SUMMER/FALL 2018

EINSTEIN

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

ENZYMOLOGIST EXTRAORDINAIRE

To create new drugs, Einstein's Vern Schramm freezes the beating heart of enzyme reactions

A Message from the Dean

When I was a medical student at Einstein more than 35 years ago, the campus looked very different—and some of the changes are nothing short of spectacular. But one thing that hasn't changed is the College of Medicine's dedication to science as part of our core mission, which motivated me back then and continues to excite me today.

A perfect example of how laboratory discoveries can improve human health is the work of Einstein's Vern Schramm, Ph.D. His distinguished career and colorful background (he started life as part of a Midwest traveling carnival) are described in our cover story beginning on page 18.

Dr. Schramm has pioneered the development of compounds called transition-state analogues, which block key enzymes from functioning. His work has led to powerful enzyme inhibitors for a wide variety of health problems, including cancer and often-lethal viruses. Last year, Dr. Schramm's analogue for treating peripheral T-cell lymphoma was approved for use in Japan—the first Einstein-developed medication ever to reach the market.

Another article in this issue focuses on serving our local community. Some 30,000 children in the Bronx may be affected by nonalcoholic fatty liver disease (NAFLD), which has been fueled largely by the obesity epidemic and can lead to liver scarring and liver failure. The Pediatric Fatty Liver Program at Children's Hospital at Montefiore is the only one of its kind in the borough

and treats about 300 patients a year. Although no drugs are available for treating NAFLD, a novel compound dubbed V2, developed by Einstein researchers, shows promise for preventing fat from accumulating in the liver.

I believe that the best medical schools not only prepare people to treat the patients of today but also conduct research to help the patients of tomorrow. That standard of excellence is what Einstein's physician-scientists taught me, and it remains even more relevant today.

GORDON F. TOMASELLI, 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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Cover Illustration by Tatyana Starikova Harris

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COLLEGIAL

LIFE

Q&A With the New Dean: Gordon F. Tomaselli, M.D.

Dr. Gordon Tomaselli, an Einstein alumnus, returned to campus in July to assume his new role as the Marilyn and Stanley M. Katz Dean. Here, he discusses his priorities, his vision for the future and more.

When you were an Einstein medical student in the early 1980s, did you have any thoughts about your career goals?
Einstein helped cultivate my goal of being a physician-scientist. We were taught by very senior, well-established professors who were terrific role models for that career path, and who made me believe it was possible. I wasn't thinking about leadership then but about job satisfaction, taking care of patients, and how the next generation of patients should be cared for. That was something that Einstein ingrained in us.

What are your priorities as dean?
First and foremost, I would like to continue strengthening the academic mission, with a focus on education and training and research, and completion of the integration of Einstein with Montefiore. In general, the priorities of the dean are to support faculty, students and staff and promote engagement with our community.

On the education side, I'm interested in two things. First, we need to teach this generation of learners in the manner they like to learn best. Obviously it's not the way I learned; it's more digital, and it requires innovation and thinking out-

side the box. And it's important to give people the tools they need to continue learning throughout their careers. I think about the body of information that I learned as a medical student, and it's a fraction of what exists today.

And the second piece, which benefited me at Johns Hopkins, is an emphasis on process thinking—taking an engineering mindset to solve problems and make things work better, from laboratory research to clinical programs. We don't want to make medical students engineers, but we want them to be able to converse with software and computer and biomedical engineers. And understanding the concepts engineers use will better inform how doctors treat patients. I think about it more in terms of computer programming: you take modules and fit those together to address a problem in biomedicine.

What is your main concern about the future of medical education?
I'm concerned about the vast expansion of information in medicine, which will require taking a new approach to learning. The other concern is the cost of education and the debt that students are taking on. There are several philanthropic fundraising platforms to explore. One is describing to potential donors the cost of medical education. Also, many schools use their endowments to support tuition remission for those who can't afford medical school. Debt-free medical education open to all qualified candidates is an aspirational goal.

What made you choose cardiology as a specialty?
I was always fascinated by the fundamental basis of biological electricity, and I cultivated that at Einstein by working in neuroscience and neuropathology with Dr. William Norton. But while I was still a resident, my mother received a cardiac transplant at age 49. She lived in Maine at the time and was the second person to receive a heart transplant at Brigham and Women's Hospital in Boston. (The first was a woman who lived around the corner from her, strangely enough.) So that personal experience certainly helped solidify my decision.

> "We need to teach this generation of learners in the manner they like to learn best. Obviously it's not the way I learned; it's more digital, and it requires innovation."

Do you plan to continue your research?
I hope to maintain a small laboratory, but I view my primary responsibility as making every effort to ensure the success of the College of Medicine. I currently have a couple of grants to investigate the molecular basis of cardiac arrhythmia by studying ion channels and their regulation.

Much of Einstein's research is in the basic sciences. Do you see that evolving?
I think that the research portfolio will grow, and I believe it will include more translational and clinical research, which will help integrate the Einstein and Montefiore campuses. Ideally, basic science research should have a connection to clinical medicine.

What is the greatest change that you've noticed between the time you were a student here and now that you're back?
I barely recognize the physical infrastructure. I do recognize 1935 Eastchester Avenue, the building I lived in for a few years. But almost everything else is different. It's amazing. The Van Etten Building was a TB sanitarium when I was here, and now it has a simulation center and is a robust and energetic place for learning, which it wasn't back then.

You've been in Baltimore for the past few decades; what are your sports allegiances?
I was raised in New York, and always have been and always will be a Yankee fan. My Uncle Joe worked at a bar outside Yankee Stadium and was good friends with [catcher] Elston Howard.

If you hadn't become a physician, what might you have done instead?
If I'd had enough talent, I'd have been an animator like my father, Rudolph Tomaselli. He's still around but not active in animation anymore. He had his own studio in Manhattan and started with Hanna-Barbera. He worked on *Felix the Cat* initially. He used to do lots of commercials, and he created the character Punchy—as in "How'd you like a nice Hawaiian Punch?" But he's most famous for being the head animator for the *Beavis and Butt-Head* movie, on which he helped supervise all the drawing boards. He always had a much more interesting job than my friends thought I had.

MORE ONLINE
Read more of this Q&A and watch the dean welcome the Class of 2022:
magazine.einstein.yu.edu/dean18

AN EDUCATION IN AGING

To help care for the surge in older Americans, Einstein Montefiore is training the next generation of geriatricians

BY AMY O'CONNOR

"I found geriatrics clinically compelling and moving, and yet it is a neglected field for such an underserved population."

Left: Betty Baumel at exercise class. Above: Ms. Baumel and Amy R. Ehrlich, M.D.

Bronx resident Betty Baumel, 87, is busy. Since losing her husband, Abraham, two and a half years ago to Alzheimer's disease, she has taken to spending time at the local senior center, singing with a chorus, attending lectures and taking pottery classes. That's when she's not dancing, visiting with one or more of her seven grandchildren, having lunch with friends or riding the bus into Manhattan for workshops at the Museum of Modern Art.

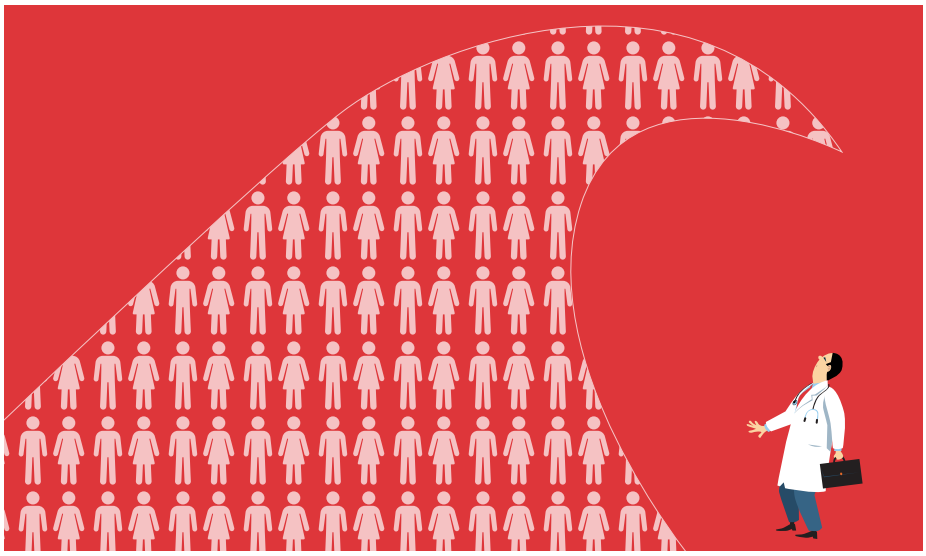
Blessed with good health, Ms. Baumel defies the stereotype of an octogenarian. While some doctors might advise any patient pushing 90 to slow down, her Montefiore physician, Amy R. Ehrlich, M.D., expects healthy, vibrant seniors to live life to the fullest. So when Ms. Baumel proudly announced she was taking a fitness class, Dr. Ehrlich cheered, but suggested going even more often—say, three times a week. "Some people you can never satisfy," Ms. Baumel says affectionately.

Dr. Ehrlich vividly remembers the ageism she witnessed during her medical training, even among dedicated clinicians. Elderly patients were called GOMERs, short for Get Out of My ER. The experience helped motivate her to become a geriatrician—a physician trained to meet the special health needs of people age 65 and over—and to teach geriatrics to the next generation of doctors. Einstein and Montefiore geriatrics educators work to disabuse today's students of their biases about aging and train them to treat the whole person, not just the symptoms. The priority is ensuring comprehensive care for patients aligned with their goals and abilities, not their birthdates.

"I found geriatrics clinically compelling and moving, and yet it is a neglected field for such an underserved population," says Dr. Ehrlich, the associate chief of the division of geriatrics in the department of medicine at Einstein and Montefiore. And she is not alone: In a 2009 survey of a representative sample of 6,590 physicians involved in 42 specialties, geriatrics ranked second in career satisfaction. "I tell medical students that geriatrics embodies the joy of medicine. There is an unbelievable individual and societal need for your services. That's why many of the students entered medicine—to have an impact on individuals and systems of care. As the population ages, the need is increasing."

THE 'SILVER TSUNAMI'

Due to the aging of the baby boom generation, 10,000 Americans turn 65 every day. The United States now has about 47 million people age 65 and over, and 7,300 geriatricians to care for them, but



the American Geriatrics Society calculates that more than 20,000 are needed. By 2030—the high tide of the silver tsunami, when the 65-and-over population will total 71 million—the country will need 30,000 geriatricians, or four times the current number.

"When our students become practicing physicians, most will have many patients over 65," says Joe Verghese, M.B.B.S., M.S., chief of geriatrics at Einstein and Montefiore and director of the Center for the Aging Brain, which provides integrated, comprehensive care for those suffering from memory loss, as well as social support for them and their caregivers. "It is enormously helpful for all students to receive geriatrics training, so they can provide the best care for their patients and their families."

Geriatricians are trained to help elderly patients maintain their function and quality of life, often while coping with multiple chronic conditions, such as hypertension, heart disease, osteoporosis, arthritis, cancer and diabetes. These experts can also care for people who are disabled, have dementia or need end-of-life or palliative care. Geriatricians are trained not only in managing complex medical issues but also in the unique social, financial and emotional needs and demands of the population.

According to Dr. Verghese, Montefiore's geriatrics services reach about 3,000 patients per year in ambulatory-care clinics, inpatient services and nursing homes. Recently developed satellite programs focusing on the brain and cognition, orthopedics, cardiology and other initiatives reflect Einstein and Montefiore's efforts to "geriatricize" clinical care and research throughout the Bronx, Westchester County and New York State.

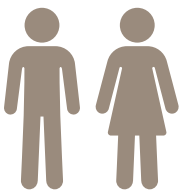
Einstein and Montefiore have created several programs to train the next generation of doctors in this grossly understaffed but highly rewarding specialty.

A TRANSFORMATIVE CLERKSHIP

"Many medical students start off with a clear idea that they want to go into one of the more 'glamorous' specialties," says Claudene George, M.D., M.S., an associate professor of medicine at Einstein and a geriatrician at Montefiore, who runs the geriatrics clerkship at Einstein. "But after their geriatrics clerkship experience, they learn to appreciate its importance."

Einstein is among the one-third of medical schools that require students to take a geriatrics clerkship. The

The 'Silver Tsunami' by the Numbers



Now

47 million

people in the United States are 65 and over, and there are 7,300 geriatricians to care for them. But more than 20,000 are needed.

In 2030

71 million

people will be 65 and over; the United States will need 30,000 geriatricians to care for them.

Source: The American Geriatrics Society

Claudene George, M.D., M.S. (standing), with patient Gertrude Williams and medical student Mallory Kerner-Rossi.

Einstein rotation immerses them in the fundamentals of geriatrics, including medication management; cognitive and behavioral disorders; patients' self-care capacity; falls, balance and gait disorders; and palliative medicine, which focuses on improving the quality of life for those who have serious illnesses or who are facing the end of life. But it's the interaction with patients and exposure to the field's distinctive approach to care that can be transformative. Students regularly report that their experience in the diverse care settings is one of their favorite aspects of the rotation.

The geriatrics rotations occur at five sites in the Bronx and Westchester County. Depending on location, students engage in clinical care at inpatient, outpatient, home care or nursing home settings. They emerge with specialized knowledge and skills: identifying medications that older people should avoid; differentiating among delirium, dementia and depression; identifying hospitalization hazards for older adults; and learning about the unique financial and social challenges facing aging patients, including elder abuse and the assignment of medical proxies.

Susmit Tripathi, a fourth-year student at Einstein, recalls being won over by the idea of serving an aging population. He was particularly impressed with the coordinated care among providers, including physicians, nurses, nutritionists and social workers—so different from the rigid hierarchies in some medical specialties. He also believes the field is underappreciated and is confident that his exposure to geriatrics will give him a broader perspective. "Many of my colleagues at other schools have only a rough idea of what geriatrics is," he says. In contrast, he is finishing a yearlong clinical research training program in neurology, with a focus on dementia and other issues of aging.

HANDS-ON CARE

A highlight of the geriatrics clerkship is morning rounds at Calvary Hospital, one of the first (founded in 1899) and largest hospitals dedicated to palliative and hospice care. Calvary's cheerful 225-bed facility in the Bronx is filled with plants and light. The hospital is within easy walking distance of Einstein and provides exceptional training in compassionate care for patients—most but not all of them elderly—who have advanced cancer or other life-limiting illnesses. Leading the students on morning

From left: Einstein students Luis Garza, Julia Kelly and Shombit Chaudhuri, with Myra Davila, M.D., and Calvary patient Celeste Reyes.

rounds at Calvary is Einstein graduate Myra Davila, M.D., a clinical assistant professor of medicine at Einstein.

"I always say, 'Death can be beautiful,'" says Dr. Davila when asked about working in a place where death is a regular occurrence. "It's part of life. It doesn't have to be sad, dark and out of your control. And it does not have to be painful. I think if people could see what we provide here it would change that perception."

A native of the Bronx, Dr. Davila was attracted to Calvary and palliative care because of her experience at Einstein, where she completed the geriatrics rotation, took multiple geriatrics electives, was president of the student chapter of the American Geriatrics Society and was matched with Dr. Ehrlich as a mentor. ("'You're going to love geriatrics,' she told me. She was right.") She also completed the Montefiore-Einstein Geriatrics Fellowship Program. (See page 9.)

"My geriatrics training was great, because you are not just consulting—you are on the front lines of healthcare," Dr. Davila says. "It's a huge myth that in geriatrics you only take care of demented old patients. For one thing, you become familiar with all the other medical

"Death is part of life. It doesn't have to be sad, dark and out of your control. And it does not have to be painful. I think if people could see what we provide here it would change that perception."

specialties, but you learn to look at them as they pertain to caring for the older patient. And as a physician, you learn a whole other set of skills—including patience—that you can't obtain anywhere else."

Dr. Davila recalls that, as a medical student, she saw an elderly man who had lost a lot of weight. "We had assumed his weight loss was a health problem," she says. Following the protocol learned during her geriatrics rotation, she sat with him and gently asked questions about his life and how he spent his days. Eventually, he revealed the real reason he wasn't eating. "He was no longer able to buy groceries for himself, and he felt ashamed," she recalls. "With that information, we were able to help him feed himself without subjecting him to medication or procedures that would not have solved the problem."

Second-year medical student Emily Chase volunteers at Calvary on weekends through Project Kindness, an Einstein program in which medical students visit patients at local hospitals. For Ms. Chase and her fellow volunteers, it's a chance to practice their communication skills and bedside manner, and to experience the satisfaction of making someone feel better. "It was great to meet the people you want to be helping and to make personal connections to them," Ms. Chase says. Those weekly meetings with Calvary patients, she says, have reaffirmed her commitment to pursue geriatrics.

A PERSONAL APPROACH

The Palliative Care Program at Montefiore provides care and teaches students at several campuses. "The training in palliative care that we offer encompasses much more than clinical care," says Peter Selwyn, M.D., M.P.H., chair of family and social medicine and director of the program. "To provide the best care, it's important for medical students to learn about many different cultures and to approach each patient as an individual," he says, citing a recent teaching moment with a large, multigenerational South Asian family whose matriarch required a ventilator and artificial feeding to live.

The medical team first assumed that such interventions would be detrimental to her quality of life, and the right path would be to withhold them. "But to the family," Dr. Selwyn says, "it was the greatest gift and opportunity to honor her and give her total care, even though they recognized that she was not going to get better."

Of the many methods Einstein-Montefiore clinicians use to teach end-of-life care, the most powerful may be their own example, which leaves a lifelong impression on students and patients.

Ms. Baumel, the patient we met at the beginning of this story, and her family have been under the care of Dr. Ehrlich and the Montefiore geriatrics and palliative-care teams for decades, starting with Ms. Baumel's mother-in-law in the late 1980s. When Ms. Baumel's husband, Abraham, died in January 2016, the nurses and social workers were there. Dr. Ehrlich also grieved with the family. "Not too many doctors visit the family when they sit shiva," Ms. Baumel says. "She did."

Asked to describe the quality of care the Baumel family has received from Montefiore, Ms. Baumel struggles to find the right words. "What comes above excellent?" she asks. E

The Montefiore-Einstein Geriatrics Fellowship

To become certified geriatricians, residents in internal medicine or family medicine must complete a geriatric medicine fellowship program. Among the nation's oldest is the Montefiore-Einstein Geriatrics Fellowship Program, founded in 1983. The geriatrics faculty includes 13 full-time physicians plus specialists in geriatric nursing and social work. They typically fill all six fellowship positions each year, and have trained some 100 geriatricians.

The program trains physicians for careers in geriatrics in academic medical centers and clinical practice, says fellowship director Rubina A. Malik, M.D., an assistant professor of medicine at Einstein and a geriatrician at Montefiore. Many of them have gone on to become leaders in this burgeoning field. She notes that while the program has a long history, it's always innovating, "offering areas of novel practices and teaching methods in the field of geriatrics," and leveraging multidisciplinary approaches to enhance education.

WATCH THE VIDEO
Meet Einstein students doing their rotations at Calvary:
magazine.einstein.yu.edu/aging18

Faculty News & Notes

New Chief of Endocrinology

Jill P. Crandall, M.D., a professor of medicine and the Jacob A. and Jeanne E. Barkey Chair in Medicine, has been named chief of the division of endocrinology in the department of medicine at Einstein and Montefiore. She served as interim chief for six months before her permanent appointment, following the retirement of Norman Fleischer, M.D. (see opposite page). Dr. Crandall plans to expand and enhance the division's clinical programs in diabetes and obesity, recruit new faculty, manage the move to the newly formed Fleischer Institute for Diabetes and Metabolism and create an obesity treatment and research center to help tackle the obesity epidemic.

