.

OUTMANEUVERING EBOLA

Few viruses provoke more dread than Ebola, which causes Ebola hemorrhagic fever. The first documented outbreak occurred in 1976 and affected villages along the Ebola River in Africa—hence the virus's name. Three of the five known Ebola virus strains (Zaire, Sudan and Bundibugyo) have caused major outbreaks in humans, and the other two (Reston and Tai Forest) cause severe disease in nonhuman primates. During the 2013–16 West African Ebola outbreak, hemorrhagic fever caused by Ebola Zaire killed 11,000 people and gravely sickened another 29,000.

The Holy Grail of Ebola research is a treatment for all three strains that affect humans. "It's impossible to predict which of the strains will cause the next epidemic, so we need to develop a single therapy that could treat or prevent infection caused by any known Ebola virus," says Kartik Chandran, Ph.D., professor of microbiology & immunology and the Harold and Muriel Block Faculty Scholar in Virology, who leads Einstein's Ebola research effort.



Ebola researchers Kartik Chandran, Ph.D., and Jonathan Lai, Ph.D.

THE VIRUSES MUST **BREAK OUT OF** THEIR LYSOSOMAL "PRISONS" SO THEY **CAN MULTIPLY.**



In two papers over eight months, Dr. Chandran, his Einstein colleague associate professor of biochemistry Jonathan Lai, Ph.D., and other researchers described two quite different approaches for developing a single therapy against all Ebola virus strains.

USING NATURAL ANTIBODIES

After analyzing the blood of a survivor of the 2013-16 Ebola outbreak, scientists from academia, industry and the U.S. government discovered naturally occurring human antibodies that can neutralize and protect animals against all three Ebola virus strains. The findings, published last May in Cell, could lead to broadly effective Ebola virus therapies and vaccines.

Other members of the research team had previously isolated 349 distinct antibodies from a survivor of the 2013-16 Ebola epidemic. Two of those 349 antibodies, known as ADI-15878 and ADI-15742, were found to kill all five known Ebola virus strains in tissue culture. When combined, the two antibodies also protected mice and ferrets that had been exposed to lethal doses of the strains that cause human disease.

The findings described in the Cell

paper showed that the two antibodies bind to the surface of Ebola viruses more specifically, to a section of a

> key glycoprotein molecule (a protein with a sugar attached to it).

These surface-bound antibodies interfere with the virus's ability to infect cells and multiply inside them. The researchers learned precisely where on the glycoproteins the antibodies attach and how the antibodies neutralize Ebola viruses-knowledge that should help in crafting broadly effective immunotherapies.

EXPLOITING AN ACHILLES' HEEL

In the September 2016 issue of Science, Drs. Chandran, Lai and colleagues described a different antibody strategy. The researchers developed a novel amalgam of antibodies that blocked all five Ebola virus strains from invading human cells in laboratory studies. More importantly, the antibodies protected mice exposed to lethal doses of Ebola Zaire and Ebola Sudan, the two most dangerous strains.

To gain entry to cells, filoviruses (the family that includes all Ebola viruses, along with the extremely dangerous Marburg virus) use their surface glycoproteins to bind to the host cell's outer membrane.

A portion of this membrane then surrounds the virus and pinches off, eventually developing into a lysosome—a small intracellular bag filled with enzymes that digest foreign and cellular components.

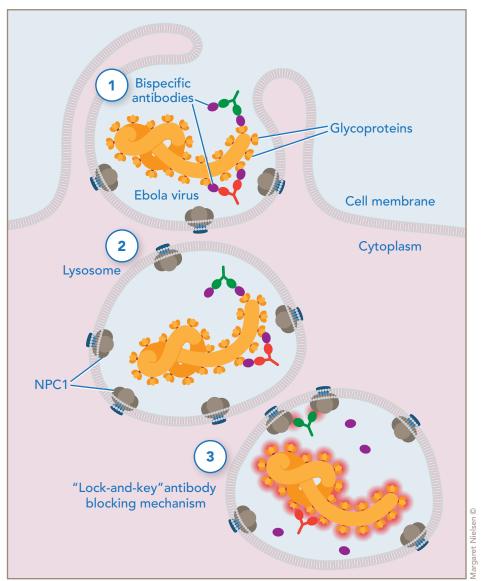
The viruses must break out of their lysosomal "prisons" so they can multiply, and here they get help from the lysosome itself. Lysosomal enzymes slice a "cap" from the virus's glycoproteins, unveiling a hidden viral protein. This viral protein "key" fits into a "lock"—a

protein embedded in the lysosome membrane called Niemann-Pick C1 (NPC1). The fitting of key into lock fuses the filovirus to the lysosomal membrane. Now the virus can propel its RNA genetic material through the lysosome and into the cell's cytoplasm, where the virus can replicate itself.

Since all filoviruses depend on this lock-and-key mechanism to reproduce, the researchers recognized this as a filovirus Achilles' heel they could exploit using synthetic monoclonal antibodies (identical antibodies produced by a single clone of cells). They obtained one monoclonal antibody to block the viral key and another (developed at Einstein by Matthew Scharff, M.D., distinguished professor of cell biology and of medicine) to block the NPC1 lock. There was just one problem: Both protein targets lay deep within the lysosomes of host cells, seemingly shielded from antibody attack.

To overcome that hurdle, the researchers came up with an ingenious Trojan horse strategy that used the viruses themselves to carry the antibodies into the lysosomes. Just as the citizens of Troy unwittingly pulled a wooden horse filled with Greek soldiers into their walled city, the researchers tricked the viruses into carrying the two monoclonal antibodies with them as they traveled deep into host cells.

The strategy crucially required a third antibody as well—FVM09 which binds to glycoproteins on the surface of filoviruses. The researchers grafted the FVM09 monoclonal antibodies onto the anti-lock antibodies as well as the anti-key antibodies, creating two types of "bispecific" antibodies (i.e., synthetic antibodies with two "business ends" that allow them to bind to two different antigens). With their FVM09 business ends, both bispecific antibodies attach to the virus while it's in the bloodstream, allowing the antibodies to



hitch a ride on the virus as it infects a cell and gets carried into the lysosome. Once inside the lysosome, the lock and key business ends of the bispecific antibodies swing into action and bind to their key and lock targets.

Tests have shown that these bispecific antibodies are highly effective in preventing Ebola infection in human cells and in mice. In the future, the antibodies will need to be tested in nonhuman primates, the current gold standard for anti-Ebola therapeutics.

Whether the antibodies will be highly effective in humans is an open question, but even a modest boost to the immune system may be enough to contain an

Tricking a deadly virus: Antibodies attached to glycoproteins accompany the Ebola virus when a portion of host cell membrane surrounds the virus and pinches off, allowing the virus to infect the cell (1). The pinched-off region develops into a lysosome, from which the virus must escape so it can multiply in the cytoplasm (2). Escape requires a previously hidden viral protein "key" that fits into a protein "lock," called NPC1, embedded in the lysosome membrane. Viral escape is thwarted when one antibody (green) blocks the NPC1 "lock," while the other antibody (red) blocks the virus's protein key (3).

Ebola infection. "With acute diseases like hemorrhagic fevers, it's simply a race to protect the body long enough so it can mount its own immune response," says Dr. Lai, co-leader of the study. "Research on Ebola infection in nonhuman primates shows that, two weeks after infection, they can generate their own antibodies and clear the Ebola virus."

BREAKING THE RULES: A COUNTERINTUITIVE HERPES VACCINE

Billions of people are at risk for sores caused by two closely related herpes viruses—herpes simplex 1 (HSV-1) and herpes simplex 2 (HSV-2). Both types spread via contact with the skin or mucous membranes of an infected person. After infection, both live in an inactive form in the ganglia (clusters of nerve-cell bodies) of sensory nerves. There they periodically reactivate and multiply, causing new sores that increase the likelihood of infecting other people.

Oral herpes appears as cold sores or fever blisters on or around the mouth and affects two-thirds of the world's population. It is usually caused by HSV-1, which also causes more-serious health problems, including infectious encephalitis and corneal blindness.

Genital herpes is contracted mainly through sexual activity and is traditionally associated with HSV-2 (although in the United States and other developed countries, up to half of all new genital herpes infections are now from HSV-1). The classic genital herpes symptoms are small blisters that break open and cause painful sores. HSV-2 infections are especially likely to reactivate. They cause an average of four to five outbreaks each year, and the resulting sores greatly increase a person's risk for HIV infection. With more than 400 million people infected with HSV-2 (some 48 million of them in the United States),

the virus plays a major role in fueling the HIV/AIDS epidemic.

Until now, no drugs have been found to eradicate either type of HSV infection and no vaccine to protect people against them, but that may soon change. At Einstein, a radically different approach to vaccine development has led to a vaccine candidate that shows promise for preventing—and possibly treating both viral scourges.

The immune system responds to viral infections by producing specific antibodies against the invading pathogen. The immune system also develops a "memory" of the virus, usually conferring lifelong immunity should that virus ever appear again. Vaccines against certain viruses work the same way. They contain viral proteins known as antigens that stimulate the immune system and prepare it to rapidly produce antibodies against the virus, even if actual exposure doesn't occur until years later.

But an effective HSV vaccine has proved elusive. Scientists who developed the half dozen vaccines tried so far have all assumed that an effective HSV vaccine must contain a particular antigen known as glycoprotein D (gD-2). It's found on the surface envelope of HSV-1 and HSV-2 and is used by the viruses to infect human cells. A gD-2 glycoprotein vaccine would presumably work by stimulating the immune system to produce neutralizing antibodies (which destroy targets without help from other parts of the immune system). In large-scale clinical trials, those vaccines did trigger high levels of neutralizing antibodies but failed to protect against HSV infection or disease, prompting



William Jacobs, Jr., Ph.D., and Betsy Herold, M.D., are working to develop a herpes vaccine.

Einstein researchers to adopt an entirely different strategy.

Rather than focus on gD-2 to stimulate antibodies, the Einstein team instead based its vaccine on HSV-2 viruses from which they deleted the gene that codes for the gD2 protein.

"We did this partly out of desperation and partly out of curiosity," says team co-leader William Jacobs, Jr., Ph.D., a Howard Hughes Medical Institute investigator, the Leo and Julia Forchheimer Chair in Microbiology and Immunology and professor of microbiology & immunology and of genetics. "But we did have a hunch that gD-2 is such a dominant antigen that the immune system focuses on responding to it while ignoring other antigens. So removing this dominant protein might expose those previously masked antigens to the immune system and stimulate the body to produce different and moreeffective antibodies."

The altered virus strain was dubbed "delta-gD-2." ("Delta" is shorthand for a gene deletion.) The vaccine containing it did not trigger the high levels of neutralizing antibodies that other experts had insisted were vital-but it worked spectacularly well in animal tests. The new vaccine had instead triggered copious amounts of antibodies associated with a different immune response called antibody-dependent cell-mediated cytotoxicity (ADCC). In ADCC, antibodies bind to antigens on the target's surface; immune-system cells then recognize the target-bound antibodies and destroy the target.

When the vaccine was given to mice or guinea pigs, it completely protected them against subsequent infection with either HSV-1 or HSV-2, says team co-leader Betsy Herold, M.D., the Harold and Muriel Block Chair in Pediatrics at Einstein and chief of the division of pediatric infectious diseases at Children's Hospital at Montefiore

and Einstein. Moreover, she notes, the gene-deleted virus in the vaccine did not multiply in the animals, which meant that the vaccine was safe.