Faculty Member Honored

Ana Maria Cuervo, M.D., Ph.D., has been elected to the American Academy of Arts and Sciences, which honors exceptional scholars, leaders, artists and innovators in a range of fields and disciplines. Dr. Cuervo specializes in autophagy, a process cells use to digest and recycle old proteins and other waste products. Her research has resulted in better insights into, and possible treatments for, a number of diseases, including Parkinson's disease, Alzheimer's disease and cancer. Dr. Cuervo is a professor of developmental and molecular biology, of anatomy and structural biology and of medicine, and is the co-director of the Institute for Aging Research. She holds the Robert and Renée Belfer Chair for the Study of Neurodegenerative Diseases at Einstein.

Remembering a Giant of Endocrinology

On May 31, the Einstein-Montefiore community learned of the unexpected passing of longtime, beloved faculty member and mentor **Norman Fleischer, M.D.**, a professor emeritus of medicine and former chief of the division of endocrinology. He was 82.

"Dr. Fleischer was a brilliant clinician, researcher and leader as well as a decent and humble person, friend, colleague and mentor," notes Yaron Tomer, M.D., a professor and the chair of medicine and a professor of microbiology & immunology, and the Anita and Jack Saltz Chair in Diabetes Research at Einstein and Montefiore. "He was one of the giants of our institution."

Norman Fleischer joined Einstein in 1972 and made countless contributions to the field of diabetes and to the Einstein and Montefiore community. An internationally recognized authority on diabetes treatment and research, he studied both type 1 and type 2 diabetes and how the body regulates insulin production and secretion. He also investigated the use of pancreatic beta cells as a possible cell-based treatment.

In 1976, Dr. Fleischer successfully submitted a grant to the National Institutes of Health (NIH) to establish the first Einstein Diabetes Research and Training Center, which has received NIH funding ever since. Dr. Fleischer also built a robust clinical endocrinology, diabetes and metabolism division, which has trained nearly 60 fellows and has 30 full-time faculty members.

"He was a consummate physician who was widely sought after and was committed to the social mission at Einstein and Montefiore," notes Harry Shamoon, M.D., a longtime colleague, a professor of medicine and the associate dean for clinical and translational research at Einstein.

After Dr. Fleischer retired as chief in 2017, a special research symposium was held to recognize his talent as a leader, scientist, clinician, mentor and humanitarian. In his opening remarks, Steven M. Safyer, M.D., president and chief executive officer of Montefiore Medicine, announced the formation of the Fleischer Institute for Diabetes and Metabolism at Montefiore and Einstein, named in Dr. Fleischer's honor.

Tenure for Nine Einstein Professors

Felipe Diaz-Griffero, Ph.D.
Professor of Microbiology & Immunology and the Elsie Wachtel Faculty Scholar

Teresa P. DiLorenzo, Ph.D.
Professor of Microbiology & Immunology and of Medicine, and the Diane Belfer, Cypres & Endelson Families Faculty Scholar in Diabetes Research

Aristea S. Galanopoulou, M.D., Ph.D.
Professor in the Saul R. Korey Department of Neurology and in the Dominick P. Purpura Department of Neuroscience

Charles B. Hall, Ph.D.
Professor of Epidemiology & Population Health and in the Saul R. Korey Department of Neurology

Jonathan R. Lai, Ph.D.
Professor of Biochemistry

Sophie Molholm, Ph.D.
Professor of Pediatrics, in the Dominick P. Purpura Department of Neuroscience and of Psychiatry and Behavioral Sciences, and the Muriel and Harold Block Faculty Scholar in Mental Illness

David J. Sharp, Ph.D.
Professor of Physiology & Biophysics, of Ophthalmology and Visual Sciences and in the Dominick P. Purpura Department of Neuroscience

Xingxing Zang, Ph.D.
Professor of Microbiology & Immunology, of Medicine and of Urology, and the Louis Goldstein Swan Chair in Women's Cancer Research

Deyou Zheng, Ph.D.
Professor in the Saul R. Korey Department of Neurology, the Department of Genetics and the Dominick P. Purpura Department of Neuroscience

Joseph A. Sparano, M.D., led TAILORx, the largest breast cancer treatment trial in history.

Chemo and Early Breast Cancer

Women with the most common type of early-stage breast cancer can safely skip chemotherapy without jeopardizing their survival or risk of cancer recurrence, according to the results of the largest-ever breast cancer treatment trial, published in June in the *New England Journal of Medicine*. TAILORx (Trial Assigning Individualized Options for Treatment) was led by Joseph Sparano, M.D., the associate director for clinical research at the Albert Einstein Cancer Center and the vice chair of medical oncology at the Montefiore Einstein Center for Cancer Care.

"The trial results provide an unprecedented level of evidence and precision to guide the use of chemotherapy in women with early-stage breast cancer," says Dr. Sparano, a professor of medicine and of obstetrics & gynecology and women's health at Einstein and the vice chair of the ECOG-ACRIN Cancer Research Group, a cancer clinical trials group. "We now know that the large majority of such women—those facing an intermediate risk for cancer recurrence—don't need chemo."

After surgery, breast cancer patients commonly receive chemotherapy as a precaution against often-fatal cancer recurrence—even patients considered at low risk for recurrence and for whom chemo's benefits were uncertain. To guide their use of chemo, doctors use a 21-gene expression test, the Oncotype DX assay, which yields a score indicating a low, intermediate or high risk that a woman's breast cancer will recur.

About two-thirds of women who are tested—an estimated 65,000 each year in the United States—receive an intermediate-range recurrence score. Whether chemo helps them was uncertain, yet often they received it as a precaution. A major goal of TAILORx was to discover whether chemo helps them.

The trial recruited nearly 10,300 early-stage breast cancer patients, at more than 1,000 sites worldwide, who had undergone surgery. Their cancers had not spread to lymph nodes and were hormone-receptor positive (i.e., their growth was fueled by hormones) and HER2-negative (i.e., they would not respond to the drug Herceptin).

At the start of the trial, each participant's tumor tissue was tested using the Oncotype DX assay. Patients with low recurrence scores (0 to 10) were assigned to receive endocrine therapy alone. Patients with high recurrence scores (26 to 100) were assigned chemotherapy plus endocrine therapy, based on evidence that women with high recurrence scores clearly benefit from chemotherapy. The largest group—the 6,700 with intermediate recurrence scores of 11 to 25—were randomly assigned to receive chemotherapy plus endocrine therapy or endocrine therapy alone.

The TAILORx findings show that women at intermediate risk for recurrence did not benefit from chemotherapy. After nine years, 93.9 percent of the women in the endocrine-only group were still alive, versus 93.8 percent of women in the endocrine-plus-chemo group.

Finding How an Antiviral Gene Works

Humans and other mammals possess an antiviral gene called *RSAD2* that prevents a remarkable range of viruses from multiplying; this has been known for years. Now, Einstein researchers have discovered the secret to the gene's success: The enzyme it codes for, known as viperin, generates a compound that stops viruses from replicating. The newly discovered compound, described in June in the journal *Nature*, offers a novel approach to attacking disease-causing viruses.

"Nature has given us a template for creating a powerful and safe antiviral compound," says study leader Steven C. Almo, Ph.D., a professor and the chair of biochemistry, a professor of physiology & biophysics and the Wollowick Family Foundation Chair in Multiple Sclerosis and Immunology at Einstein. Dr. Almo and his colleagues at Einstein, including Tyler Grove, Ph.D., a research assistant professor, and scientists at Pennsylvania State University found that the compound, called ddhCTP, disrupts the replication machinery of the Zika virus. The next step will be to test the compound against an array of viruses.

Studies had shown that viperin's expression inhibits a broad spectrum of disease-causing viruses, including hepatitis C, rabies and HIV-1. But just how it exerts its antiviral effects had remained a mystery. The current study shows that viperin catalyzes the conversion of the nucleotide CTP (cytidine triphosphate) into a structurally similar compound, or analogue: the nucleotide ddhCTP, which sabotages viral replication.

"We think that ddhCTP may be able to inhibit all flaviviruses, a class of viruses that includes Zika as well as dengue, West Nile, yellow fever, Japanese encephalitis and hepatitis C," Dr. Almo says.

ddhCTP image courtesy of Tyler Grove, Ph.D.

Soccer Heading Worse for Women's Brains Than for Men's

Women's brains are much more vulnerable than men's to injury from repeated soccer heading, says a new study by Einstein researchers published in July in *Radiology*.

Study leader Michael L. Lipton, M.D., Ph.D., and colleagues performed diffusion tensor imaging (DTI), a form of MRI, on 49 male and 49 female amateur soccer players enrolled in the Einstein Soccer Study. Both groups reported a similar number of headings over the previous year (an average of 487 headings for the men and 469 for the women).

DTI detects subtle brain damage by measuring the direction of the diffusion of water in the brain's white matter. The volume of damaged white matter in women soccer players was five times greater than that for male players. The women had eight brain regions where greater levels of heading were associated with subtle brain damage, compared with only three regions in men.

Researchers speculate that differences in neck strength, sex hormones or genetics might explain the findings.

Should soccer players stop heading? "Rather than ban heading altogether—which probably isn't realistic—we need a better handle on how many headings get players into trouble," Dr. Lipton says. "What is important about this study is that men and women need to be looked at differently." Dr. Lipton is a professor of radiology and of psychiatry and behavioral sciences, the associate director of the Gruss Magnetic Resonance Research Center at Einstein and the director of MRI services at Montefiore.

Autophagy Governs Circadian Clock

Our brains' circadian clocks control key physiological processes—sleep, body temperature, organ function and maintaining blood glucose levels. Disruption of the clock can lead to diabetes and other metabolic diseases. In a mouse study published in June in *Cell Metabolism*, Rajat Singh, M.D., M.B.B.S., and colleagues discovered that autophagy—the cellular process for cleaning up and recycling old proteins and other material—helps regulate circadian rhythms and also governs the daily fluctuations in blood glucose levels.

The researchers found that autophagic digestion also selectively targets proteins controlling the circadian clock, most notably the clock protein CRY1. CRY1 is a key regulator of circadian cycles and also helps maintain blood glucose levels by inhibiting the liver from forming and secreting glucose.

The researchers found that by digesting CRY1 mainly between 3 p.m. and 11 p.m., autophagy encourages the liver's output of glucose during those hours—the period when mice are not feeding and therefore need a boost in blood glucose to fuel their activities. Feeding the mice a high-fat diet accelerated CRY1 degradation via autophagy, which contributed to obesity-associated hyperglycemia. Conversely, blocking CRY1 degradation led to a decrease in blood glucose levels.

Dr. Singh is an associate professor of medicine and of molecular pharmacology at Einstein.

Extending Life and Health Spans

Raised levels of insulin-like growth factor 1 (IGF-1) in humans are associated with an increased risk for several types of cancer, including prostate, breast and colorectal cancer—while reductions in the growth factor's influence have been linked to longevity. But until now, no one had tested whether targeting IGF-1 could help to delay aging.

In a study published in June in *Nature Communications*, Derek M. Huffman, Ph.D., and colleagues extended the lives of female mice using a monoclonal antibody (mAb) that targeted their IGF-1 receptors as a way to inhibit IGF-1 signaling.

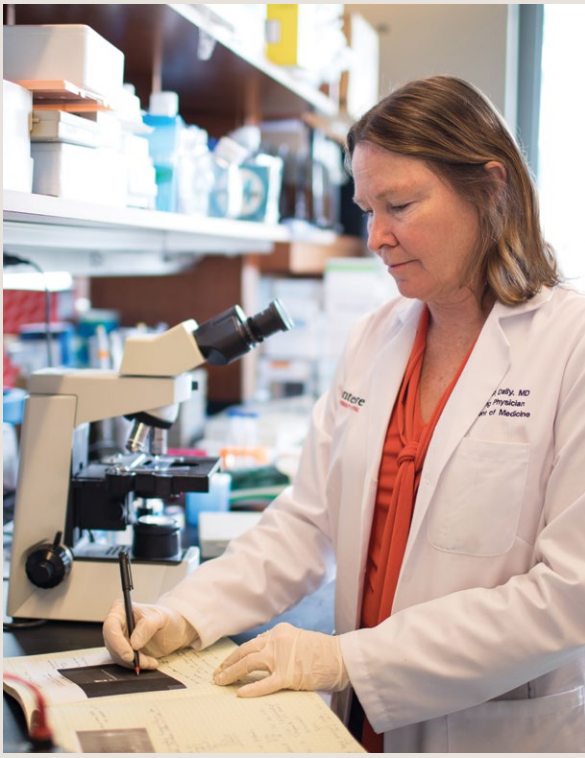
Male mice injected with the mAb showed little improvement compared with male controls, but mAb-treated female mice fared much better with respect to life span and health span: Compared with female controls, the mAb-treated females had a median life span that was 9 percent longer. They were also less likely to develop cancer, and had more-youthful diastolic cardiac function, exercise tolerance, grip strength and motor coordination, and lower levels of pro-inflammatory proteins (cytokines and chemokines) associated with aging.

Significantly, these beneficial effects were achieved even though treatment wasn't started until the mice were well past middle age. This suggests that mAbs targeting the IGF-1 receptor could eventually be optimized for use in older women to extend their life span and health span.

Dr. Huffman is an associate professor of molecular pharmacology and of medicine, and co-director of the Chronobiosis and Energetics/Metabolism of Aging Core at Einstein.

Lab Chat

Johanna P. Daily, M.D., M.S., studies *Plasmodium falciparum*—the most lethal of the five parasitic species that cause malaria. She regularly travels to sub-Saharan Africa, the region hardest hit by the disease. There she studies the immune response of malaria patients, particularly children. Dr. Daily joined Einstein in 2009 and is a professor of medicine and of microbiology & immunology.



What is the focus of your research?

I want to understand why some children infected with *P. falciparum* develop no symptoms, while others fall into a coma and die from cerebral malaria. The best vaccine is 50 percent effective, and part of the problem is that we don't understand the basis of immunity to the parasite. If we can determine the molecular mechanisms underlying immunity, maybe we can use that information to develop a more robust vaccine.

What kind of work have you done in Africa?

I've had a number of wonderful collaborations with Einstein-Montefiore colleagues. I worked with Dr. Kathy Anastos to study the effects of HIV co-infection in malaria-infected patients. I'm now working with Drs. Gregoire Lauvau and Raquel Furtado to study the immune profiles of a cohort of infected Malawian children we've followed for more than a year. We've made some really interesting discoveries about the immune response in patients who don't develop clinical symptoms during malaria infection.

How did you become interested in infectious disease?

During my infectious disease fellowship, I did field work in Senegal to examine malaria drug resistance. I really enjoyed being in the field, collecting data and putting a story together. Infectious disease is fascinating—there's always a new pathogen emerging and always something new to learn.

What kinds of activities do you enjoy?

My partner is a jazz musician; he plays the trombone. We see jazz shows around the city, which brings us to places we might not otherwise go. I love living in New York—I still find it exciting and new.

Do you have any other hobbies?

I recently started taking piano lessons at the Bloomingdale School of Music. I took beginner lessons with other adults, and it was a lot of fun.

What are you reading right now?

One book is the Trevor Noah autobiography, *Born a Crime*. He has an amazing story of his upbringing in South Africa. The other, *Patient H.M.*, by Luke Dittrich, which I listen to while I work out in the gym, is a history of the lobotomy in neurosurgery. It's a breathtaking book, because I've been trained in evidence-based medicine, and that's not what was happening there.

When do you do your best thinking?

I do think it's on the treadmill! And sometimes I attend talks unrelated to my own work, where I'll pick up new ideas and relate them to my research. I'm definitely not thinking about science when I'm playing the piano!

What do you like best about working at Einstein?

When I was looking for a job in New York 10 years ago, I felt a natural camaraderie at Einstein during my visit. Since then, any time I've asked people for assistance or ideas, they've been fully on board. You want to have a rich scientific community that will help you take your science to a level you can't even imagine, and that's definitely happened here.

MAJOR NIH RESEARCH AWARDS

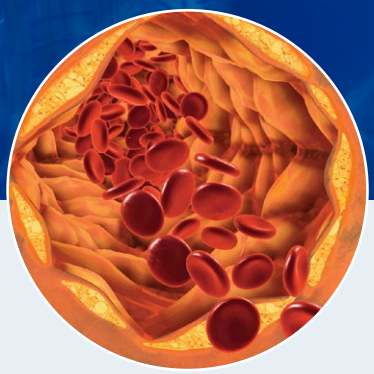
Einstein scientists will study TB infection, the origins of obesity and more, thanks to recent grants from the National Institutes of Health.

Immune Evasion in TB Infection

Mycobacterium tuberculosis, the tuberculosis (TB) bacterium, is notorious for evading the body's immune response. John Chan, M.D., Steven Porcelli, M.D., and Michael Berney, Ph.D., have found evidence that *M. tuberculosis* evades anti-TB immunity by activating an immunosuppressive pathway controlled by the host enzyme indoleamine 2,3-dioxygenase (IDO). The National Institutes of Health (NIH) has awarded them a five-year, $4 million grant to study how immunosuppression mediated by IDO activation helps *M. tuberculosis* circumvent immune defenses. Their research could lead to interventions for better TB control. Dr. Chan is a professor of medicine and of microbiology & immunology and an attending physician in infectious disease at Montefiore; Dr. Porcelli is a professor and the chair of microbiology & immunology, a professor of medicine and the Murray and Evelyne Weinstock Chair in Microbiology & Immunology; and Dr. Berney is an assistant professor of microbiology & immunology.

Investigating Autoimmunity

The more than 70 types of autoimmune diseases occur when immune cells aberrantly attack the body's own cells or tissues. CD8 T cells strongly contribute to the pathology seen in type 1 diabetes and many other autoimmune diseases. The NIH has awarded Teresa DiLorenzo, Ph.D., and Steven C. Almo, Ph.D., a five-year, $3.6 million grant to study the molecular interactions that occur when CD8 T cells target and damage tissue. CD8 T cells attack disease-causing microbes and tumors too, so knowledge gained from studying them should reveal information about T-cell biology in general. Dr. DiLorenzo is a professor of microbiology & immunology and of medicine and the Diane Belfer, Cypres & Endelson Families Faculty Scholar in Diabetes Research at Einstein. Dr. Almo is a professor and the chair of biochemistry, a professor of physiology & biophysics and the Wollowick Family Foundation Chair in Multiple Sclerosis and Immunology at Einstein.



Exploring Obesity's Origins

Intrauterine growth restricted (IUGR) newborns weigh less than average but later risk becoming obese or overweight. Studies suggest that IUGR-related obesity may stem from epigenetic alterations during fetal life—in particular, changes in DNA methylation patterns. The NIH has awarded Maureen J. Charron, Ph.D., and Mamta Fuloria, M.B.B.S., a five-year, $3.5 million grant to study DNA methylation of CD3+ T cells, which contribute to obesity by triggering fat-cell inflammation. The researchers will examine the CD3+ T cells of IUGR babies at birth and at age 2, to see whether changes in DNA methylation patterns persist. The study may identify early biomarkers for predicting obesity later in life. Dr. Charron is a professor of biochemistry, of obstetrics & gynecology and women's health and of medicine. Dr. Fuloria is an associate professor of pediatrics and a neonatologist at Children's Hospital at Montefiore.