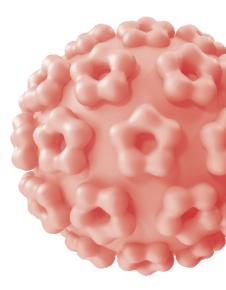
Vaccinated mice later exposed to HSV-1 or HSV-2 had no detectable virus in the vagina, the skin or neural tissue, where the viruses lurk in latent form and often emerge later to cause an outbreak. By contrast, unvaccinated mice challenged with HSV-1 or HSV-2 all showed evidence of the virus in those three sites, and all developed disease. This showed that ADCC antibodies were responsible for protecting against both types of herpes virus.

Nevertheless, reviewers were skeptical when the researchers submitted their findings to a leading journal. As noted above, the new vaccine didn't trigger neutralizing antibodies. "There was a chorus of comments insisting that 'everybody knows that an efficacious herpes vaccine requires neutralizing antibodies," Dr. Jacobs recalls.

Now the scientific community seems to be coming around to Dr. Jacobs' and Dr. Herold's unconventional approach to vaccinology. Their results were published in 2015 in eLife and in 2016 in the Journal of Clinical Investigation Insight. Also in 2016, the researchers were awarded a three-year, \$3.1 million grant from the National Institute of Allergy and Infectious Diseases for further studies. "It has made people go back to the drawing board and recognize that inducing ADCC may be an important vaccine strategy for other viral pathogens as well, including HIV," says Dr. Herold.

The Einstein team recently showed that their vaccine protects mice and other animal models against an array of HSV-1 and HSV-2 samples provided by Amy Fox, M.D., M.S., professor of pathology and of pediatrics at Einstein and director of Montefiore's clinical virology lab. Plans are under way to





assess the vaccine in phase 1 clinical trials.

The team hopes its work could also lead to a therapeutic vaccine for people already infected with HSV. "If you could reduce the number of outbreaks from, say, six a year to one a year, that would make a lot of patients very happy," says Dr. Herold. "And just maybe, we could prevent the virus from ever reactivating, or eliminate the reservoir of virus altogether."

Dr. Jacobs, whose research career has focused mainly on tuberculosis, is now studying

how to adapt this

vaccine to fight TB—particularly latent TB infection. where the mycobacterium hides indefinitely within immune cells known as macrophages, only to emerge years later when the immune system is compromised (due to

aging, for example, or to infection with HIV).

"The HSV vaccine selectively induces ADCC," he says. "So if we can figure out what proteins are expressed on the surface of macrophages infected with TB, we should be able to develop an HSV vaccine that stimulates the corresponding antibodies, which would presumably induce an ADCC response against the infected macrophages."

GUNNING FOR CHIKUNGUNYA

Of the hundreds of viruses that sicken humans, few sound more exotic than chikungunya (pronounced CHE-kungun-ya). This mosquito-borne virus causes fever and debilitating joint pain, which can persist for months or years. The disease was first observed in 1952 in present-day Tanzania. Locals named it "chikungunya," which in the native patois means "that which bends up"—a reference to victims' contorted posture due to the severe aches and pains caused by the infection.

Chikungunya has long infected millions of people in the tropics and subtropics each year. But in 2016, several dozen cases were reported in the United States—mostly among travelers returning from affected regions, although local transmission was found along the U.S. southern border. Public health officials aren't panicking just yet. But thanks to climate change and global travel, chikungunya may not remain exotic to Americans much longer. Plus, there's no vaccine and no treatment.

Margaret Kielian, Ph.D., professor of cell biology and the Samuel H. Golding Chair in Microbiology, is among a handful of researchers worldwide who study chikungunya—one of many disease-causing viruses that are enveloped viruses, meaning they're surrounded by lipid membranes containing viral proteins. During infection, all enveloped viruses must fuse their membranes with some part of the host cells. Over the years, her lab has studied how chikungunya and other enveloped viruses enter and exit cells—vital information for developing vaccines and antiviral therapies.

In a study published in December 2016 in PLoS Pathogens, Dr. Kielian and her Einstein colleague Maria Guadalupe Martinez, Ph.D., associate in cell biology, described for the first time how alphaviruses (which include chikungunya) are transmitted from cell to cell during infection. Alphavirus infection dramatically alters a host cell's cytoskeleton—the microtubules and other proteins that support cells and help maintain their shape. The infected cells





Margaret Kielian, Ph.D. (right), and former Einstein doctoral student Whitney Fields, Ph.D.

send out long, thin "fingers," or extensions, that touch uninfected neighboring cells, enabling the virus to travel from one cell to another.

"This mode of viral transmission using these extensions to travel from an infected cell to a noninfected cell-may effectively shield some copies of the virus from host antibodies that could neutralize them," says Dr. Kielian. "This may explain why symptoms can persist for so long and why conventional vaccines have thus far failed to efficiently protect against infection. By learning more details of this mechanism, we might be able to find new targets for antiviral therapies or develop effective vaccines for chikungunya."

REVERSE-ENGINEERING A DENGUE FEVER VACCINE

The standard way to make vaccines against viruses—find antigens that will prime the immune system to beat back infection—doesn't work against dengue fever, a painful and debilitating mosquito-borne disease that affects tens of millions of people a year, primarily in tropical and subtropical areas.

The problem: there are four types of dengue, and becoming infected with one doesn't confer protection against the others, explains Dr. Kielian, a dengue expert. Even worse, a second infection with a different type of dengue can cause a potentially deadly reaction called antibody dependent enhancement (ADE). In ADE, antibodies made against the first type of dengue bind to the second type of dengue, creating complexes that actually help the virus infect cells more efficiently. This leads to a supercharged infection that causes widespread inflammation that can lead to a form of septic shock—a life-threatening complication of infection.

A dengue vaccine, like dengue infection itself, could also lead to ADE unless it's designed to produce antibodies that

neutralize all four types of dengue. A recently licensed vaccine has proven somewhat effective against three of the four types. Drs. Kielian and Lai are working to create a better and truly universal dengue vaccine, using an approach called reverse vaccinology. Rather than starting with a piece of the virus that can stimulate production of neutralizing antibodies, researchers using reverse vaccinology work backward, starting with the antibodies.

"If you have an antibody that you know can neutralize a virus or other pathogen, in theory you can engineer an antigen protein that binds to that antibody," says Dr. Lai. "If that antigen were injected into a person who had never been infected, it would stimulate the production of protective antibodies. Then you'd have a vaccine."

Researchers had previously identified two broadly neutralizing antibodies that bind to a particular section of the viral envelope present in all four types of dengue—an important step in reverse-engineering a dengue vaccine. Drs. Lai and Kielian used sophisticated protein-engineering techniques to look more closely at this viral section where antibodies interact with all four types.

The Einstein scientists found differences in the way the antibodies interacted with each type of dengue; notably, they found that both antibodies interacted with some viral regions shared by all four types of dengue. Their findings, published in Virology in 2015, provide important new clues for choosing precisely the right viral components for a vaccine that will work against all four types of dengue virus.

Disease-causing viruses likely will always be with us. But thanks to the work of Einstein-Montefiore scientists, new strategies should be available for treating or preventing some of these diseases—the sooner the better.



LAI ARE WORKING TO CREATE A BETTER AND TRULY UNIVERSAL **DENGUE VACCINE, USING** REVERSE VACCINOLOGY.

MAVENS OF MEDICINE

Looking Out for the Littlest Patients

A Q&A with Judy L. Aschner, M.D.

r. Aschner is the physician-in-chief at Children's Hospital at Montefiore (CHAM) and professor and Michael I. Cohen, M.D., University Chair of Pediatrics at Einstein. She is an internationally recognized leader and physician-scientist in pediatrics, neonatology and perinatal biology whose research has helped reveal factors that contribute to altered lung development and pulmonary hypertension in infants with lung and heart disease. As chair of the department of pediatrics, Dr. Aschner has overall responsibility for its patient care, research, advocacy and educational missions. Last September, the National Institutes of Health awarded Dr. Aschner a \$6.13 million grant to direct a multicenter study of one thousand children cared for in neonatal intensive care units (NICUs) after birth. The study will follow the children up to age 10 to see if environmental exposures in the NICU—particularly to plasticizers called phthalates and to metals such as manganese—influence lung health, growth, development, behavior and other outcomes.

How did you become a pediatrician?

I was one of those medical students who liked every rotation—while on medicine I wanted to do medicine, and the same for obstetrics and surgery. But during my pediatrics rotation I fell in love. It was just the right fit, yet I resisted it at first. During the late 1970s, if you were a female medical student, there was this expectation that you'd become a pediatrician. I fight against all expectations, so I tried to talk myself out of it for a long time. Finally I realized I'd just be shooting myself in the foot to do anything else, since pediatrics was where my passion was and where I felt I could make the biggest difference.

Why neonatology as a specialty?

My first child was born the day after I graduated from medical school, so I didn't start my pediatric internship until six months later. That experience of taking care of my child every day at home helped me feel immediately comfortable in the NICU, despite all the technology and how sick and small some of the babies were. By the time I did my second NICU rotation, I was smitten— I loved the need to make quick decisions, the immediate gratification you get and mastering the skills required in an intensive care setting.

What motivated you to come to Montefiore?

For nearly a decade I was at Vanderbilt, where I'd been recruited to be chief of neonatology. I'd drawn up two five-year plans, and after six or seven years I'd achieved most everything I'd set out to do. I felt I had one more big job left in me and realized that the platform of a pediatric chair would allow me to build

and grow really meaningful programs. As I began exploring that option, the social justice mission at Montefiore was crucial in my decision to accept the position here, a little over four years ago.

How important is the close partnership between Einstein and Montefiore to your work?

It's critical. I see my department as the poster child for what synergies between the institutions should look like. A great example on the clinical front is the Montefiore-Einstein Regional Center for 22q11.2 Deletion Syndrome on the Montefiore Hutchinson Campus, chosen for its proximity to Einstein. It cares for children with a genetic condition called 22q11 deletion syndrome (22q11DS) and was driven by the expertise and research of Bernice Morrow, Ph.D., professor of genetics at Einstein. Children with 22q11DS often have numerous health problems, and the clinic is a really strong collaboration among the departments of genetics and pediatrics with specialists in cardiology, psychiatry, immunology, genetic medicine, speech and language therapy. Children see three or four providers from different subspecialties with one clinic visit. Patients and their families realize they are getting comprehensive care. We've now established many of these multidisciplinary clinics at CHAM.

What about research synergies?

Recently, my department and Einstein's neuroscience chair, Kamran Khodakhah, Ph.D., jointly recruited Praveen Ballabh, M.D., a neonatologist and neuroscientist who works in the NICU but spends most of his time in his lab at the Kennedy Center. He's using a

"Montefiore attracts healthcare providers who could have chosen other well-known institutions but who believe in our mission and are committed to our community and to the people within it."

rabbit model to study how to prevent the long-term neurological morbidity associated with intraventricular hemorrhage—bleeding inside or around the brain's ventricles. It's a major complication of prematurity that affects about 12,000 babies each year in the U.S. He has started taking some of his bench discoveries into the clinical arena to see whether they'll work there. I hope this will be the first of many joint research recruitments.

Why should people go to Montefiore for pediatric care rather than to competing institutions?

I don't think any hospital in the area has faculty and staff as talented, committed and compassionate as we have at CHAM. And then there's the culture here at Montefiore. It attracts healthcare providers who could have chosen other well-known institutions but who believe in our mission and are committed to our community and to the people within it. I like to say that at Montefiore we create a medical home for our children and our families and an academic home for our faculty and trainees.