Cardiovascular Disease in HIV+ Individuals

People living with HIV face increased risk for cardiovascular disease (CVD). Evidence suggests that gut microbiota altered during HIV infection may contribute to HIV-related CVD. Qibin Qi, Ph.D., and colleagues received a four-year, $3.3 million NIH grant to study whether gut microbiota trigger HIV-related CVD by disrupting metabolites (intermediate metabolic products) and increasing inflammation and immune activation. Their research involves 400 men and women, two-thirds of whom are HIV+. Their gut microbiomes and metabolite profiles will be studied and—to assess for CVD—they'll undergo carotid artery ultrasound imaging and tests for serum and cellular inflammation and immunology markers. Since treatment may be able to influence both gut microbiota and related immune and inflammation activity, the findings may have major public health implications. Dr. Qi is an associate professor of epidemiology & population health.

Insights into Antibody Creation

The immune system depends on mutations in genes that code for antibodies to spawn the wide variety of antibodies that protect against pathogens. The enzyme responsible for these mutations, activation-induced deaminase (AID), sometimes mutates other genes as well, leading to B-cell lymphoma and other cancers. Matthew Scharff, M.D., and Stony Brook University's Thomas MacCarthy, Ph.D., were awarded a five-year, $2.9 million NIH grant to learn how AID targets specific regions within antibody genes. Understanding how AID induces gene mutations could lead to new vaccine strategies and reveal risk factors for cancers in which AID is implicated. Dr. Scharff is a distinguished professor of cell biology and of medicine and holds the Harry Eagle Chair in Cancer Research/National Women's Division. Dr. MacCarthy is an assistant professor of applied mathematics and statistics at Stony Brook University and did his postdoctoral training at Einstein.

ENZYMOLOGIST EXTRAORDINAIRE

Vern Schramm's journey to Einstein and his contributions to science and health

BY LARRY KATZENSTEIN

Four billion years ago, when the first gene awoke within the first primordial cell and life began, that first gene may well have coded for an enzyme.

Enzymes are proteins that govern metabolism. Human cells contain some 10,000 distinct kinds. Enzymes act as catalysts, speeding reactions within biochemical pathways that perform the key tasks of life—converting food to energy, making neurotransmitters, getting rid of waste material, contracting muscles. Without enzymes, these vital reactions would occur far too slowly to sustain life.

Unfortunately, enzymes also trigger cancer, bacterial infections, hypertension and many other health problems. In fact, enzyme inhibitors account for some 30 percent of all marketed drugs, including aspirin, Viagra, cholesterol-lowering drugs and ACE inhibitors for treating hypertension. Today, as pharmaceutical research increasingly focuses on curing disease by curbing enzyme levels, a key contributor to this effort is Einstein's Vern Schramm, Ph.D., a professor of biochemistry and the Ruth Merns Chair in Biochemistry.

Dr. Schramm has pioneered the development of compounds called transition-state analogues, which inactivate enzymes involved in numerous human diseases. They bind specifically to their enzyme targets and do so thousands of times more powerfully than most other enzyme inhibitors yet developed. This binding of analogue to enzyme short-circuits disease by preventing enzymes from catalyzing their normal reactions. Such compounds have the potential to transform healthcare.

In 2017, Dr. Schramm's analogue for treating peripheral T-cell lymphoma was approved for use in Japan—the first Einstein-developed drug ever to reach the market. A transition-state analogue against the Ebola and other viruses is being developed and may soon be stockpiled for future outbreaks. More are in various stages of development, including analogues for treating stomach ulcers and antibiotic-resistant bacteria.

This article describes Dr. Schramm's analogues and what they do. It starts with the man himself: his journey from South Dakota to Einstein and to his

Clockwise from upper left: The traveling carnival operated by Vern's family; Vern at age 20; a Gilbert chemistry set; Vern at age 10; Vern, second from left, with carnival friends.

status as one of the world's pre-eminent enzymologists. He was elected in 2007 to the National Academy of Sciences, the nation's most prestigious honorary society for scientists.

SEEKING TO SOLVE THE UNSEEABLE

Ask Vern Schramm about his earliest memory and he'll take you back to a hot Midwestern summer in the early 1940s: a 3-year-old traveling with a carnival on dusty roads through South Dakota and into Iowa and Minnesota—four days entertaining folks in one small town, then moving on to another.

"The carnival was the family business—the brainchild of my maternal grandfather, who started it in 1926," he recalls. "It was a pretty big operation and needed five semitrailer trucks to transport everything. It had a Ferris wheel, several rides like the Tilt-a-Whirl with its spinning cars, many sideshows—throwing balls at a pyramid of bottles to win a teddy bear, that kind of thing—along with a few monkeys and two elephants named Judy and Alice."

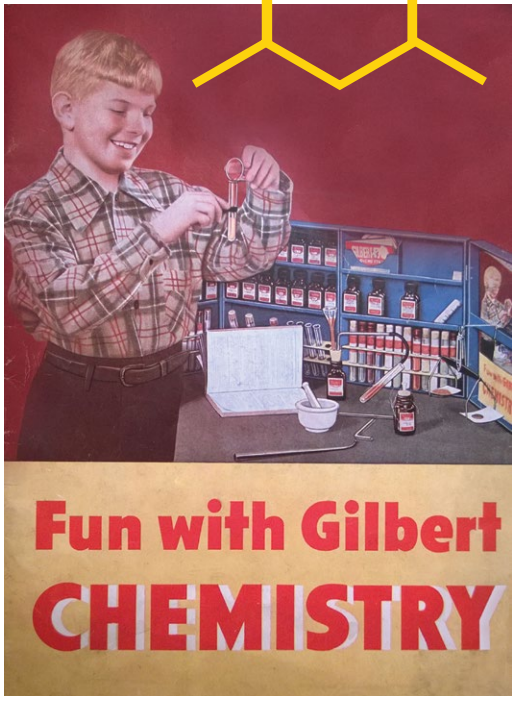


Image courtesy of the Eli Whitney Museum

The third of five children, Vern (as he likes to be called) was born in 1941 in the small town of Howard, SD (population 1,000), where the carnival was based. He was born at home, not in a hospital—standard for that time and place.

When the carnival was sold in 1946—mostly because of the strain caused by constant travel and the vagabond lifestyle—Vern's family concentrated on its electrical business. The storefront was full of televisions, washing machines and dryers, either for sale or in various stages of repair.

But for Vern, the machine shop in back was the place to be: a huge space once used for repairing carnival equipment during the winter, still filled with broken merry-go-round horses and other carnival remnants and the machines and welding torches for fixing them.

"It was an amazing place where you could do anything with metal," he says. "My brother and I had free rein to go back there and we'd weld and cut and torch. That was our playground during childhood, which I think contributed to my inventive nature."

Vern credits his interest in chemistry to his Gilbert chemistry set, a Christmas gift from his parents. "Chemistry sets in those days had compounds like sulfur and potassium nitrate and, of course, we could make charcoal ourselves. With all the ingredients for gunpowder, I helped my brother and his friend the preacher's son make Fourth of July fireworks. This inspired me to try making nitroglycerin—but fortunately I wasn't a very good chemist at age 12 and never blew anything up. But I certainly tried."

GO EAST, YOUNG MAN

His other passion was reading. "I read all the time when I was in high school," Vern says. "I read encyclopedias, books about chemistry, the classics—almost all the books in our high school library." He was not a good student, however. "I liked to learn but didn't like to study," he recalls.

Vern attended the local college, the South Dakota State College of Agricultural and Mechanic Arts, where, not surprisingly, he majored in chemistry. But in his junior year, he was offered a research assistantship and free tuition if he'd switch to a microbiology major. He stayed on after graduating, working full-time as a technician with no plans for the future. Then came the phone call that changed his life.

"One day at school I got a call from someone at the Harvard School of Public Health wondering if I'd like a fellowship to complete a master's degree in the department of nutrition. I said 'Yeah, okay.'" Unbeknownst to Vern, South Dakota State's chair of microbiology had recommended him to a good friend who worked in the department.

"Going from South Dakota State to Harvard was like moving to outer

space," says Vern, who—aside from his forays with the family carnival—had ventured out of state just once before.

As Vern was finishing his master's degree, he spotted an ad on a library bulletin board. The Australian National University (ANU) was seeking Ph.D. students. By then he had married Deanna, a South Dakota State classmate, and the couple had an infant daughter. His application to the Ph.D. program in biochemistry was accepted, and he and his family headed for Canberra, Australia.

John Morrison, the ANU professor who'd informed Vern of his acceptance and took him on as a grad student, was a highly respected enzymologist. His special interest was tight-binding enzyme inhibitors, which would become a focus of Vern's own scientific career.

After earning his Ph.D. in biochemistry, Vern returned with his family to the United States, where he did a postdoctoral fellowship at NASA's Ames Research Center in California. He then got a faculty position in biochemistry at Temple University Medical School in Philadelphia. There he studied the mechanisms by which enzymes transform the molecules they act on, known as substrates, into entirely different molecules called products, and how those reactions occur so incredibly rapidly.

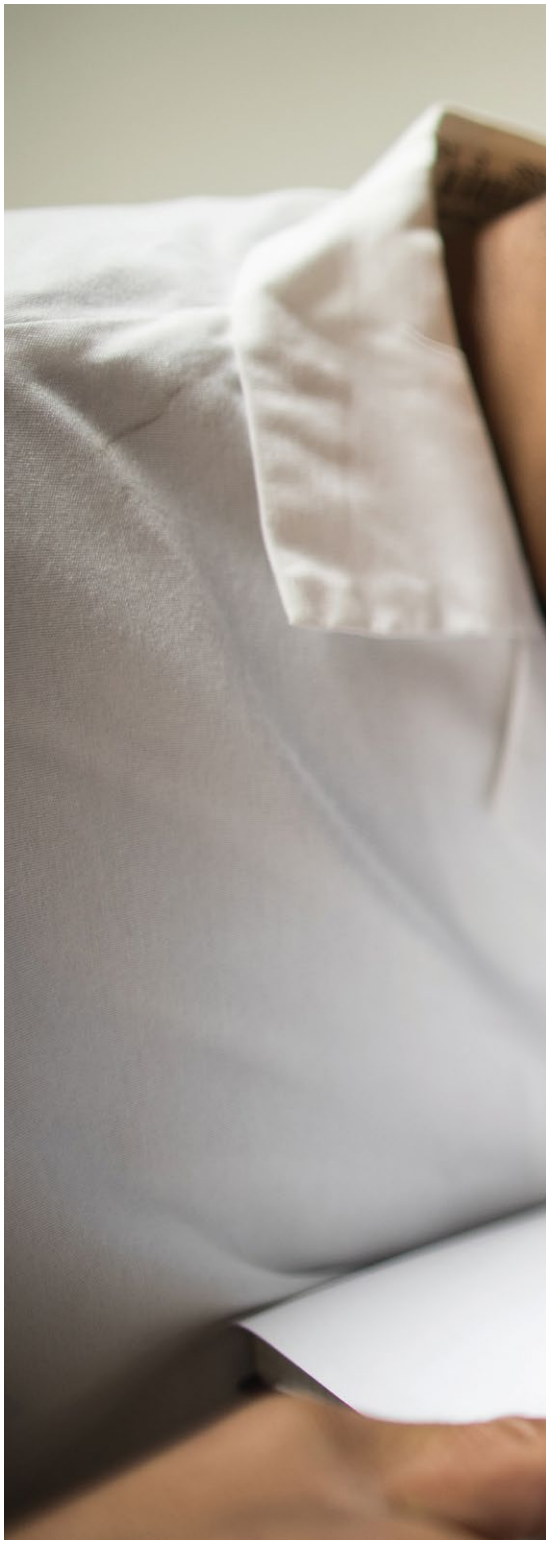
NATURE'S VITAL CATALYSTS

Enzymes have evolved over millions of years to bind to certain substrates and catalyze reactions with optimal efficiency—typically 10^{10} to 10^{15} times faster than would be possible without them. An enzyme's three-dimensional shape—its conformation—results from its amino-acid sequence. That shape, in turn, determines the enzyme's specificity: the particular substrates it can physically attract.

Enzymes have evolved over millions of years to bind to certain substrates and catalyze chemical reactions with optimal efficiency.

An enzyme molecule will bind to and interact with one substrate molecule after another. But only a small portion of the enzyme—its active site—binds the substrate molecule tightly enough to catalyze an enzyme reaction. The enzyme's active site bristles with catalytic groups that break the substrate's chemical bonds and rearrange its atoms to form a chemically different product. But for catalysis to occur—for substrates to become products—a structure called the transition state must form during the enzyme reaction.

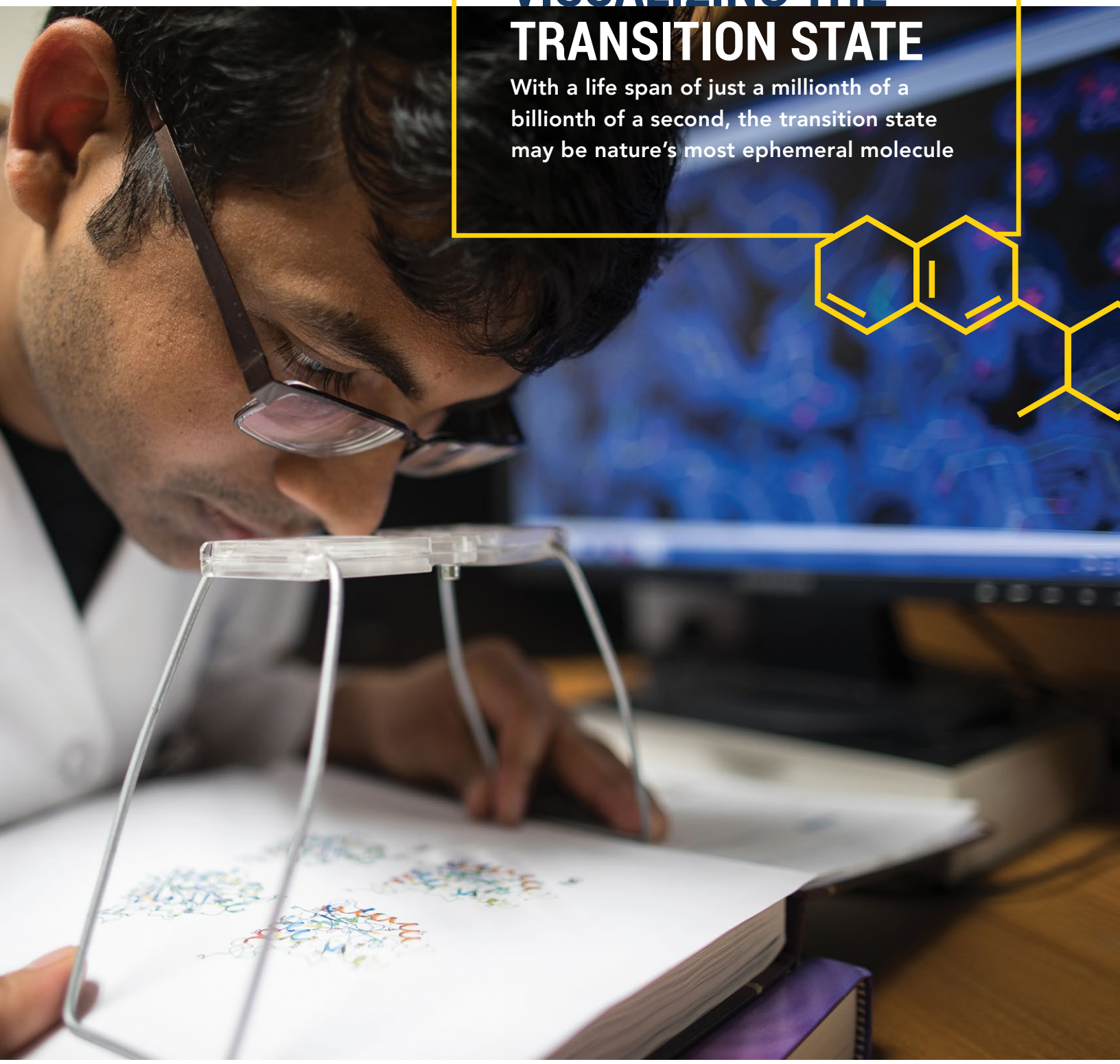
Seventy years ago, two-time Nobel laureate Linus Pauling hypothesized that enzymes bind tightly to substrates during transition states, which accelerate the conversion of substrates into products. Vern's great achievement was finding a way to visualize transition states' incredibly brief lives—they exist for just a millionth of a billionth of a second—and use that information to attack some of humankind's most intractable diseases.



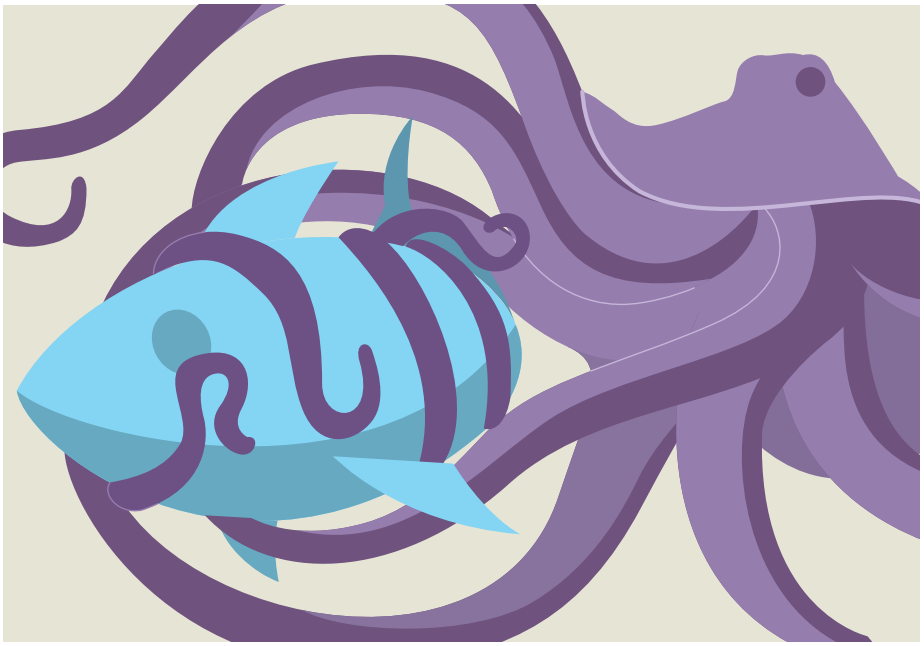
At right: Rajesh Harijan, Ph.D., a postdoctoral fellow in Vern's lab, examines enzyme-inhibitor molecules.

VISUALIZING THE TRANSITION STATE

With a life span of just a millionth of a billionth of a second, the transition state may be nature's most ephemeral molecule



ENZYMOLOGIST EXTRAORDINAIRE



© Margaret Nielsen

Grasping the transition state: Picture an octopus that explores a captured fish with all eight tentacles. The tighter the collective grip, the faster the fish can be swallowed.