MAKING A DIFFERENCE



Alumni Profile: Sten Vermund, M.D., '77

ou could say that bad weather has guided Dr. Sten Vermund's life. In 1973, he received an offer letter from the University of California at San Francisco (UCSF)—his first-choice medical school. He had applied to Einstein, but the pace and culture of New York were intimidating to the Norwegian American

who grew up in the Midwest. He was finishing a B.A. in human biology at Stanford and intended to stay in California. Still, he accepted Einstein's admissions interview out of curiosity and on the recommendation of his Stanford advisor, a child psychiatrist who had trained at Montefiore.

That admissions interview coincided with a severe winter ice storm that paralyzed public transportation. He took the subway in from Queens, where he'd stayed with a friend, and was stuck for an hour on a cold, snowy platform. He recalls the "unusually loquacious and friendly" straphangers he met there—a diverse group that "violated all my New York City stereotypes." The subway trip took more than three hours, but he arrived at Einstein just in time.

Few other prospective students had braved the storm, so Dr. Vermund spent more than triple his allotted time learning about Einstein and its mission. What he heard matched his own interests—in social justice. community engagement and tackling health disparities in underserved communities.

Dr. Vermund turned down UCSF and enrolled at Einstein. "I had a feeling about Einstein that continues to this day—I just fell in love with it," he says.

Not long afterward, he fell in love with his lab partner too. Thanks to Einstein's practice of assigning students to classroom seats alphabetically, Dr. Vermund found himself next to Pilar Vargas in first-year histology. Dr. Vargas, who already had a Ph.D. in developmental biology when she enrolled at Einstein, soon began mentoring the "goofy" younger man (as she described him to friends) through several classes together, and Dr. Vermund began to appreciate her nonscientific attributes. "I was persistent," he says of their eventual union. In 2017, they celebrated their 39th wedding anniversary. They have two adult sons.

That 1973 ice storm altered Dr. Vermund's career as well as his personal life. He had intended to become a child psychiatrist, but his Einstein experience led him instead to pediatrics. After graduating from Einstein, he went to developing countries to conduct epidemiology studies on infectious diseases. He later spent six years with the National Institutes of Health, 11 years as a professor at the University of Alabama and 12 years at Vanderbilt University, where he founded Vanderbilt's Institute for Global Health. He now serves as dean of the Yale School of Public Health and is an international leader in HIV/ AIDS and global health research.

Dr. Vermund came to Einstein by chance, but he has stayed connected by choice—including through service on Einstein's Alumni Board of Governors. He and Dr. Vargas are generous and loyal supporters, helping younger generations receive the same superior education, resources and access they enjoyed. "I feel the same way about Einstein that I did after that 1973 interview," he says. "It really is a very special place."



"I had a feeling about Einstein that continues to this day—I just fell in love with it." Not long afterward, he fell in love with his lab partner too.

Sten Vermund met his wife-to-be, Pilar Vargas, in histology class at Einstein. The two have been married for nearly 40 years.



Alumni Day on Campus and Alumni Gala

n May 22, 2017, Einstein hosted Alumni Day on campus, featuring an educational symposium, an alumni/faculty luncheon and a campus tour. An Alumni Gala honoring the 50th anniversary of the Class of 1967, the Einstein Alumni Association and the reunion classes (those who graduated in years ending in 2 and 7) followed later that evening at the J. W. Marriott Essex House in Manhattan.

The Einstein Alumni Association would like to thank the alumni who generously supported the gala event at a leadership level:

LEGACY: Freeman P. Botnick, M.D. '67, and Jeffrey Breall, M.D. '87

LEADER: Stephen Greenberg, M.D. '67

INNOVATOR: James Schumacher, M.D. '77

SUPPORTER: Allen Chernoff, M.D. '92; Michael Jones, M.D. '07;

Jack Kanarek, M.D. '92

DONOR: Richard M. Halford, M.D. '67; Ted G. Krontiris, M.D. '77;

George P. Liakeas, M.D. '97; Daniel Nussbaum II, M.D. '67;

James Post IV, M.D. '97; Doug Simon, M.D. '82



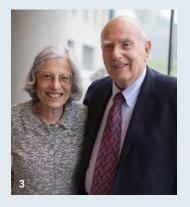






Alumni Day

- 1. From left: Joshua M. Stern, M.D.; Alexander I. Sankin, M.D.; Dean Allen M. Spiegel, M.D.; Dr. Galler; Mark P. Schoenberg, M.D.; Kelvin P. Davies, Ph.D.; Sylvia O. Suadicani, Ph.D.
- 2. Jeffrey Breall, M.D. '87, and Lauren Breall
- 3. Gail E. Solomon, M.D. '62, and Harvey L. Hecht, M.D. '62
- 4. 50th Reunion class tour











Gala

- 1. Janina R. Galler, M.D., president, Einstein Alumni Association Board of Governors, with Steven M. Safyer, M.D., president and CEO, Montefiore
- 2. Raja M. Flores, M.D., chief, thoracic surgery and Ames Professor, cardiothoracic surgery, Mt. Sinai Medical Center, with Kathryn Quadracci Flores
- 3. 50th Reunion class
- 4. Class of 1977
- 5. Class of 1992

MAKING A DIFFERENCE

Professional & Leadership Division 46th Annual Golf and Tennis Tournament



"This event is about camaraderie and friendly competition, but most importantly, it's about working together as proud members of the Einstein team."

uaker Ridge Golf Club in Scarsdale, NY, was the site of the Einstein Professional & Leadership Division's 46th Annual Golf and Tennis Tournament, held on June 12. Proceeds went to the Price Family Foundation Fund for Translational Research, an important new Einstein initiative supporting innovative treatments for childhood diseases, including pediatric cancer and diabetes. Einstein trustee Michael F. Price served as honorary chair for this year's event.

The day began with a gala luncheon

at which the division chair, Greg Gonzalez, welcomed the attendees. "This event is about camaraderie and friendly competition, but most importantly, it's about working together as proud members of the Einstein team," he said. Golf, tennis and cocktails followed to round out a successful day.

Peter Bernstein and Raymond S. Cohen, who are both division executive board members, co-chaired the event. Please see the sidebar for the full list of tournament committee members.

HONORARY EVENT CHAIR

Michael F. Price

EVENT CHAIRS

Peter Bernstein Raymond S. Cohen

JOURNAL CHAIRS

Neil A. Clark Jeffrey A. Fiedler Greg Gonzalez Martin Luskin

AUCTION CHAIRS

Marlon Bustos Peter E. Zinman

TENNIS CHAIRS

Marc Altheim Jack M. Somer

PROFESSIONAL & LEADERSHIP DIVISION CHAIR

Greg Gonzalez

















- 1. Neil A. Clark, Martin Luskin, Allie Reid, Peter Duncan and David Luski
- 2. Tennis, anyone?
- 3. Greg Gonzalez and Melissa Ceriale
- 4. Jeffrey A. Fiedler and Peter Zinman
- 5. Michael B. Prystowsky, M.D., Ph.D., professor and chair, department of pathology, Albert Einstein College of Medicine
- 6. Raymond S. Cohen
- 7. Andrew M. and Samuel Weinberg
- 8. Martin Luskin
- 9. Peter Bernstein

To learn more about the Einstein Professional & Leadership Division and upcoming events, please contact Eve Marsan at 718.920.8985 or eve.marsan@einstein.yu.edu.





MAKING A DIFFERENCE

Women's Division Spirit of Achievement Luncheon



From left: Spirit honoree Alyson Moadel-Robblee, Ph.D., director, Bronx Oncology Living Daily program; Jill Martin, former Spirit Award winner and Today show contributor; and Spirit honorees Luz Towns-Miranda and Sandra Lee.

he Einstein Women's Division hosted its 63rd annual Spirit of Achievement Luncheon on May 16 at the Rainbow Room in Manhattan.

The honorees included Sandra Lee, a multiple Emmy Award winner and lifestyle expert; Alyson Moadel-Robblee, Ph.D., the director of the Bronx Oncology Living Daily (BOLD) program, and Luz Towns-Miranda, Ph.D., a former faculty member in Einstein's departments of psychiatry and of family and social medicine. The afternoon's emcee was Jill Martin, a contributor to NBC's Today show and a past Spirit honoree. Women's Division co-presidents Terri Goldberg and Trudy Schlachter organized the event, along with former Women's Division president Carol Roaman and executive vice president Andrea Stark.

Proceeds from the luncheon benefited the Women's Division's initiative to support comprehensive healthcare for women through research, discovery and teaching, and to provide specialty care for all women in the diverse communities that Einstein and Montefiore serve.

SPIRITED TRIBUTES

Steven M. Safyer, M.D., president and CEO of Montefiore, introduced Sandra Lee, highlighting her battle with breast cancer and her courage in speaking out to raise awareness of the need for early cancer detection. In accepting her award, Ms. Lee emphasized the importance of nutrition in health and her work as UNICEF's special nutrition emissary and as national spokesperson for No Kid Hungry and Stand Up to Cancer.

Luncheon proceeds supported comprehensive healthcare for women through research, discovery and teaching.

Dr. Safyer also presented Dr. Moadel-Robblee with her Spirit award. Dr. Moadel-Robblee, a health psychologist, discussed her career in research, teaching and counseling, and her interest in the psychological, social and cultural factors that affect people with cancer. She shared a video about her work as founding director of the BOLD program at the Montefiore Einstein Center for Cancer Care, as well as the profound impact her mother's battle with cancer has had on her life's work.

Today show contributor Lilliana Vazquez presented the Spirit award to Dr. Luz Towns-Miranda, a member of the Einstein-Montefiore family from 1985 to 2009. Dr. Towns-Miranda has been involved with Planned Parenthood and has worked to improve mental health services for families, women and children throughout New York City. She is also the proud mother of Lin-Manuel Miranda, the creative force behind the Tony Award-winning Broadway musicals Hamilton and In the Heights, and Luz Miranda-Crespo, chief financial officer at the MirRam Group, a strategic consulting firm in New York City.



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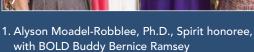












- 2. Steven M. Safyer, M.D., president and CEO, Montefiore
- 3. Ruth L. Gottesman, Ed.D., trustee, Einstein and Montefiore, with Judy L. Aschner, M.D., physician-inchief, Children's Hospital at Montefiore
- 4. Helen Radin, executive vice president, Einstein Women's Division; Spirit honoree Sandra Lee; and Women's Division co-president Terri Goldberg



- 5. Linda Altman, Einstein trustee and former Women's Division president (center), with daughters Liz Gaelick (left) and Leslie Kaskel (right)
- 6. Cherie Stahl with Women's Division board member Carole Olshan
- 7. From left: Terri Goldberg and Trudy Schlachter, Women's Division co-presidents; Carol Roaman, former Women's Division president; and Women's Division executive vice president Andrea Stark
- 8. From left: Dean Allen M. Spiegel, M.D.; Dr. Moadel-Robblee; Sandra Lee; Dr. Safyer; and Philip O. Ozuah, M.D., Ph.D., executive vice president and COO, Montefiore

MAKING A DIFFERENCE

Women's Division

War Paint Theatrical Event Spotlights Science

he Women's Division hosted cocktails and conversation this past spring at Aureole restaurant in Manhattan, followed by a trip to the Broadway musical War Paint.