GRASPING THE TRANSITION STATE

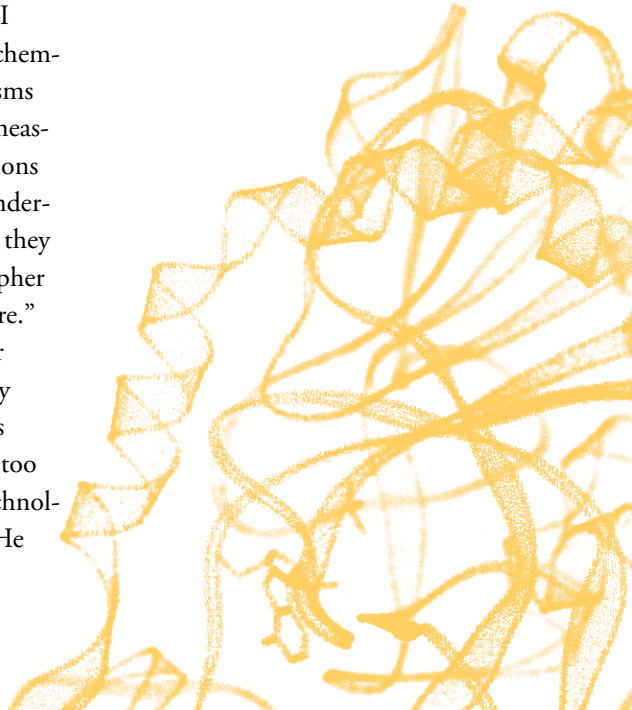
Picture an octopus that has captured a fish and explores it with all eight tentacles, seeking the optimal combination of grips to immobilize it: the tighter the collective grip, the faster the fish can be swallowed. Something similar happens when an enzyme captures a substrate molecule and clasps it to its active site.

Instead of tentacles, the enzyme's active site uses its catalytic groups to explore the surface of the captured substrate, seeking interactions tight enough to break its chemical bonds and catalyze the reaction. Finally—and only when multiple interactions have reached optimal strength at exactly the same time—comes the transition state: a swirl of atoms and electrons amidst chemical bonds that are breaking and releasing energy to speed the reaction to completion. The fleeting transition state that forms is neither substrate nor product, but rather a ghostly combination of both of them.

The transition state is the beating heart of enzymology—and of life: Its formation provides the essential chemical changes needed for all of biology's metabolic functions. But what did these short-lived structures look like? Vern was well suited to solve that mystery.

"Ever since I was an undergraduate, I'd been interested in how enzymes worked and how they perform amazing chemical reactions so hard to achieve using organic chemistry," he says. "I wanted to know about the atomic chemistry that governs enzyme mechanisms and investigate enzyme kinetics—measuring how changing certain conditions alters reaction rates. I felt that to understand enzymatic reactions and how they proceed so fast, you needed to decipher the transition state's atomic structure."

Vern began that effort soon after arriving at Temple in 1971. Directly observing transition-state structures was impossible: They disappear far too quickly to be seen with imaging technology such as X-ray crystallography. He



How to Freeze
A FEMTOSECOND

Transition states last for a millionth of a billionth of a second—far too brief a period to be observed directly. Vern knew that two features are needed to describe all molecular interactions in biology: their geometric shape and the distribution of their electrons. He realized he could use isotope effects to describe both features and, by doing so, solve the transition-state structures of enzymes.

Isotopes are different-mass versions of naturally occurring atoms, such as the hydrogen, carbon and nitrogen atoms that typically form substrate molecules. An ordinary hydrogen atom, for example, has an atomic weight of one (one proton), while its isotope deuterium has an atomic weight of two (one proton plus one neutron). Isotopes soared to the forefront of scientific consciousness after World War II: tritium, for example—hydrogen's heaviest isotope, with an atomic weight of three—was a key ingredient in the hydrogen bomb.

Kinetic isotope experiments involve taking the substrate of an enzyme reaction and replacing its hydrogen, carbon and nitrogen atoms with heavier isotopes. Running those mass-altered substrate variants one at a time through the enzymatic reaction gives an atom-by-atom readout of how those atoms respond to the transition state.

"Each atomic substitution alters the substrate's bond-vibrational frequency in the transition state, causing a small but measurable change in the reaction time compared with the time required when the enzyme reacts with normal, 'unsubstituted' substrate molecules," Vern says. "Those isotope effects on the reaction rate are exquisitely difficult to measure, but I love doing that analytical chemistry work."

Combining the results of those isotope-effect experiments provided crucial insights into the transition state's geometric shape and electron distribution—information needed to deduce the transition state's atomic structure. The final step: Use computational quantum chemistry to search through thousands of the enzyme's theoretically possible transition states to find the model that most closely matches the experimental results from kinetic isotope studies.

"That structure is the most complete picture of an enzyme's transition state that we can get," Vern says. "Now that we have a blueprint of the transition state, we can design stable transition-state analogues that will mimic its structure and, we hope, powerfully inhibit that enzyme."

READ MORE
Learn how persistence paid off for Vern, who used isotopes to find transition states despite the skepticism of his peers:
magazine.einstein.yu.edu/isotopes18

realized that the only way to "see" transition states was by measuring kinetic isotope effects: Swapping out a substrate's hydrogen, carbon and nitrogen atoms for their slightly heavier isotopes and observing how those slight changes alter the substrate's reaction with its enzyme.

In 1984, Vern and his colleagues published their first-ever transition-state structure, for the enzyme AMP nucleosidase. Over the next few years they solved transition states for half a dozen more. "This was purely fundamental research—science at its most basic," he says. "Back then we'd given no thought to designing drugs." That would come later, when Vern saw the therapeutic potential in targeting a single enzyme.

REVELATIONS FROM A RARE DISEASE

Each year several children in the world are born healthy but by age 3 or 4 become helpless against bacterial or viral infections because their infection-fighting T cells have disappeared. In 1975, University of Washington hematologist Eloise Giblett discovered the cause: A genetic defect meant the children couldn't synthesize the enzyme purine nucleoside phosphorylase (PNP). Without PNP, the children's T cells couldn't multiply to fight infections, which overwhelm the limited number of T cells available to combat them.

Dr. Giblett's discovery meant that children born with this condition could be saved through stem-cell transplants that normalize PNP levels. It also showed that *purposely* knocking out PNP could be a useful strategy against diseases caused by excess T cells, especially since these children weren't otherwise harmed by their lack of PNP. Vern and other scientists realized that a drug specifically targeting PNP would have tremendous health implications.

Two types of blood cancer—T-cell leukemia and T-cell lymphoma—result from rapidly dividing T cells. In addition, most of the more than 70 autoimmune diseases are caused by dividing T cells that mistakenly attack a person's own tissues. A drug that specifically inhibits PNP would presumably work against all of them.

Also in the 1970s, enzymologist Richard Wolfenden at the University of North Carolina was working on a strategy for inhibiting enzymes. He'd followed up on Linus Pauling's idea that enzymes bind tightly to their substrates during the transition state and was writing equations to show how that happens. When substrate and enzyme are together at the transition state, his equations predicted, the energy buildup that occurs as the substrate's bonds are broken will dramatically increase the strength of enzyme-substrate binding by a factor of 10^{10} to 10^{15}. The tighter the binding at the transition state, the faster the reaction can proceed.

If scientists could develop what Wolfenden dubbed transition-state analogues—compounds combining features of the substrate, the transition state and the product—something else should occur: In a sea of thousands of substrate molecules, an enzyme molecule would preferentially seek out a lone transition-state analogue molecule, enticed by the prospect of forming a transition-state structure with what resembles a substrate molecule.

But unlike a "real" substrate molecule, the analogue resists chemical change when the enzyme binds to it. So now the enzyme—rather than propelling a chemical reaction—finds itself part of a stable duo: imprisoned by the analogue and bound to it millions of times tighter than if the enzyme had met up with an actual substrate molecule.

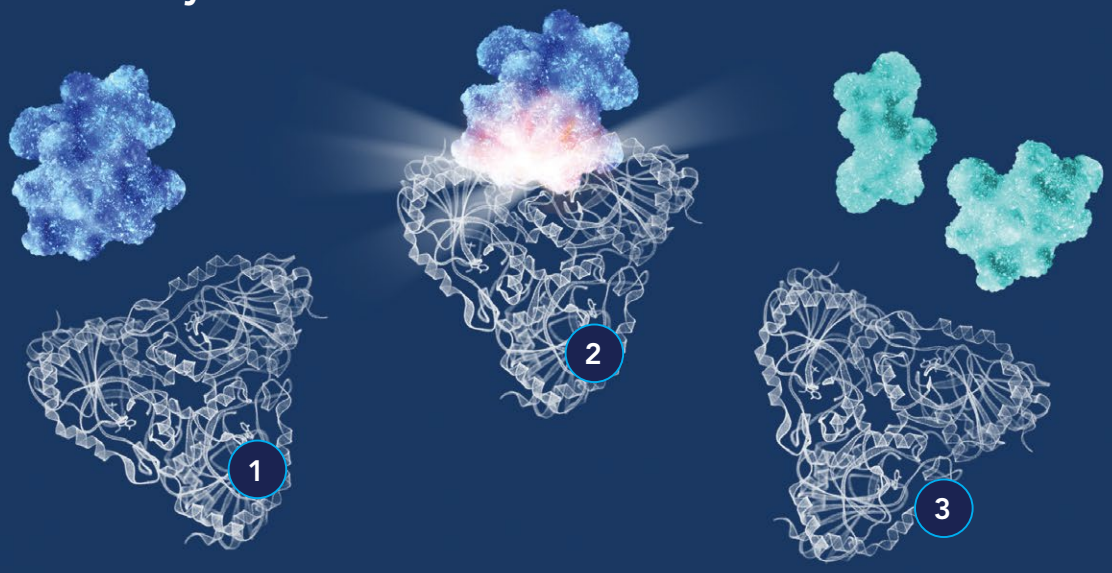
"Wolfenden's work set the stage for the search for transition-state analogues," Vern says. "But until we started our research there was no way to understand what an enzyme's transition state looked like and therefore no way to rationally design stable transition-state analogue molecules that mimic it. We realized that solving the transition state for any enzyme would put us in a good position for designing analogues to inhibit it, including PNP."

In 1987, Einstein recruited Vern to chair its biochemistry department. He agreed to take the job while continuing his research. He and his colleagues solved PNP's transition-state structure in 1993. The next step—using that structure as a blueprint for synthesizing transition-state analogues for use as drugs—would prove to be formidable. Luckily, chemists halfway around the world were looking for a challenge.

The chemists worked at Industrial Research Ltd., a government research institute in Lower Hutt, New Zealand. One day in 1991 they were visited by Paul Atkinson—a former Einstein biology professor and native New Zealander. He'd recently moved back home to direct AgResearch, a New Zealand government research facility. He soon learned that another research team—the Carbohydrate Chemistry Group—was looking for new partners.

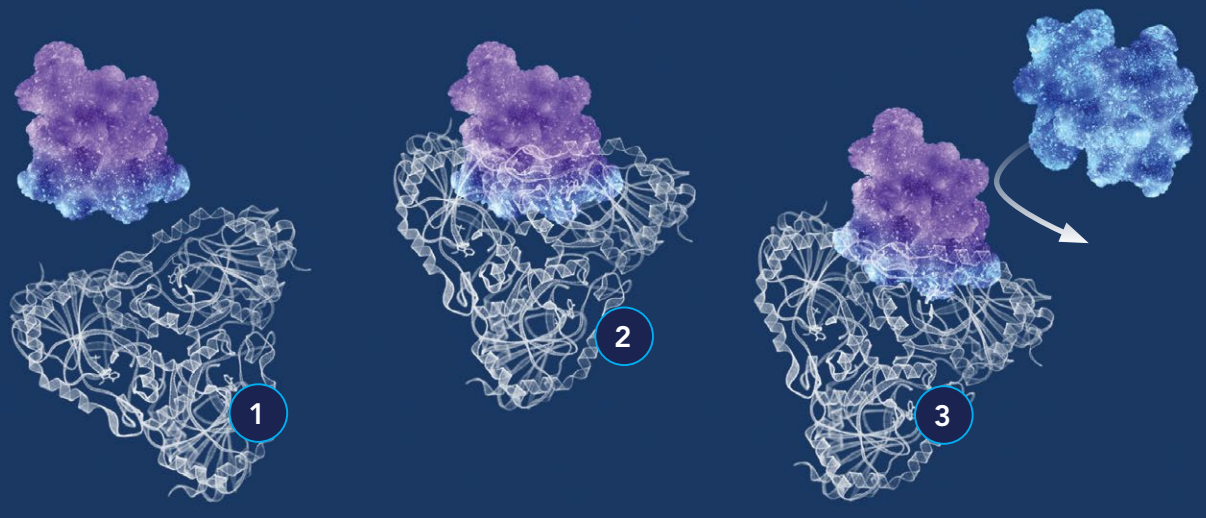
"Paul knew about my work here at Einstein," Vern says, "so he told the team leader, 'You should go talk to Vern Schramm. He's doing some interesting carbohydrate chemistry that you might want to get involved with.'"

A Normal Enzyme Reaction



(1) An enzyme molecule's active site is attracted to and binds with a substrate molecule (blue); a transition state then forms (2) to accelerate the substrate's conversion into a product or products (3).

What a Transition-State Analogue Does



Transition-state analogues inhibit the enzyme reactions that cancer cells, parasites and other disease-causing cells depend on. (1) The enzyme molecule is attracted to what appears to be a substrate molecule but is actually a transition-state analogue (blue-purple molecule); (2) the analogue binds the enzyme millions of times more tightly than a normal substrate molecule would, because the analogue's bond-breaking energy is converted to binding energy; (3) with the enzyme's active site permanently blocked by the analogue, it can no longer react with substrate molecules.

THE FIRST MARKETED EINSTEIN DRUG

Mundesine's development resulted from an unusual and ongoing research collaboration among scientists on opposite sides of the world—in the Bronx and in New Zealand

Two of the New Zealand chemists arrived in the Bronx a year later. "We drove to a waterfront restaurant in New Rochelle," Vern recalls. "Over drinks, I sketched on a bar napkin the structure of a molecule I thought would be a good transition-state analogue for PNP. The concept of transition states was new to them, but they understood the chemistry needed to synthesize the inhibitor I wanted. We shook hands and agreed to work together, sharing equally in any revenue generated."

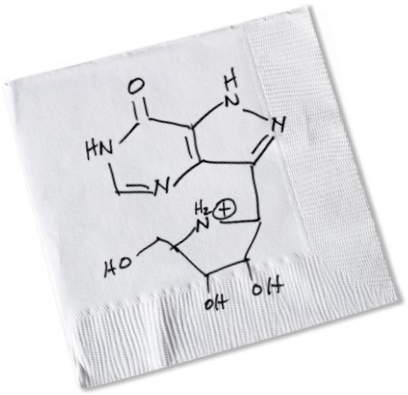
Back in New Zealand, synthesizing what became known as "the bar-napkin inhibitor" was a difficult four-year effort requiring 21 steps. Finally, the first PNP transition-state analogue was successfully synthesized, nearly identical in structure to Vern's bar-napkin sketch.

In 2000, Einstein licensed the analogue to a commercial partner, BioCryst Pharmaceuticals, Inc., for testing against blood cancers. BioCryst took the analogue through phase 2 human trials and then sublicensed it to Mundipharma, which brought it through pivotal clinical trials leading to regulatory approval. This first of Vern's PNP inhibitors, now known as Mundesine®, was approved in Japan in 2017 for treating advanced cases of peripheral T-cell lymphoma.

It took 20 years for Vern's PNP inhibitor to become the approved drug Mundesine. Ironically, the drug's potency prolonged its approval process. "Pharmaceutical companies didn't understand how to use transition-state analogues at first," he says. "There was a big learning curve before they realized just how effective these compounds are at very low doses."

Indeed, just a few milligrams of Mundesine stop T cells throughout the body from dividing. But it's their specificity that makes Mundesine and other transition-state analogues unique.

Ordinary chemotherapies can cause serious side effects by killing dividing cells, both normal and cancerous, throughout the body. But Mundesine affects only rapidly dividing T cells that cause blood cancers. Mundesine starves them of PNP, the enzyme T cells need to get rid of the chemical 2'-deoxyguanosine, which accumulates to lethal levels without PNP. Thanks to its highly specific mode of action, Mundesine is well tolerated and causes few serious side effects; it's one of the few anticancer agents that can make that claim.



Vern sketched on a bar napkin the molecule he thought would work to inhibit the enzyme PNP. Mundesine, approved in Japan in 2017, closely resembles Vern's original sketch.

Opposite: Vern (second from left) with his New Zealand collaborators, from left: Peter Tyler, Ph.D., Gary Evans, Ph.D., and Richard Furneaux, Ph.D.

When a Drug Becomes A GIRL'S LAST HOPE

Basic scientists like Vern rarely know if their work will affect human health. "Fundamental discoveries are usually single steps in a long path toward applications," Vern says. "Typically you wouldn't even know if you've contributed to a new drug." But Vern was lucky: long before Mundesine was approved for use in Japan, he learned that the drug he designed could save lives.

Mundesine's approval in Japan for T-cell lymphoma came after 19 clinical trials that spanned 10 years and involved about 500 patients with several types of cancer. The trials were intended for adults; but an early exception was made for a 2-year-old California girl (at right) with T-cell leukemia, for which Mundesine has not yet been approved.

Photo courtesy of Jeff and Linda Lambertson

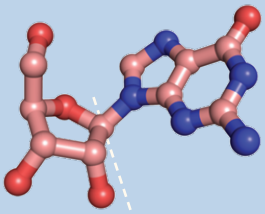
"We heard that the girl—we didn't know her name—had failed all standard therapies for T-cell leukemia," says Vern. "As a father, I could imagine how devastating that must be for a family. The company sponsoring her trial received periodic reports from her grateful dad, and their emotional impact exceeded anything else I'd experienced as a scientist." Vern finally learned more about the successful treatment of the girl, Katie Lambertson, from a 2014 magazine article.

The 10-Step Recipe for Making

ENZYME INHIBITORS

TARGET AN ENZYME ...

associated with human disease. Make sure that inhibiting this enzyme will not disturb normal physiological processes.



1

LABEL THE SUBSTRATE ...

with isotopes to reveal vibrational changes in its chemical bonds during the reaction's transition state.

2

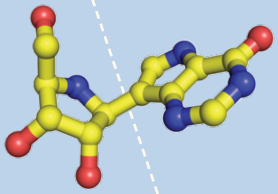
ISOLATE AND PURIFY ...

the enzyme to be studied.

3

DESIGN AN ANALOGUE STRUCTURE ...

that resembles the transition-state blueprint.



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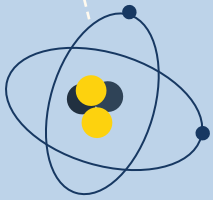


USE COMPUTATIONAL QUANTUM CHEMISTRY ...

to convert the kinetic isotope results into a blueprint of the transition-state structure.

5

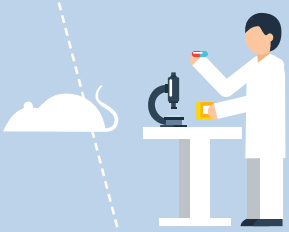
Following a tried-and-true recipe, Vern and his New Zealand colleagues have solved the transition states for some 30 enzymes and have developed analogues for about half of them.

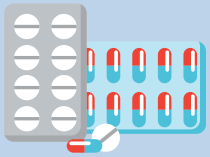
The packaging for Mundesine tablets, now on the market in Japan.

Photos courtesy of Mundipharma

DO LAB TESTING ...

to make sure the transition-state analogue can inhibit the enzyme.





LICENSE THE ANALOGUE ...

to a pharmaceutical company that will advance it through human trials.

6 7 8 9 10

COLLABORATE WITH COLLEAGUES ...

to synthesize the analogue.

LEARN WHETHER THE ANALOGUE ...

can penetrate the appropriate cells to inhibit the target enzyme and affect cells in the desired way.

POP THE CHAMPAGNE ...

when the analogue is approved for treating human disease.

FURTHER USES FOR ENZYME INHIBITORS

By targeting PNP and other enzymes, Vern and his colleagues have created powerful compounds for potential use against a variety of microbes, including the Ebola virus

Over the past 15 years, Vern and his New Zealand colleagues (now at the Ferrier Research Institute of Victoria University of Wellington) have developed even more powerful second- and third-generation transition-state analogues. They're intended for use against the numerous health problems traceable to PNP and other enzymes.

• **From STDs to Deadly Viruses.** A PNP inhibitor that failed against a parasite has emerged as the first broad-spectrum antiviral agent, effective against some of the world's most lethal viruses.

The protozoan parasite *Trichomonas vaginalis* seemed a perfect target for a PNP inhibitor. It causes trichomoniasis, a common sexually transmitted disease. And the parasite's unique version of PNP meant that inhibiting it wouldn't harm people.

"We synthesized a transition-state analogue we called Immucillin-A," Vern says. "It did a terrific job inhibiting the enzyme but failed to kill the parasite." PNP, it turned out, was not essential for the parasite's survival. But later, when BioCryst tested all its Einstein-licensed drugs against viruses, Immucillin-A prevented more than 20 RNA viruses from multiplying, including Ebola, Marburg, Zika and yellow fever.

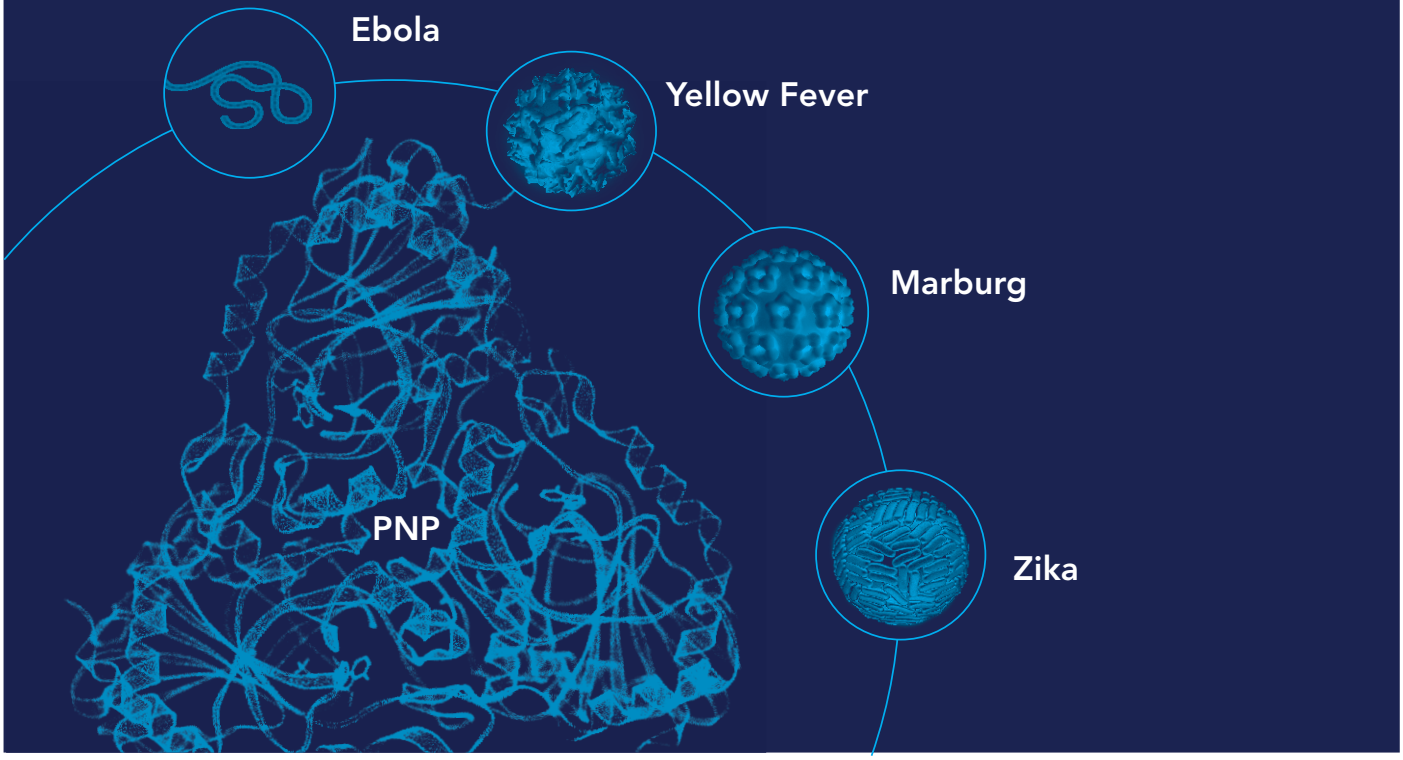
Immucillin-A doesn't actually function as a transition-state analogue against viruses. Instead, virus-infected cells absorb the analogue and metabolize it into RNA building blocks that are defective; replicating viruses unwittingly use the defective RNA building blocks, which sabotage their efforts to multiply.

"That was something we never could have predicted from our own work," Vern says. "I credit Einstein's office of biotechnology and business development, which Executive Dean Ed Burns created in 2000, for finding commercial partners like BioCryst to give our discoveries the best possible chance of being turned into drugs."

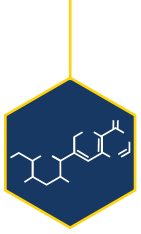
BioCryst teamed with United States government agencies to further develop the analogue, now called galidesivir. It was found safe when given intramuscularly to healthy human volunteers.

A Fortuitous Finding Goes Viral

An inhibitor designed to target the enzyme PNP in *Trichomonas* works in a totally different way to prevent deadly viruses from multiplying.



Olivia Acland / Barcroft Images / Barcroft Media via Getty Images



ENZYMOLOGIST EXTRAORDINAIRE

BioCryst has reported the results of studies in which nonhuman primates were infected with lethal doses of the Marburg or Ebola viruses. Forty-eight hours later, they received injections of galidesivir—which allowed them to survive the otherwise fatal infections. Galidesivir also demonstrated antiviral effects in nonhuman primates infected with the Zika virus.

Following more studies involving animals infected with Ebola and Marburg, galidesivir will be evaluated in additional human safety trials. If those tests are successful, galidesivir may then be manufactured and stockpiled for use in future outbreaks of the viruses.

• **Malaria.** While Ebola is scary, malaria—caused by single-celled parasites belonging to the *Plasmodium* genus—causes many more deaths: an estimated 429,000 per year.

Vern targeted *Plasmodium falciparum*, the deadliest malarial species, by exploiting its Achilles' heel: it can't directly synthesize purines, the vital building blocks for making DNA. Instead, the parasites need their own version of PNP to make hypoxanthine, which they then convert to purines. Inhibiting *P. falciparum*'s PNP would cut off its supply of hypoxanthine—and deprive the parasite of the purines it needs to survive. A PNP inhibitor, now called BCX4945, was developed to do just that.

BCX4945 proved effective against laboratory cultures and was then tested on three nonhuman primates infected with a strain of *P. falciparum* that is lethal without antimalarial therapy. When orally administered twice a day for seven days, BCX4945 cleared the infections from all the animals between the fourth and seventh day of treatment. No signs of toxicity were observed.

Results were announced in 2011, but the inhibitor has yet to be evaluated in human trials. "It's frustrating to have a potential cure for malaria sitting on the shelf," Vern says, "but the downside of licensing your compounds is that you lose control over which ones are developed. Companies are sometimes reluctant to spend hundreds of millions of dollars on human trials if sales can't replace development costs."

RESISTANCE-FREE ANTIBIOTICS

In a 2014 report, the World Health Organization called microbial resistance to antibiotics "an increasingly serious threat to global public health" and offered this warning: "A postantibiotic era—in which common infections and minor injuries can kill—is a very real possibility in the 21st century."

By wiping out most microbes they encounter, standard antibiotics actively select for antibiotic-resistant strains. The few microbes that inevitably survive the antibiotic onslaught can multiply and thrive in a milieu free of competitors. Survivors transmit their resistance traits to succeeding generations, requiring ever more potent antibiotics, leading to bacterial strains that show even greater resistance: a vicious and dangerous cycle.

In Vern's lab, a top priority is developing new antibiotics—enzyme inhibitors that "disarm" rather than destroy disease-causing bacteria.

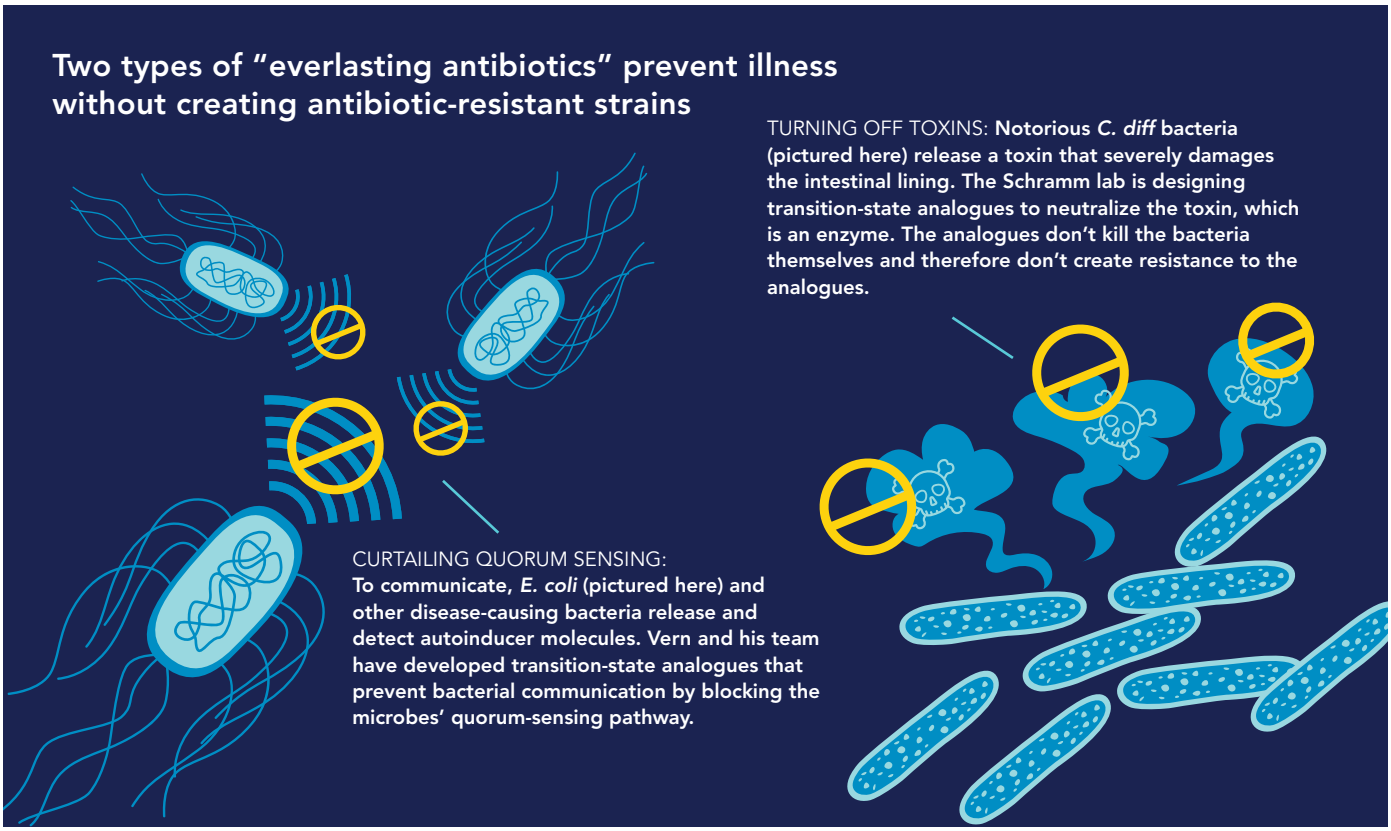
Dubbed "everlasting antibiotics," these drugs could treat infections without exerting the selective pressure that produces antibiotic-resistant strains. One type works by sabotaging communication among bacteria, and another by neutralizing disease-causing toxins. "Bacteria disarmed in these ways will simply join the body's billions of other harmless bacteria," Vern says.

• **Quelling Quorums.** Individual bacteria produce and detect signaling molecules called autoinducers that tell them how many of their colleagues are nearby. Sensing a high number of autoinducers tells disease-causing bacteria that their colleagues are present in sufficient numbers (i.e., a quorum) to change from bystander to virulent mode—attacking their hosts by releasing toxins and forming slime-coated, hard-to-treat biofilms, responsible for infections that often afflict people who have indwelling catheters.

"We hypothesized that blocking the quorum-sensing pathway in bacteria would cut the telephone wires and prevent them from communicating with each other," Vern says. He knew that the bacterial pathway for synthesizing autoinducers required an enzyme called MTAN, so he and his colleagues designed and developed a family of transition-state analogues to target it.

The MTAN inhibitors were cultured overnight with the toxin-forming bacterial species *Vibrio cholera* (the species that causes cholera) and *E. coli 0157:H7* (a potentially lethal strain of *E. coli*). The inhibitors disrupted quorum sensing in both species and significantly reduced biofilm production—without killing the bacteria. "Quorum sensing isn't essential for survival of these bacteria," he says. "So they're not killed by our MTAN inhibitors and therefore shouldn't develop resistance to them."

To see if bacteria might eventually develop resistance, Vern's lab grew 26 successive generations of the *Vibrio* and *E. coli* bacteria, all of them cultured with one of the quorum-sensing inhibitors. "The 26th generation of both bacterial species was just as sensitive to the



inhibitor as the first was," he says.

• **Turning Off Toxins.** The intestinal bacterium *Clostridium difficile* can be lethal and is difficult to treat. Infections with *C. diff*, as it's called, predominate in hospitals, where antibiotic use is common. Today's antibiotics can deplete much of a person's healthy gut microbiome but usually don't eliminate *C. diff*, which can then flourish in the gut. Ever more powerful antibiotics have recently spawned increases in highly virulent, antibiotic-resistant *C. diff* strains.

C. diff sickens about half a million Americans yearly and causes about 30,000 deaths. Illnesses and deaths occur because *C. diff* releases toxins that damage the gut wall, leading to diarrhea and potentially fatal colitis. Toxin B, the major tissue-damaging toxin, is an enzyme. Vern and his team are designing transition-state analogues against *C. diff*'s toxin B and not the bacteria themselves. "*C. diff* would not know that these antitoxin compounds are present," he says, "so there's no pressure on the bacteria to develop resistance."

SAFE TREATMENT FOR ULCERS

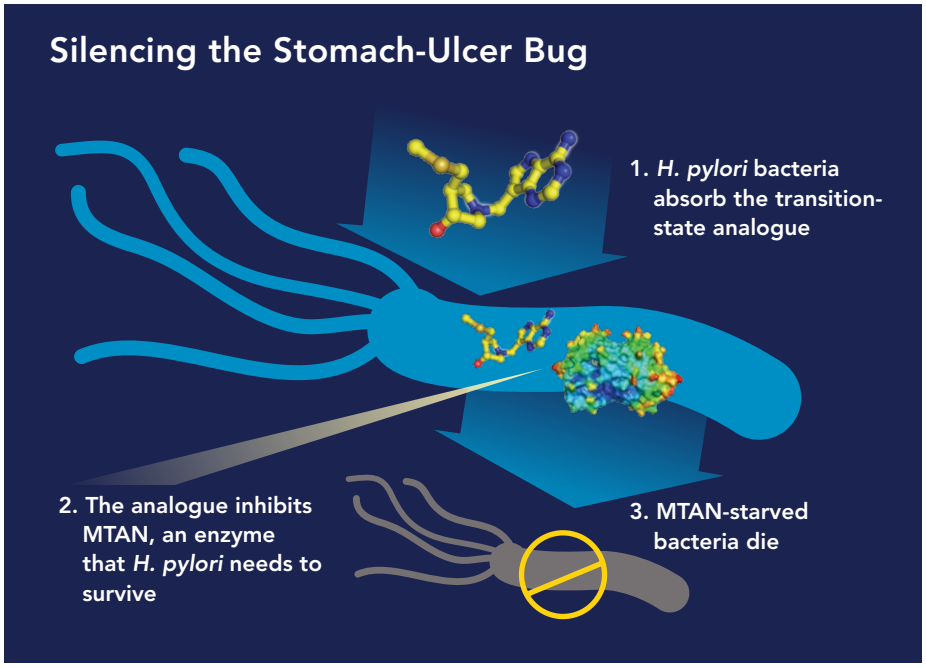
In 1982, Australian scientists Barry J. Marshall and J. Robin Warren reported that a previously unknown bacterial species called *Helicobacter pylori* causes most cases of stomach ulcers and duodenal (small-intestine) ulcers, which had long been thought to result from stress or other lifestyle factors. The discovery earned Marshall and Warren the 2005 Nobel Prize for Physiology or Medicine and transformed ulcers from a chronic, often disabling condition to a bacterial disease curable with antibiotics.

Over the past 30 years, however, *H. pylori* has become increasingly resistant

> "The *C. diff* bacteria would not know that these antitoxin compounds are present, so there's no pressure on the bacteria to develop resistance."

READ MORE
Discover Vern's strategy for attacking solid tumors: magazine.einstein.yu.edu/tumors18

ENZYMOLOGIST EXTRAORDINAIRE



to antibiotics. Even today's extra-intensive antibiotic regimen fails to eradicate *H. pylori* in 20 percent of patients. Moreover, antibiotics play havoc with patients' normal gut microbiome, clearing the way for *C. diff* to establish itself.

A 2017 study that followed 260 stomach-ulcer patients treated with *H. pylori* eradication therapy found a "significant rate" of *C. diff* colitis: 12 of the patients—4.6 percent of the total—developed the often-fatal illness. Antibiotics that eliminate *H. pylori* without putting patients' lives at risk were clearly needed.

In the midst of his quorum-sensing research targeting the enzyme MTAN, Vern read that *H. pylori* has a very unusual metabolic pathway. It depends on MTAN not for quorum sensing but for survival. "We realized our MTAN inhibitors that halted quorum sensing in other bacteria could work as antibiotics against *H. pylori*," he says.

In research published in 2015 in the *Journal of the American Chemical Society*, he and his colleagues reported that 10 of their MTAN inhibitors were up to 2,000 times more powerful at preventing *H. pylori* growth than many antibiotics now used to treat the infections.

"We think our MTAN inhibitors will capture the market for treating stomach ulcers," he says. "They're far more potent than existing *H. pylori* antibiotics, and our studies found they don't harm normal gut bacteria and so won't increase patients' risk for developing *C. diff* infections—a major drawback to current ulcer therapy." Several of those inhibitors were recently licensed to a biotech company interested in developing them into *H. pylori* drugs.

THE ROAD AHEAD

Modern medicine emphasizes finding drugs that target enzymes. Yet when it comes to developing drugs using transition-state analysis, Vern and his New Zealand colleagues have few rivals—which is surprising, because the strategy epitomizes rational drug design.