Women's Division co-presidents Terri Goldberg and Trudy Schlachter welcomed the group to Aureole and introduced members of the War Paint creative and production teams, which included Tony Award-winning playwright Doug Wright and Tonynominated composer Scott Frankel, along with producers Patrick Catullo and Aaron Glick. The War Paint representatives discussed myriad aspects of the show, which chronicles the rivalry

between cosmetics titans Helena Rubinstein (an honoree at the 1961 Spirit of Achievement Luncheon!) and Elizabeth Arden. Attendees departed for the theater following a lively questionand-answer session.

Actresses Patti LuPone and Christine Ebersole play Rubinstein and Arden, the 20th-century entrepreneurs who revolutionized the cosmetics industry by emphasizing the science behind their products, and also inspired generations of women. The production is based on Lindy Woodhead's 2004 book War Paint and on the 2007 documentary The Powder and the Glory by Ann Carol Grossman and Arnie Reisman.

To join the Einstein Women's Division's initiative to support research on women's and men's cancers, or to learn more about the Women's Division, please contact Mary Anna Smith at 718.920.6036 or maryanna.smith@einstein.yu.edu.













- 1. From left: Terri Goldberg, Einstein Women's Division co-president; War Paint producer Aaron Glick; composer Scott Frankel; librettist Doug Wright; producer Patrick Catullo; and Women's Division co-president Trudy Schlachter
- 2. Katherine Abraham
- 3. Ellen Kaplan Koppelman with Spirit honoree Alyson Moadel-Robblee, Ph.D.
- 4. Corinne Pulitzer
- 5. Eileen O'Kane Kornreich with Janie Schwalbe



"I feel empowered and deeply grateful for the scholarship that's allowing me to achieve all that is possible with an Einstein education."

- Hope Miodownik, Class of 2019



Read more about Hope's story magazine.einstein.yu.edu/hope

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For more information, please contact the office of alumni relations at 718.430.2013 or alumni@einstein.yu.edu.





MAKING A DIFFERENCE

Class Notes

1960s

Gail Solomon Hecht, M.D. '62, and Harvey L. Hecht, M.D. '62, are retired and living in Scarsdale, NY. Their daughter, Elizabeth, graduated from Einstein in 1997 and is a professor of radiology at New York—Presbyterian/ Columbia University Medical Center. Their son Jonathan is an associate professor of pathology at Beth Israel Deaconess Medical Center in Boston, and their son Daniel is a lawyer.

Charles Krone, M.D. '62, continues to practice gastroenterology at the Tucson Surgery Center, and is developing an IBS/gastro-intensive disorder wellness center there. He and his wife, Suki, along with their children and grandchildren, are "living, working and relaxing" at their homes in Tucson and Elgin, AZ.

Philip Paris, M.D. '62, is retired and enjoying life in Northern California. The family-medicine specialist is also a founder of *Stop Stigma Now*, a volunteer group battling the stigma often attached to opioid addiction.

Allan Scher, M.D. '62, enjoys his grandchildren, Riley, five, and Charlie, one and a half. Dr. Scher retired in 2003 as a radiation oncology specialist from Morristown Medical Center and is a past president of the Radiological and Oncology Societies of New Jersey.

1970s

Dan Lorber, M.D. '72, is director of endocrinology and associate director of the Lang Center at New

York-Presbyterian Hospital in Queens, NY. He lives in Port Washington, NY.

Walter Orenstein, M.D. '72, is

president of the National Foundation for Infectious Diseases. He also chaired the National Vaccine Advisory Committee from 2012 to 2016 and is a member of the World Health Organization Strategic Advisory Group of Experts' working groups on polio and measles and rubella. He co-edited the seventh edition of Vaccines, a standard textbook in the field of vaccinology, which will be published later this year. His wife, Diane, recently started working at the Centers for Disease Control and Prevention. Their daughter, Eleza, works in a radiology practice in Atlanta, and their son, Evan, is a clinical informatics fellow in pediatrics at Children's Hospital of Philadelphia. Dr. Orenstein derives great joy from his two grandchildren, Aviva and Max, ages six and two.

Mary Flannery, M.D. '77, specializes in child and adolescent psychiatry. In November 2014, she became "triple boarded" in pediatrics, general psychiatry and child and adolescent psychiatry. She lives in White Plains, NY, and notes that she is enjoying her six grandchildren.

Frank Gillingham, M.D. '77, has retired as an emergency-room physician after serving as chief of emergency medicine and chief medical officer at Westlake Medical Center and Glendale Memorial Hospital. He is the co-founder of GeoBlue, an international medical insurance affiliate of the Blue Cross Blue Shield Association. He and his wife, Andrea, live in Santa Rosa Valley, CA, and have four children. Jeff is an attorney and CPA in California; Alex is a

former pitcher for the Colorado Rockies and now works as an accountant; Lauren is a fifth-grade teacher in Simi Valley, CA; and Olivia is a first-year cadet at the U.S. Air Force Academy.

Theodore Krontiris, M.D. '77, of Pasadena, CA, has retired from the City of Hope National Medical Center in Duarte, CA. This year, he and his wife,

Duarte, CA. This year, he and his wife, Sue, celebrated their 45th wedding anniversary. The couple has three daughters and two grandchildren, Nina, 13 months, and Arthur, five months.

Helen Muhlbauer, M.D. '77, lives in New York and runs her own file-review business. During her 40-year career in psychiatry, addiction psychiatry and psychosomatic medicine, Dr. Muhlbauer served disadvantaged populations; she did some of her most rewarding work on subway platforms and in crack houses with the New York Police Department and mobile crisis teams. She worked for many years at Einstein and Columbia University and earned four teaching awards. Dr. Muhlbauer also serves as part-time medical director of the government business division of an insurance company, helping medically disadvantaged patients. She conducts telemedicine in several states, serving patients who have no direct access to medical specialists.

Michael Myers, M.D. '77, specializes in weight management and lives in Huntington Beach, CA.