"Companies designing enzyme inhibitors typically start by searching through millions of compounds in their chemical libraries, hoping they'll chance on one that inhibits their target enzyme," Vern says. "They'll find one that works pretty well and spend years refining it for clinical trials. We start by identifying the enzyme we want to target. Once we solve its transition state, we synthesize a transition-state analogue to mimic it. If we've done things correctly, that analogue becomes the compound that will go into clinical trials."

His different approach, he notes, "requires many cutting-edge scientific technologies that pharmaceutical companies find daunting." But he predicts they'll see the light. "If we get three or four drugs FDA-approved using this process, which could occur in the next decade, transition-state analysis will become a standard procedure that pharmaceutical companies will use to design and develop new drugs."

As for his own research, he says, "the enzymes we're now targeting are posing some very tough challenges—transition states that are hard to solve and analogues that will be difficult for our New Zealand colleagues to synthesize." But he thrives on such challenges.

"You have to be optimistic as a scientist," Vern says. "There are always four reasons to think an experiment might fail, but you've got to do the experiment anyway and be prepared for all those failures before you do the correct one. That sense of optimism helps us move forward. There are a lot more enzymes out there that we need to target." E

At left: Yacoba Minnow, a Ph.D. student in Vern's lab, carries out pipetting for an experiment.

PASSIONATE
PURSUITS

The Bird Artist

BY GREG DAUGHERTY

By day, she's a technical writer in Einstein's department of information technology, translating complex jargon into clear English.

In her leisure time, she can sometimes be found at her dining room table, translating scenes from nature into colorful paintings.

Although the two disciplines—keystrokes on the one hand, brushstrokes on the other—may seem worlds apart, Prathima Pailoor sees a link. "Both involve creativity," she says. "With technical writing, it's about how to present the material in a better way so that people will understand it and even want to read it." Her current work focuses on creating simplified user guides to help members of the Einstein community with the software applications the IT department supports.

THE ARTIST'S MUSE

Einstein had a preview of her work recently when her acrylic painting *Your Majesty* was chosen as the cover art for the 2018 issue of *Ad Libitum*, the annual literary and arts magazine showcasing the work of Einstein's students, faculty and staff. Based on a photograph, it depicts a peacock, India's national bird and a particular favorite of Ms. Pailoor. "I love everything about the peacock," she says. "The colors, the way it walks, the way it dances." She may understand the peacock and its movements better than most artists: As a young, classically trained dancer in Bangalore, she says,

she performed the role of a peacock in traditional Indian dances.

Ms. Pailoor joined Einstein in 2017 after a stint as a technical writer for the state government in North Dakota. Her husband, Anil, is a clinical technologist at Montefiore. Their daughter, Priya, is a freshman at Johns Hopkins University.

A LIFELONG HOBBY

Born and reared in Bangalore, India's third-largest city (now known as Bengaluru), Ms. Pailoor graduated from Bangalore University with a degree in commerce and accounting, then went on to earn several postgraduate diplomas, including one in technical writing. She worked as a technical writer for a software company in Bangalore before immigrating to the United States in 2015.

She says she has been painting for "as long as I can remember" and credits her mother as her inspiration. "She paints, and most of my family members paint, although nobody has taken it up as a profession," Ms. Pailoor says.

These busy days, painting is a now-and-then activity. "Once I pick up a brush I do a lot of painting," she says. She doesn't have a studio but says she finds the family's dining room table "ideal—you can spread out your paints and brushes and rags." Ms. Pailoor works in both watercolors and acrylics. She likes watercolors for their sense of mystery and acrylics for their opacity, which makes it easier to correct mistakes.

Ms. Pailoor says she was surprised and honored to be selected as *Ad Libitum*'s cover artist, which has encouraged her to keep at her craft. She next wants to try her brush on some winter scenes.

Would she recommend painting as an avocation to other people? "Absolutely," she says. "Dabbling with colors can open other dimensions, which may turn out to be enriching—emotionally, psychologically and at times financially." E

A peacock, at left, painted by Prathima Pailoor graces the cover of Einstein's 2018 *Ad Libitum* arts magazine. Numerous smaller birds, at far left, are also among her subjects. Other favorites are portraits of women, like the two pictured above, and rural scenes, like the ox pulling the wagon, below. She says she is inspired by the vibrant colors and intricate patterns of Rajasthani art, named for the state of Rajasthan in western India.

PEDIATRIC FATTY LIVER DISEASE

A Silent Epidemic

BY GARY GOLDENBERG

Nobody likes to be told to give up his or her favorite foods—least of all a child who feels perfectly fine. Just ask 12-year-old Juan Mendoza of the Bronx. Three years ago, during a routine checkup, blood tests revealed that Juan had abnormal liver enzymes signaling nonalcoholic fatty liver disease (NAFLD). It's a condition in which fat silently accumulates in liver cells over many years. Unless Juan changed his diet and lost weight, he risked liver scarring and liver failure (cirrhosis) in the years ahead.

Juan was too young to appreciate the danger, but his mom, Maria Garcia, was alarmed. "I had never heard of fatty liver disease," she says. "After looking it up on the Internet, I realized we had to visit the clinic."

Ms. Garcia was referring to the Pediatric Fatty Liver Program at Children's Hospital at Montefiore (CHAM), which opened in 2015 to care for the burgeoning population of children with NAFLD. The clinic is the only one of its kind in the Bronx and now follows about 300 patients a year—a number certain to increase.

NAFLD wasn't even described until 1980. Fueled largely by the obesity epidemic—one-third of Americans are now obese—it has become the country's most commonly diagnosed liver problem. NAFLD affects people of all races and ethnicities but is most common in people of Hispanic origin, such as Juan. Up to one-fourth of Americans are now living with NAFLD, which is being diagnosed in children as young as 2. By some estimates, 10 percent of children have the disease, meaning that 30,000 kids in the Bronx may be affected.

"It's a huge, silent epidemic," says program director Bryan Rudolph, M.D., M.P.H., an attending physician in pediatric gastroenterology and nutrition at CHAM and an assistant professor of pediatrics at Einstein. "Many families are unaware of the disease and many pediatricians are not as worried about NAFLD as perhaps they should be. New professional-society guidelines call for kids to be screened for NAFLD between the ages of 9 and 12 if they are obese or are overweight and have additional risk factors. But the guidelines are not universally followed."

Juan Mendoza, 12, walks with his mom, Maria Garcia, during a visit to the Pediatric Fatty Liver Program at Children's Hospital at Montefiore.

At Juan's first visit to the clinic, Dr. Rudolph performed tests to confirm the diagnosis and rule out other liver diseases. Currently, the only way to

Illustrations: Margaret Nielsen

Nonalcoholic Fatty Liver Disease Explained

One of the liver's jobs is to store fat made from calories that the body doesn't need right away. This stored fat (in the form of triglycerides) is typically burned to produce energy. But being overweight, having poor eating habits, getting too little exercise or having diabetes can cause triglycerides to accumulate in liver cells, leading to NAFLD. (Before NAFLD was discovered, fat accumulation in the liver was thought to be limited to people who drank large amounts of alcohol.)

For most patients, NAFLD progresses no further than having a fatty liver—a benign condition called steatosis. But steatosis sometimes goes rogue, with fat deposits inflaming liver cells and damaging the liver. This severe form of NAFLD, known as nonalcoholic steatohepatitis (NASH), typically worsens over decades without causing symptoms.

NASH can ultimately lead to hepatic fibrosis (scarring of the liver) and, eventually, cirrhosis (liver failure) or liver cancer. NASH is now the third most common reason for liver transplantation and is predicted to rank as the number one reason by 2020.

Being overweight often works in tandem with genetics to cause NAFLD. Research over the past decade has highlighted the importance of *PNPLA3*, a gene involved in lipid metabolism. A variant of *PNPLA3* increases the triglyceride (fat) content of liver cells and is especially common among Hispanics, perhaps explaining why NAFLD most often affects people of Hispanic origin.

People with the *PNPLA3* variant have a greatly increased risk for developing NAFLD—but only if they're also overweight. A 2017 study in *Nature Genetics* found that lean individuals—even those with two copies of the variant—face only a modestly increased risk for NAFLD and its complications compared with people who lack the variant.

People who have two copies of the *PNPLA3* variant may benefit the most from modifying their lifestyles. A 2014 paper in the *Journal of Gastroenterology and Hepatology* described a controlled study involving 154 NAFLD patients placed on a regimen of exercise and reduced calories for one year. Compared with other patients, those patients with two copies of the *PNPLA3* variant fared best with respect to several factors, including weight loss and greater reduction in their liver-cell fat content.

Being overweight often works in tandem with genetics to cause nonalcoholic fatty liver disease.

Bryan Rudolph, M.D., and Rose M. Morales, C.P.N.P., examine Juan Mendoza.

conclusively diagnose NAFLD is with a liver biopsy, in which a slender needle is inserted through the abdomen to retrieve a tiny sample of liver tissue. The invasive test is relatively safe and painless. (Young patients are sedated.) Juan's mother vetoed a liver biopsy for her son, although she was eager to make sure that he changed his eating habits and got more exercise.

In the absence of drugs to treat NAFLD, low-calorie diets and exercise are the main interventions for people with the disease. Lowering cholesterol and triglyceride levels and, for people with diabetes, controlling blood sugar levels can also help.

Einstein-Montefiore researchers who study NAFLD include Victor Schuster, M.D. (see p. 45), and Preeti Viswanathan, M.B.B.S., an attending pediatrician at CHAM and an assistant professor of pediatrics at Einstein. Dr. Viswanathan is investigating whether liver toxicity induced by acetaminophen (Tylenol) uses the same pathways as NAFLD. If so, therapies for the former might help in treating the latter.

A HEALTHIER LIVER

Guided by the clinic's nutritionist, Ms. Garcia learned how to cut calories and fats from her native cuisine. Juan

In the absence of drugs to treat NAFLD, low-calorie diets and exercise are the main interventions for people with the disease.

resisted, as any preteen might—and so did her husband.

"While I was making changes, my husband would offer Juan the old foods," she recalls. Nonetheless, Juan eventually started eating better, and he even gave up some of his coveted video game–playing time to join his mom on her daily hour-long walks. Today, he's leaner and fitter, and his liver enzymes have improved.

When not in the clinic seeing Juan and other patients, Dr. Rudolph reaches out to local pediatricians to teach them about NAFLD screening and treatment. He's also conducting a study to assess whether noninvasive testing can be used to diagnose NALFD in children and to monitor disease progression. The testing relies on novel imaging studies and biomarkers in the blood, urine and stool, which are being compared with liver-biopsy results to assess their accuracy.

The test results will also be used to create a noninvasive diagnostic algorithm—a step-by-step procedure for helping physicians decide whether patients have NAFLD. So far, nearly 200 children have been recruited for the study.

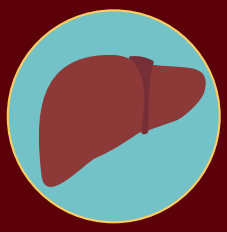
Dr. Rudolph is optimistic about Juan's future. "Lifestyle changes can prevent liver complications and even reverse early-stage cirrhosis," he says. "The liver has an amazing capacity to regenerate."

Summing up the last three years, Ms. Garcia says, "This has been a learning experience for the whole family. First, there was Juan's diagnosis. And a year ago, my husband had to go to the emergency room because of hypertension. Now, Juan is trying to persuade his father and his brothers to eat better. I think it's helping." E

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) FACTS

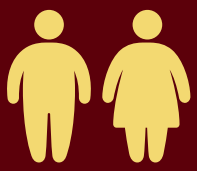
UP TO ONE-FOURTH OF AMERICANS

are now living with NAFLD. It has become the country's most commonly diagnosed liver problem.



5%

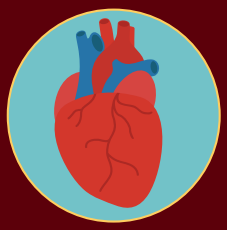
or more of liver cells contain fat droplets.



10%

of children in the Bronx have the disease, meaning that 30,000 kids in the borough may be affected.

The rise in NAFLD cases contributes to a shortage of usable donor livers for transplantation.



Having NAFLD is associated with an increased risk for developing cardiovascular disease (coronary heart disease) and stroke.

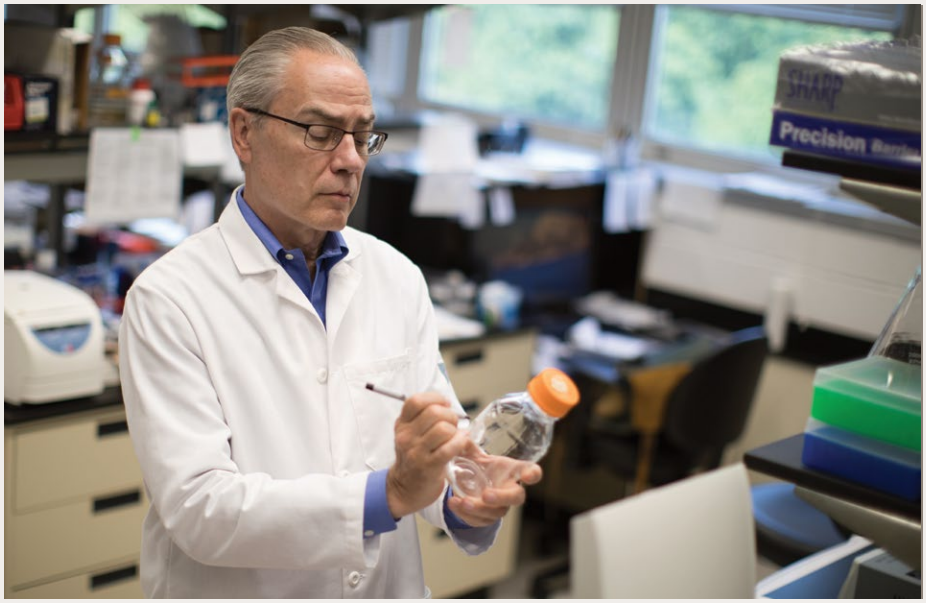
Einstein's Fatty Liver Drug Candidate

Given the increase in cases of NAFLD and the lack of therapies, scientists are searching for drugs that could prevent fat from accumulating in the liver. More than 200 trials of potential NAFLD drugs are ongoing, including several late-stage clinical trials. While it's too early to tell whether any drug candidate will pass muster, one of the most intriguing is V2, a small molecule now under study at Einstein.

V2's discovery involved some serendipity. Back in 1995, Victor Schuster, M.D., was looking for factors that regulate prostaglandins—signaling lipids that have various hormone-like effects, depending on where they are located in the body. For example, prostaglandins found near peripheral blood vessels help dilate arteries and lower arterial pressure. While doing this research, Dr. Schuster discovered a protein, which he dubbed prostaglandin transporter (PGT), that regulates the uptake and metabolic clearance of prostaglandins in tissues throughout the body.

Fast-forward to 2015, when Dr. Schuster, the Ted and Florence Baumritter Chair in Medicine and a professor of medicine, wanted to learn more about what PGT molecules do. He successfully created PGT "knockout" mice that lived to adulthood despite lacking the *PGT* gene. As expected, the knockout mice had no trace of PGT protein anywhere in their bodies.

"To our surprise, the PGT-free mice had one-third the body fat of normal mice, even while consuming twice as much food," says the researcher. "Usually, excess calories have to go somewhere, and they often get parked in the liver. But their liver cells were completely spared."



Victor Schuster, M.D., and colleagues are testing the safety and effectiveness of compounds that target a protein involved in nonalcoholic fatty liver disease.

The mice appeared to be healthy overall, and actually lived longer than normal mice.

Dr. Schuster is at a loss to explain why the absence of PGT—which performs critical functions throughout the body—wouldn't harm the animals. Yet people also can survive without it: The medical literature describes some 140 humans who are missing one or both copies of the *PGT* gene.

"For the most part they're fine, suggesting that if we can find a drug that blocks PGT in people, we'll have a safe way to treat NAFLD," he says. "Furthermore, we are aiming to block PGT only in liver cells, which should make it even safer."

By screening libraries of drug compounds, Dr. Schuster found a few that had an affinity for PGT. Unfortunately, all were large compounds, which the gastrointestinal tract generally has trouble absorbing into the bloodstream.

Enter Einstein's Evripidis Gavathiotis, Ph.D., an associate professor of biochemistry and of medicine and a drug-design expert. Using *in silico* (computer-based) modeling, which can predict how substances will interact based on their molecular structures, Dr. Gavathiotis came up with 100 novel potential anti-PGT compounds, one of which—dubbed V2—showed the most promise in tissue-culture studies. Dr. Schuster says it's the only potential NALFD drug that targets PGT.

Dr. Schuster and his colleagues are now testing the safety and efficacy of V2 and related molecules in a mouse model of NAFLD. His work is supported by a 2018 Scholar-Innovator Award from the Harrington Discovery Institute in Cleveland.

MONTEFIORE-EINSTEIN

MAVENS OF MEDICINE

Dancing With Life and Death

A Q&A with Dr. Peter Selwyn

Peter Selwyn, M.D., M.P.H., is perhaps best known for his work in HIV/AIDS care, chronicled in his memoir *Surviving the Fall: The Personal Journey of an AIDS Doctor*. He has also made significant contributions to the fields of substance abuse and palliative care. Dr. Selwyn has spent nearly his entire career at Montefiore and Einstein, where he is a professor of family and social medicine, of epidemiology & population health, of medicine and of psychiatry and behavioral sciences; chair of family and social medicine; and director of the Palliative Care Program at Montefiore.

What was it like starting your residency at Montefiore in the early days of the AIDS epidemic?

It was overwhelming seeing all these young people getting sick and dying. Montefiore essentially became an AIDS hospital. Things were bleak until 1987, when AZT, the first antiretroviral, came out. It wasn't very effective as a single drug, but it was a symbolic shift. For the first time, it seemed that this disease might be treatable.

From a professional perspective, do you miss the intensity of that era?

Certainly not the desperate intensity of caring for people with an incurable illness. At the same time, it was exciting being in the danger zone. Residents and attendings were all learning together because no one knew what this disease was about. And it was remarkable to see everyone—epidemiologists, infectious disease specialists, virologists—come together in such a short time to lay the groundwork for developing effective therapeutics.

What are the key challenges in HIV/AIDS today?

Access to care, especially internationally. And while people with HIV are living longer, they are experiencing a whole range of early chronic illnesses: heart disease, diabetes, lung disease—and on and on. This is the second wave of HIV.

How did you get involved in palliative care?

In the first decades of the AIDS epidemic, everyone was a de facto palliative-care specialist, including me. My interest in the field grew even as HIV infection became a manageable illness. There's a major need for end-of-life care, with not enough physicians trained to provide it. Unfortunately, there's also resistance to palliative care. After World War II, the idea that the miracles of modern medicine could keep almost anyone alive became the norm. Death became marginalized and sanitized, pushing aside palliative-care discussions. It didn't help that the issue became politicized, with distortions about "death panels." But when you give people choices about hospice care or home care and align the care with their needs and values, they embrace palliative care.

You've created a support program for caregivers at Montefiore. What does it involve?

About five years ago, as part of Montefiore's employee wellness program, I started the Healing Loss Workshops, which help employees deal with grief and loss and the burden of being caregivers. It's based on models of peer-group support and the work of Elisabeth Kübler-Ross, a pioneer in the field of death and dying, with whom I studied in the 1980s.

Movement and dance have become part of your life, beginning with 5Rhythms. What is this?

5Rhythms, which has been called "exercise for the right brain," is based on a movement meditation practice developed by the dancer Gabrielle Roth. I was intrigued by how creating a space for people to move freely and unself-consciously can have such an emotional healing effect. I began collaborating with Gabrielle and her organization to bring 5Rhythms to our community. We now have several classes for our staff and patients at Montefiore.

In 2016, you performed in a dance/theater piece in Greenwich Village called *Grand Rounds*. How did that come about?

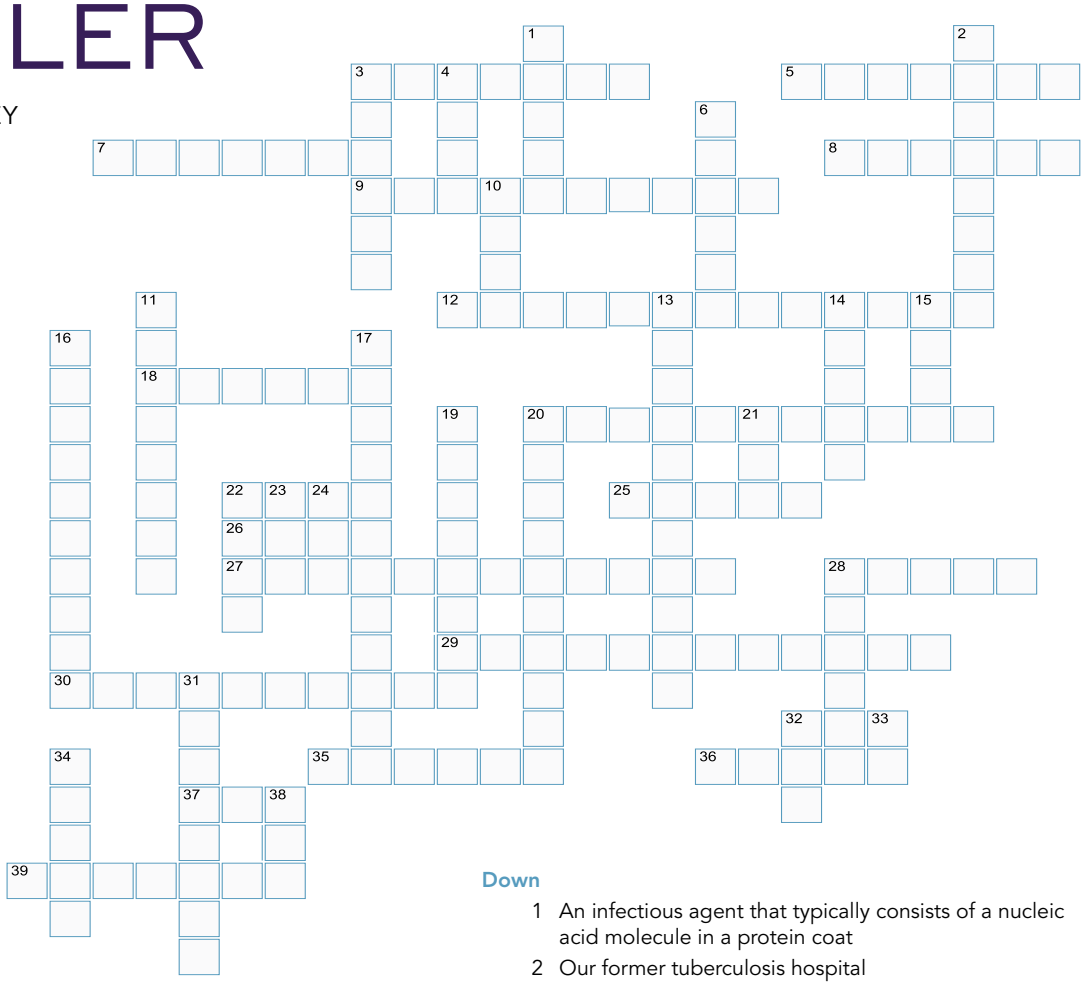
An old friend from the early days of the AIDS epidemic put me in touch with Tamar Rogoff, a dancer-choreographer who was creating a performance piece about death and dying. One thing led to another and she asked if I would like to be part of the cast. I immediately said "Yes." It was a natural evolution of my experience with 5Rhythms. I had a couple of little solos. I enjoyed the physical movement and doing something completely outside my normal day-to-day routine.

Is the Montefiore-Einstein merger influencing your work?

Having a better-integrated system will certainly support the mission of my department, which is to promote access to excellent primary care, promote community health and advocate for social justice and health equality. For example, on the Montefiore side, we will have more opportunities to collaborate with Einstein's experts in epidemiology and population health. In turn, they will have more access to Montefiore's wealth of clinical data. It's a good synergy. E

ALBERT'S PUZZLER

BY DEIRDRE BRANLEY



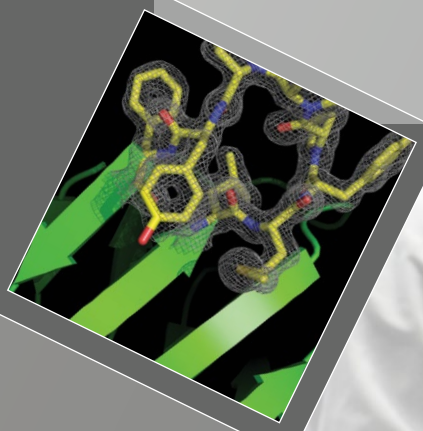
Across

3 A small protein
5 The octagon at Einstein
7 Deduced, not observed, in Latin
8 Single cell, lives in groups, not always parasitic
9 Einstein's central artery?
12 Price Center's partner
18 A catalyst for change
20 You may have spelled this building wrong
22 New immunotherapy tested at Montefiore
25 Severe
26 Jeepers!
27 Where you can stay, close by
28 Medical record
29 Where you can nosh & kibitz
30 A building down the road & colorfully translucent
32 It funds aging research, for short
35 Brown brick building on the corner
36 What happens to other people
37 Common carbon compound ending
39 Tranquil Japanese garden feature in our courtyard

Down

1 An infectious agent that typically consists of a nucleic acid molecule in a protein coat
2 Our former tuberculosis hospital
3 A molecule that serves as a starting material for a polymerization process
4 Medical prefix meaning "about"
6 Condition when you are deficient in red blood cells
10 A ____ hypothesis is a statement of "no effect"
11 Road on the other side of the tracks, affectionately
13 Home to the Winter Lobby
14 Where students meet their Match
15 An assessment method based on a student's performance, for short
16 Student homes
17 Leading cause of death in the U.S.
19 Disease with insulin problems
20 Einstein's exercise hub
21 Opposite of cold
22 Where small people are seen, briefly
23 It's only a number
24 One of the first oncogenes discovered
28 Cancer-killers' home (hint: see "A Look Back," page 65)
31 What some viruses come wrapped in
32 Bethesda-based support, briefly
33 Silver's symbol
34 Atom with an electronic imbalance
38 We have come to it: the ____

See how well you did at:
magazine.einstein.yu.edu/puzzler18



MOTIVATIONS

The Front Line of Philanthropy at Einstein Montefiore

IN THIS ISSUE

To learn more, please visit montefiore.org/fundforME and einstein.yu.edu/donors/fundforME

A Message from the President of the Alumni Association Board of Governors:

JANINA R. GALLER, M.D. '72

One of the greatest joys of my position as president of the Alumni Association Board of Governors is helping foster remarkable partnerships among alumni, current students, donors, physician-researchers, volunteers, staff and our community. *Motivations* is a fitting venue to showcase some of these inspiring partnerships and how they ultimately affect social change, scientific investigation, medical education and clinical care. In the pages that follow, we introduce you to Dr. Jose Ortiz, '92, an alumnus who exemplifies a commitment to student success (*Continued Connection*, p. 51); the Ronald M. Burde, M.D., Surgical Simulation Laboratory's philanthropy-fueled, innovative approach to state-of-the-art teaching and care (*Spotlight*, p. 54); and the Center for Immunotherapeutics' pioneering progress in cancer research (*Your Impact*, p. 58).

Whatever the level of your own involvement, we value and rely on your input. *Motivations* debuted in our last issue to great success. Fundraising and volunteerism rose, alumni felt more engaged with the institution and our community experienced continued growth. But we know we can always improve. What do you enjoy about *Motivations*? What would you like to see featured in these pages? How can we serve you best? My goal is for you to donate, to volunteer, to feel more engaged and to continue developing and connecting.

A new academic year allows me to reflect on my time at Einstein as a student more than 40 years ago. I was drawn here for the academic rigor, a commitment to compassionate medicine, outstanding teaching faculty and a strong focus on social justice. The moment I stepped on campus, one thing was clear: I knew I was in the right place. Reading through *Motivations*, I know I still am. And I'm glad you're here with me.

With warm wishes,

Janina R. Galler MD

CONTINUED CONNECTION:

JOSE ORTIZ JR. M.D. '92

Jose Ortiz Jr., M.D. '92, reflects on his time at Einstein, his path to professional success and how to increase diversity in medicine

After moving to Eau Claire, WI, to join the Mayo Clinic, Dr. Jose Ortiz Jr. went on a hunting trip with his new colleagues. Later that day, he called a friend, a fellow Hispanic, back home in New York to tell him about his outing. "Hey, I shot this turkey," Dr. Ortiz told his friend. "And he replied, in all seriousness, 'Oh no! What did the guy do?'"

Dr. Ortiz got a good laugh out of that, but it was a sharp reminder that he was the odd man out. Hispanics like him were a rarity in rural Eau Claire County, where people of German and Norwegian descent predominate. Rather than withdraw, Dr. Ortiz reached out by befriending his coworkers, soaking in the culture and visiting with locals to understand his new patients better.

The desire to make connections where none exist is a recurring motif in his 20-plus-year career, and the secret to his success. Today, he is an accomplished hand surgeon and chief of staff at Mayo's branch in Eau Claire. Early on, however, one might have bet that he'd never even earn a medical degree.

Jose Ortiz Jr., M.D., mentors a student in the Medical Experience Program at the Mayo Clinic Health System in Wisconsin.

DROPPING OUT—AND GETTING BACK IN

Dr. Ortiz dropped out of college after his third year because he needed money more than he needed a diploma. Five years working at Yale University Hospital kindled his interest in orthopedics and provided the income he needed to resume his studies. In 1988, he was accepted to Einstein, a triumph for a student of any background. But he recalls feeling out of place, academically and culturally. "That first year, I kept waiting for someone to come into class and tell me, 'We made a mistake; you're not supposed to be here,'" he says.

Determined to fit in and prove his worth, Dr. Ortiz won election as co–class president in each of his four years at Einstein. He sat on a search committee for an office of diversity dean, championed Shabbat elevators, established study groups and launched a student newspaper—efforts that exemplified Einstein's commitment to social justice and service to community. By the time he graduated in 1992, he was among the select group of students elected to Alpha Omega Alpha, one of medicine's foremost honor societies.

Not surprisingly, Dr. Ortiz chose to do his residency at New York University, which includes rotations through

At left: Class of 1992 Einstein friends enjoy a barbecue at the Falk Recreation Center in the early '90s. From left are Dr. Ortiz, Raja M. Flores, William Alago Jr. and Sandy Ganea-Alago.

Above: Dr. Ortiz, center, holds his baby son, Jose A. Ortiz III, who was the mascot for the Class of 1992 softball team. Standing, from left, are Sam Bakshian, Stewart Weinzimer, Maseith Moghaddasi, Samuel Abramovitz, Dov Linzer and Allen Chernoff. Kneeling is William Alago Jr.; sitting is Raja Flores.

Bellevue Hospital, where patient diversity is the stuff of legend. "When I was chief resident, I remember getting a call about an emergency room patient complaining that air was causing her knee to hurt. 'She's crazy,' the on-call resident told me. 'I'll notify psychiatry.' I asked if she was from Puerto Rico, and when he said 'Yes' it all started to make sense. Some Puerto Ricans believe that when you give birth, air can get inside you and cause all sorts of health problems. Had I not known that, she would have been sent to the wrong physician—and who knows what would have happened to her. Too often, things get lost in translation."

INCREASING DIVERSITY

For Dr. Ortiz, this was a clear lesson that medicine needs more people of color. "One way to increase diversity is to get kids interested in healthcare as early as kindergarten, and to show it's possible for them to become doctors," he says.

"Another issue is that some minority college students aren't ready for medical school," Dr. Ortiz adds. "But it's not enough for medical schools to say, 'We can't accept students who aren't qualified.' They must find ways to make those students ready." To this end, he helped create the Medical Experience Program, a Mayo Clinic initiative that provides high school and college students with opportunities to shadow hospital physicians in a range of specialties. "You need to see it, touch it and feel it to understand that you can have it," he says.

The cost of higher education is still another barrier to diversity, he says. "That's a big stumbling block for a lot of us. Just weeks ago I paid off my last student loan—after more than 20 years in practice."

ADVICE FOR FLEDGLING DOCTORS

Dr. Ortiz was fortunate to have a mentor in Pablo Vazquez-Seoane, M.D. (now at the South Texas Spinal Clinic), who encouraged him while at Einstein to establish himself as a leader, conduct research and strive to close any gaps in skills between himself and others vying for a competitive residency such as orthopedics. "That ethic—to reach out and work hard—became my road map to success," he says.

He has advice for today's Einstein students: "A while ago, when I was visiting Puerto Rico, I heard a physician say, 'What you are, I once was; what I am, you will become.' He meant that even if things are tough, you aren't facing anything different from those who came before you. Don't be discouraged. Have faith in yourself. The hardest thing about medical school is getting in. Once you're here, all you have to do is apply yourself. You've already shown you have the aptitude to realize your dream to become a physician. That's why they let you in." E

"Young people from underrepresented and disadvantaged populations who are drawn to the healthcare field face great obstacles along the path to matriculation. Changing that fact is my goal—and my dream."

—Dr. Juan Robles '11
Assistant Professor, Department of Family and Social Medicine

The Fund for Montefiore Einstein

By giving today, you power a better tomorrow.

Dr. Juan Robles left Honduras when he was 12 to join his mother, who had settled in the Bronx. One of Dr. Robles' most powerful memories of his first year in the United States centers on the treatment he received from Dr. Alan Shapiro, a pediatrician at the South Bronx Health Center for Children and Families at Montefiore.

"I will never forget the humanity and sensitivity Alan showed my family as we tried to navigate the health system in a strange new country," Dr. Robles recalls.

He also saw that the excellent care he was receiving wasn't the norm. "I quickly became aware of the disparities that made it harder for my neighbors to receive the quality care I was getting," he says. "Many of the kids I knew did not have access to clinicians like Alan. It was this major gap in patient opportunity and medicine that inspired my passion to become a doctor." Dr. Robles has since dedicated his life to giving his fellow immigrants access to the guidance, tools and role models that enabled his success.

Your contribution to The Fund for Montefiore Einstein plays an essential role in helping us embody excellence, serve our community and foster the thousands of human connections that students, faculty and staff members like Dr. Robles make with patients and caregivers each day.

Who in your life has powered you?

Make a donation in that person's honor by returning the enclosed envelope or donating online at **montefiore.org/fundforME** or **einstein.yu.edu/donors/fundforME** and we'll let him or her know about your generosity.

For more information, contact the office of development at 718.920.6656.

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SPOTLIGHT:

SIMULATED EYE SURGERY EQUALS REAL LEARNING

BY GARY GOLDENBERG

Donors and alumni turn a vision into reality with a state-of-the-art surgical simulation center for ophthalmology residents

Anurag Shrivastava, M.D., an associate professor of ophthalmology and visual sciences and the assistant dean for Montefiore Medical Center, winces when he recalls the first time he operated on a living human eye. He was a junior resident, and although he had observed cases and received a modicum of hands-on classroom training with rudimentary instruments and animal eyes, that preparation hadn't given him much confidence. Having an experienced surgeon at his side, talking and assisting with each step, kept the patient safe—ultimately allowing Dr. Shrivastava to learn these skills over the course of his training.

"My heart was beating out of my chest," he remembers. "I was excited, because this was something I'd been waiting to do for years. But it was very stressful—and potentially very dangerous for the patient."

That first patient did just fine. Years later, however, when Dr. Shrivastava became director of the ophthalmology residency program at Montefiore, he vowed to modernize the way fledgling eye surgeons master their art and craft.

"The conventional approach to learning skills during residency was 'see one, do one, teach one,' as the old saying goes," he says. "That's an exaggeration, but we did dive right into the operating room with almost no formal training or preparation with simulators. That wasn't a good approach in ophthalmology because of the complexity of the microscopic surgeries, combined with the extremely small margins of error."

Even cataract removal—the most commonly performed eye operation—is dauntingly complex. The surgeon must coordinate four different controls (two for the hands and two for the feet) while peering through a microscope and operating on a delicate organ that can't be completely immobilized. Further complicating the issue, patients, although sedated, are awake during surgery so that they can respond to the surgeon during portions of the procedure. It's no wonder that Dr. Shrivastava's first day in surgery was terrifying.

SIMULATED SURGERY

Today, before ever wielding a scalpel in the operating room, junior ophthalmology residents at Montefiore spend months cutting, repairing and suturing in the laboratory. This is no ordinary lab; it is a state-of-the-art digital classroom.

Officially known as the Ronald M. Burde, M.D., Surgical Simulation Laboratory, it features real operating microscopes and artificial eyes with remarkably lifelike movements and anatomical structures, which, when used along with animal eyes, allow simulation of almost any ophthalmic procedure. The new laboratory is located in the Moses Research Tower on the Montefiore campus and named in honor

Ana Rubin Panvini, M.D., resident '19, practices cataract extraction on an artificial eye with Anurag Shrivastava, M.D.

At left: The Ronald M. Burde, M.D., Surgical Simulation Laboratory helps doctors gain confidence as they practice operating on artificial eyes. From left are Jimmy K. Lee, M.D., Erin Walsh, M.D., Roy Chuck, M.D., Ph.D., and Rob Fargione, M.D., resident '17.

of the late Dr. Burde, who chaired the ophthalmology department from 1988 to 2000.

"In ophthalmology, you have to perform a particular operation 150 to 200 times before you can master it," says Roy Chuck, M.D., Ph.D., the Paul Henkind Chair in Ophthalmology, a professor and the chair of ophthalmology and visual sciences and a professor of genetics. "The learning curve in the first 20 or 30 cases is very steep. Having residents do surgical simulations in the Burde Laboratory helps flatten that learning curve by quite a bit."

Studies show that ophthalmology residents who train on simulators can reduce their real-life surgical complication rates by as much as 50 percent—to the great relief of patients and trainees alike. "In the past, we usually couldn't identify residents who were having problems until they went to the operating room," Dr. Shrivastava says. "Now we can spot their weaknesses early and give them one-on-one training in the lab. They don't move on to patients until they're as ready as possible."

As they progress through their three-year residencies, trainees graduate from simple eyelid procedures to more-complex intraocular operations, such as cataract extraction, corneal transplantation, glaucoma surgery and strabismus repair—each of which they can simulate in the Burde Laboratory.

The Burde Laboratory also features a newly constructed multipurpose computer library and a teleconferencing facility, which allows Montefiore trainees to attend remote lectures and surgical demonstrations by leading surgeons from around the country. And Einstein faculty members in turn can share their expertise with the rest of the world. Combining these resources with a lecture portal that Dr. Shrivastava has under active development will put Montefiore ophthalmology at the absolute forefront of residency education, using technology that extends its reach beyond borders.