Joel Schiffenbauer, M.D. '77, specialized in rheumatology. He is now retired and living in Gaithersburg, MD. Martin Schwartz, M.D. '77, specializes in diagnostic radiology. He lives in Pacific Palisades, CA, and is proud that his oldest daughter is considering attending Einstein.

Stuart Shapiro, M.D. '77, works for the National Institutes of Health in HIV research administration and lives in Rockville, MD.

Marvin Snow, M.D. '77, specializes in dermatology. He lives in Woodmere, NY, and is excited that his son, Michoel, received his M.D. /Ph.D. from Einstein this year.

Joseph Weinstein, M.D. '77, is an ophthalmologist living in Bethpage, NY. He has been included in Castle Connolly Medical's America's Top Doctors book. His youngest son, Marc, recently became engaged. Dr. Weinstein is also thoroughly enjoying his grandchildren: a newborn, a four-year-old and a seven-year-old.

1980s

Irene Grant, M.D. '82, is a clinical assistant professor of community medicine at New York Medical College. She specializes in infectious diseases and served as moderator and keynote speaker at the 2017 Euro Global Summit on Clinical Microbiology and Mycotoxins conference in the Netherlands.

Kurt Nolte, M.D. '82, specializes in forensic pathology and has served as chief medical examiner of New Mexico since 2014. His is the only statewide, academically based medical examiner's office in the U.S. His wife, Bronwyn,



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is senior associate dean for faculty affairs at the University of New Mexico School of Medicine. Last year the couple traveled to Cuba and Japan. Their elder daughter, Cailin, 23, graduated from Boston University with a degree in music. Their younger daughter, Averill, 20, is a student at the Maryland Institute College of Art.

Robert Realmuto, M.D. '82, is "semiretired" after spending 30 years as chair of the department of emergency medicine at Orange Coast Memorial Hospital in Fountain Valley, CA, where he lives. He spends his free time enjoying his family—"and the golf course!"

Knut Roalsvig, M.D. '82, founded and served as medical director of an independent group gastroenterology practice in southern New Hampshire. Dr. Roalsvig's son, Andreas, lives in Brooklyn, NY, and is working in the film industry. His daughter, Emma, attends Johns Hopkins University and is studying English and the classics.

Susan Brill, M.D. '87, is chief of adolescent medicine at Saint Peter's University Hospital in New Brunswick, NJ, and a clinical associate professor of pediatrics at the Robert Wood Johnson School of Medicine at Rutgers University. She was named one of Castle Connolly Medical's "Top Doctors in Adolescent Medicine" in both 2015 and 2016. Her oldest son, Yonatan, is a software engineer and has three children. Dr. Brill's daughter, Chaya, a speech pathologist, also has three children. Her youngest son, Binyamin, is 22 and living in Jerusalem.

Cary Friedman, M.D. '87, is a psychiatrist in private practice in Cambridge, MA. He also serves as a training and supervising analyst at the Boston Psychoanalytic Society and Institute, supervises residents at Cambridge Hospital and is on staff at Mount Auburn Hospital. He has been happily married to Rick for 15 years and has "three wonderful children": Samantha, Jeremy and Maggie.

Mary Ross-Dolen, M.D. '92, retired from her psychiatry practice to stay home with her two children: Sam, now a sophomore at Indiana University, and Hannah, a high school junior. Dr. Ross-Dolen is married to Eric Dolen, M.D. '93, an interventional radiologist at Riverside Radiology in Columbus, OH.

BACK



Lunching in Lubin

Lubin Dining Hall, 1959: a place and time for coats, ties and newspapers. We can't be sure, but according to James Cohen, the manager of food services, who's been on the job for nearly 25 years, Lubin was probably present at the creation—serving up strictly kosher cafeteria-style breakfasts, lunches and dinners to students, faculty and visitors when Einstein first opened its doors in 1955.

Lubin's dining days ended in 2015, following the debut of the Forchheimer Building's Main Street Café. Today, the Lubin kitchen is used for preparing the food—still kosher—sold in the café. The dining hall provides space for special events, such as last summer's New York Blood Center drive.

The transition made sense, says Mr. Cohen. "When Einstein merged with Montefiore two years ago, there was an effort to consolidate services and reduce overhead," he explains. "Also, the campus had expanded, and the logistics of people entering and leaving Forchheimer made Main Street Café a central hub."

A few things have stayed the same ever since 1959. The former dining hall retains its minimalist ambience. And the chicken pot pie and matzo ball soup are still favorites.



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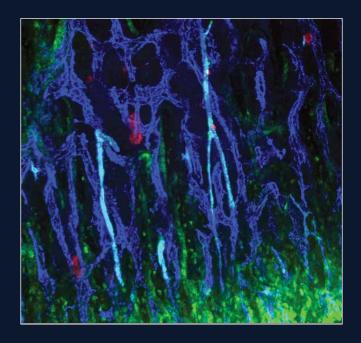


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EINSTEIN IMAGE

Hematopoietic stem cells (HSCs) perform the key task of producing all the body's blood cells. They occupy tiny niches in the bone marrow, along with stromal (connective tissue) cells, fat cells, endothelial cells and other cell types. The laboratory of Paul Frenette, M.D., has found that some of these niche-cell neighbors are vital for keeping HSCs alive and for helping them regenerate and move. (HSCs travel back and forth between the bone marrow and the bloodstream.) This low-power immunofluorescence image shows bone marrow taken from the sternum (breastbone) of a mouse. While HSCs themselves are not visible in this image, we can see stromal cells (green) and the two main types of blood vessels found in bone marrow: arterioles (red) and sinusoidal cells (blue). Noboru Asada, M.D., Ph.D., formerly a postdoctoral fellow in Dr. Frenette's lab, conducted the research. Dr. Frenette is a professor of medicine and of cell biology and director of the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research.