The Burde Laboratory will serve as the testing ground for the department's Center for Ophthalmic Innovation, a novel effort to encourage advances in eye care. "When our faculty has ideas for developing new techniques and technologies or improving old ones, they'll be able to test those ideas in the laboratory, apply them in clinical practice and then refine them as needed back in the lab," Dr. Chuck says. "No other ophthalmic microsurgery lab in the country is based on that concept."

SUPPORT FROM ALUMNI AND DONORS

Dr. Burde's widow, Sharon, a longtime friend and supporter of the ophthalmology department, has been instrumental in developing the Burde Laboratory, attracting contributions from her husband's colleagues and from former trainees all over the United States. Says

Lectures and group-learning sessions take place in the Ronald M. Burde, M.D., Surgical Simulation Laboratory. At right is Arthur N. Hershaft, member of Albert Einstein College of Medicine's Board of Trustees and supporter of the ophthalmology department.

Members of the Class of 2018 practice intraocular implants. From left are Rachel Shah, M.D., Poonam Misra, M.D., Ryan Gise, M.D., and Isaac Chocron, M.D.

Dr. Chuck: "They look back and realize that it would have been so much better if they didn't have to learn on patients at the very beginning. Their support is a wonderful gift to the next generation of ophthalmologists, and a fitting legacy to a former department chair."

Support for the Burde Laboratory has also come from business executive Arthur N. Hershaft. Some 50 years ago, he began experiencing vision loss because of central serous retinopathy, a condition in which fluids collect under the retina. Experimental laser treatments stabilized his eyesight, transforming him into an avid supporter of biomedical research and innovation. A Bronx native now living in Manhattan, Mr. Hershaft has a particular fondness for Einstein, where he has served on the Board of Trustees for more than a decade.

When Mr. Hershaft turned 80, friends asked him where they could make a donation in his honor. "I consulted [then-dean] Allen Spiegel for guidance, and he mentioned the department of ophthalmology," he says. "I didn't even know Einstein had such a department. I later learned it conducts a wide range of research and handles 150,000 patient visits a year—one of the largest caseloads in the nation. Few people know what the department is doing and its value to the community. It's the biggest secret here."

Mr. Hershaft's philanthropy and that of his friends and family have helped the Burde Laboratory become an important innovation in medical education. They and their fellow donors have enabled the laboratory to train, teach and prepare residents for careers in ophthalmology today and far into the future.

"When people ask me why I support Einstein," Mr. Hershaft says, "I tell them that you can make a real difference here. You can get involved in any number of ways, and the decisions and contributions you make can directly shape the school. There aren't too many medical institutions where you can have that kind of role." E

WATCH THE VIDEO
Meet a glassblower who underwent life-changing eye surgery:
magazine.einstein.yu.edu/eyes18

YOUR IMPACT:

IMMUNOTHERAPY: TODAY'S GREAT HOPE AGAINST CANCER

A family history of cancer spurs a couple to support cutting-edge research

BY GARY GOLDENBERG

Janet and Marty Spatz are all too familiar with cancer. Janet is a breast cancer survivor; her mother died of stomach cancer, her brother of Hodgkin's lymphoma. And Marty's mother succumbed to lung cancer. "It seems like everyone we know has been touched by it," Janet says.

Determined to do something, the Spatzes went online to look for "cancer research funding opportunities,"and one of the first listings was Albert Einstein College of Medicine. "As longtime Bronx residents, Marty and I were quite familiar with Einstein and its reputation," Janet says.

The Spatzes decided to support Einstein's growing efforts in immunotherapy—arguably the most promising cancer-treatment advance of the past decade. "I know what chemotherapy does to your body, killing the good cells along with the bad," Janet says. "Harnessing your immune system to fight cancer sounded like a wonderful idea."

Donations from Marty and Janet Spatz have enabled scientists, researchers and doctors at Einstein and Montefiore to make great strides against a variety of cancers.

WHAT IS OLD IS NEW

Immunotherapy dates back to a late-19th-century surgeon named William B. Coley. He'd found dozens of cases in the literature in which a bacterial infection appeared to cause remission of an otherwise incurable cancer. The far-thinking physician designed a bacteria cocktail aimed at stimulating an immune response to soft-tissue sarcomas. Dr. Coley's "toxins" cured a few patients but killed others, and his treatment fell out of favor. It would take scientists more than a century to grasp why Dr. Coley's immunotherapy worked and to try to improve on it.

One such scientist is Steven C. Almo, Ph.D., the Wollowick Family Foundation Chair in Multiple Sclerosis and Immunology, a professor and the chair of biochemistry and a professor of physiology & biophysics at Einstein. Dr. Almo is spearheading Einstein's new Center for Immunotherapeutics, aimed at developing novel treatments for cancer and other diseases.

Dr. Almo's own research focuses on T cells—immune cells that recognize and destroy cells infected by pathogens or that have turned cancerous. The U.S. Food and Drug Administration has approved the marketing of several immunotherapies that fight cancers by revving up T cells to attack them.

Immunotherapy drugs can be quite effective but often cause harmful side effects. "The problem is that these drugs tend to affect all T cells," Dr. Almo says. "Selectively activating only those T cells relevant to a particular disease should help reduce off-target effects."

Dr. Almo begins his quest for better immunotherapies by looking for molecules called receptors bristling from the surface of T cells he's interested in, such as those that respond to melanoma or to lung cancer. Receptors on T cells serve as sentries: they recognize telltale proteins, known as ligands, present on certain cells. The ligands engage with and turn on T-cell receptors, much as a key fits into and opens a lock. The

"I know what chemotherapy does to your body, killing the good cells along with the bad. Harnessing your immune system to fight cancer sounded like a wonderful idea."

Opposite page graphic courtesy of Steven C. Almo, Ph.D.

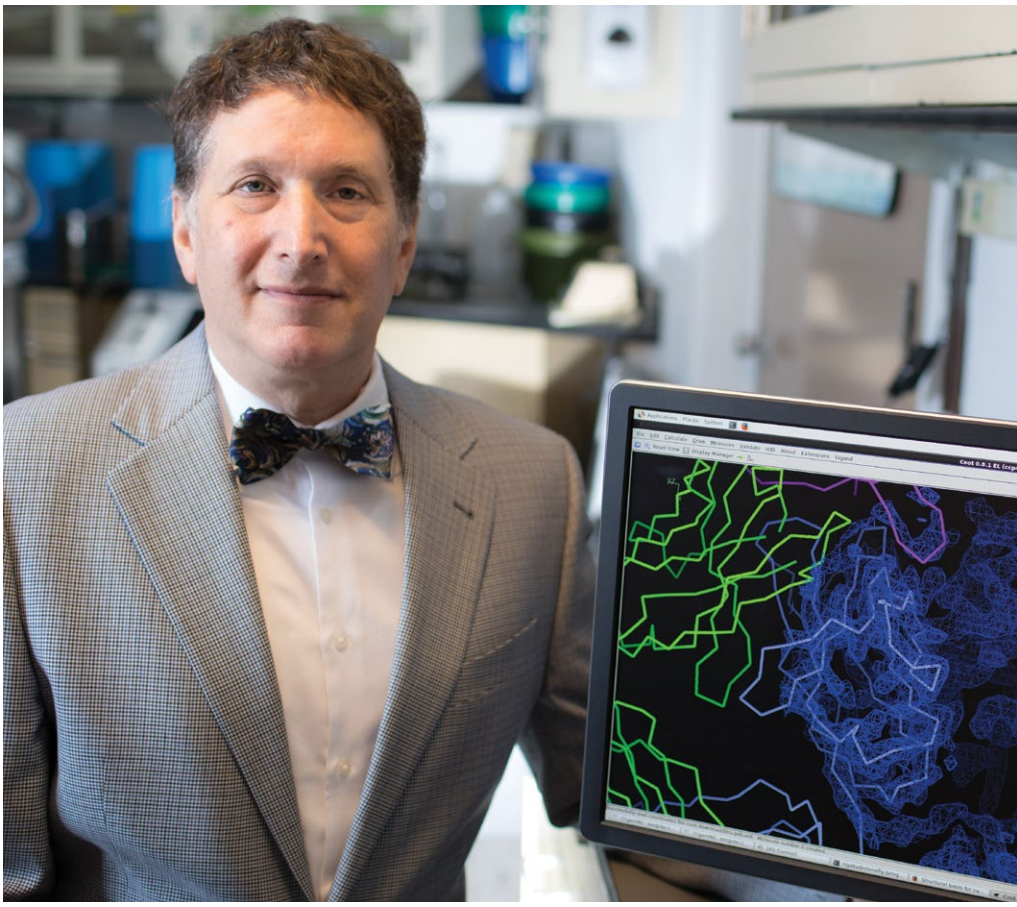
"Selectively activating only those T cells relevant to a particular disease should help reduce off-target effects."

stimulated receptors determine how their T cells behave—spurring them to attack or (in the case of certain receptors) putting the brakes on T-cell action.

After identifying the receptors on a particular type of T cell, Dr. Almo uses advanced techniques such as X-ray crystallography and computational biology to determine the receptors' precise molecular structure. This information helps him determine the structure of the ligand that uniquely fits into that receptor. Scientists can develop the ligand into an immunotherapy drug to turn specific T cells on or off as desired.

RADIATION TO THE RESCUE

Focused radiation is another promising therapy for boosting the immune response to cancer. "Tumor cells contain a lot of defective mutated proteins," explains Chandan Guha, M.B.B.S., Ph.D., a professor of radiation oncology, of pathology and of urology at Einstein and vice chair of radiation oncology at Montefiore. "When we use radiation to kill tumor cells, those abnormal proteins are released, along with 'danger' signals that alert the immune system to detect the mutated proteins. The immune cells can then target living tumor cells that contain those same proteins and kill them."



Above: Steven C. Almo, Ph.D., displays an X-ray crystallographic image that his lab created.

At right: He looks for crystals suitable for analyzing.

Dr. Guha has shown that focused delivery of radiation makes tumor cells more vulnerable to immune attack, while also training the body's own immune defense to more strongly attack the tumor cells.

"Instead of delivering standard cancer radiation therapy in frequent low doses over several weeks, delivering large radiation doses in just a few sessions causes more-extensive DNA damage that tumor cells can't repair so well," Dr. Guha says. "That means more tumor cells die, releasing large amounts

Dr. Guha is using low-intensity focused ultrasound (LOFU) to bolster the immune system's response to tumors.

of tumor-specific proteins that create a stronger 'danger' signal for arousing the immune system."

In another study, Dr. Guha is using low-intensity focused ultrasound (LOFU) to bolster the immune system's response to tumors. LOFU produces thermal and mechanical stress inside the tumor cells, causing some of their proteins to unfold and break down into peptides. When the stressed cells are killed by chemotherapy or radiation therapy, the release of those peptides triggers an immune response to the cancer. In animal models of lung and prostate cancer and melanoma, LOFU plus radiation shrank tumors, reduced the risk of tumor recurrence and decreased the spread of tumor cells.

IMMUNOLOGY WITHOUT BORDERS

Thanks to philanthropists such as the Spatzes, researchers in the Center for Immunotherapeutics can evaluate the use of immunotherapy against numerous health problems, one of which is HIV infection. "Although today's therapies for HIV can reduce viral loads to undetectable levels, some HIV still lurks within infected cells and can reactivate once treatment stops," Dr. Almo says. "We're working with members of the Einstein-Rockefeller-CUNY Center for AIDS Research to find ways to amplify and activate T cells to eliminate those HIV reservoirs."

Dr. Almo is also pursuing immunotherapies that selectively suppress T-cell activity rather than activating it. Such drugs would combat autoimmune diseases that occur when the body mounts an overzealous immune response against its own tissues.

As for the Spatzes, Janet and Marty retired to Florida several years ago, but from afar they root for Einstein's specialists in immunotherapy—and for their beloved New York Yankee baseball team. "Put that in the article," Janet insists. "Once a Yankee fan, always a Yankee fan." E

Chandan Guha, M.B.B.S., Ph.D., pictured at top right, works in his lab with Ph.D. student Justin Vercellino.

Above: They examine colonies of tumor cells that were treated with low-intensity focused ultrasound.

CLASS NOTES

1960s

Melvin Schapiro, M.D. '60, and his wife, Barbara, recently reunited with Helen and Ron Ross; Marne and Jerry Ruskin; and Annette and Aaron Satloff—graduates of Einstein's class of 1960 and their wives—on Catalina Island. This trip served as their first gathering since their graduation.

Howard Schwartz, M.D. '60, was selected as "Man of the Year" by the Jewish Federation of Southern Arizona at the annual Jewish Community Awards Celebration.

Edward M. Stim, M.D. '60, celebrated his 85th birthday this year. He writes two personal blogs: "Physician's Notebooks" and "Adventures of Kimi, Woman of Japan."

Henry H. Wortis, M.D. '60, is still active in research and teaching at Tufts University School of Medicine. His current interest is developing vaccines that protect against chronic inflammatory diseases. He directs an immunology training program and a postbaccalaureate biomedical diversity training program at Tufts. Dr. Wortis and his wife, Sheli, are involved in politics and spend time with their grandchildren in western Massachusetts.

Steven L. Jaffe, M.D. '65, is the author of a recently released book, *Sacred Connections: Studies of Spirituality in Recovering Adolescent and Young Adult Substance Abusers*.

Robert S. Hoffman, M.D. '69, F.A.C.P.S., delivered two lectures at the annual Southern Headache Society meeting in Asheville, NC, last September. His eldest grandson, a junior in Carnegie Mellon University's acting program, has a brother who hopes to join him in the same program this fall. Dr. Hoffman's twin granddaughters study at Washington University and Brandeis University. The rest of his grandchildren range in age from 8 months to 17 years. He is expecting his 12th grandchild.

1970s

Sterling J. Jaidt, M.D. '70, retired in 2015 and now resides in California, focusing on digital art and design.

Jacob Ackerman, M.D. '71, just welcomed a second great-grandson. This past summer, Dr. Ackerman won first place in a pingpong fundraising tournament, which raised money to help battered wives. Since there were 40 entrants under the age of 45, it was a thrilling win. He believes his practice in Einstein dorms from 1967 to 1971 set him up for success.

Norman Luban, M.D. '71, has retired from his neurology private practice. He now evaluates neurologically disabled members of the military and teaches science at a local high school. He and his family spend their summers on Cape Cod.

Toby Tucker Hecht, Ph.D. '73, is excited to be a part of the National Cancer Institute's Canine Immunotherapy Trials Network, composed of scientists and veterinary oncologists who study dogs with spontaneous tumors. Their findings could help researchers better use and combine immunotherapy agents in humans.

Arthur Pickoff, M.D. '75, retired as chair of pediatrics and of community health and as assistant dean for clinical research at the Wright State University Boonshoft School of Medicine. Today, he is happily continuing a different kind of education at the Cincinnati School of Bartending.

Samuel M. Salamon, M.D. '77, and his wife, Ruthie, have lived in Cleveland since 1985, where he has built his ophthalmology private practice. Their proudest "achievements" are their dozen grandchildren, half of whom live two blocks away from them; the other half live in Israel.

Steven Wolinksy, M.D. '79, has treated patients at Orange Dermatology Associates PC in New York since 1984. He and his wife, Vita, have five children and 11 grandchildren. He has kept active by running nine marathons in the United States and seven in Israel.

STAY IN TOUCH

Keep your classmates up-to-date by submitting your news to *Einstein* magazine. We look forward to including you in our next issue. E-mail us at alumni@einstein.yu.edu.

1980s

Barbara Bartlik, M.D. '81, has published a new book, *Integrative Sexual Health*, a volume in the Dr. Andrew Weil Integrative Medicine Library. The book is a comprehensive, evidence-based academic text on healing sexual dysfunction; it combines recent ideas and practices from conventional and alternative medicine.

Pesach Lichtenberg, M.D. '84, has established a nongovernmental organization. It has built two homes in Jerusalem that serve as humane alternatives to psychiatric inpatient units for people in acute emotional distress, including severe psychotic and affective states. More homes are planned.

Marjorie Merod, M.D. '84, has welcomed her first grandchild, Emily Louisa Stevens.

Max Shapiro, M.D. '84, lives in Beverly Hills, CA, and has three children currently enrolled in medical school.

Sharon Jaffe, M.D. '85, was named *Orlando Style* magazine's 2018 "Woman of the Year" in recognition of her community involvement and her compassion, knowledge and expertise in helping couples conceive.

Harry J. Sacks, M.D. '86, F.A.A.P., is now vice president of medical affairs and corporate medical officer at OptiNose, Inc., a pharmaceutical company focused on developing new products for patients with diseases treated by otolaryngologists and allergists.

Joan Bregstein, M.D. '87, has been an attending physician in the NewYork-Presbyterian Morgan Stanley Children's Hospital pediatric emergency department for the past 23 years. She is also an associate professor of pediatrics at Columbia University. She is happy to report that her daughter, Shana Burstein, is currently enrolled as a medical student at Einstein in the Class of 2021.

Ellen J. Brand, M.D. '88, practices at Danbury Hospital in Connecticut as director of obstetric anesthesia. In December 2017, she spoke at the New York State Society of Anesthesiologists' Postgraduate Assembly meeting. Her older son, Jordan, graduated from Florida State University.

1990s

Barry Kraushaar, M.D. '90, stays busy practicing at Northeast Orthopedics and Sports Medicine in Nanuet, NY. His twins have enrolled in college and one is already studying organic chemistry. He and his wife, Helene, are plotting their course for the next stage of life. They hope all their classmates are well and enjoying the fruits of their hard work.

Hugh Bases, M.D. '94, was promoted to clinical associate professor of pediatrics at New York University School of Medicine and is also the program director of the Developmental-Behavioral Pediatrics Fellowship. His daughter is a sophomore in college and his son is a junior in high school.

David Markenson, M.D. '94, currently serves as treasurer and board member of the Colorado Medical Society, president of the Arapahoe-Douglas-Elbert Medical Society and division vice president for graduate medical education for the continental, mid-American and mountain divisions of the Hospital Corporation of America's Physician Service Group. He oversees undergraduate and graduate medical education for more than 30 hospitals across the country and serves as the national chair of the scientific advisory council for the American Red Cross.

David Elfenbein, M.D. '95, and his wife, **Leslie Moskowitz-Elfenbein, M.D. '95**, moved in July 2016 to Crested Butte, CO, where Dr. Elfenbein opened his own practice—Pinnacle Orthopedics and Sports Medicine. Dr. Moskowitz-Elfenbein started an ophthalmology practice with the local hospital.

Efrat Meier, M.D. '95, works as a private-practice ob-gyn in Bergenfield, NJ. He recently remarried—his new spouse is Zvi Goldfischer of West Hartford, CT—and he now has four stepchildren in addition to his four children.

Brian Blaufeux, M.D. '96, was promoted to regional chief medical informatics officer for the Westchester County, NY, region of Northwell Health.

MOTIVATIONS

2000s

Roger Greenberg, M.D., Ph.D. '00, was elected to the American Academy of Physicians and received the V Foundation Team Science Award for research on BRCA mutated cancers in 2018.

Sandra Torres, M.D. '04, was promoted to regional chief of Urgent Care ProHEALTH Medical Management, LLC, in Roslyn, NY.

Satra Gradiska, M.D. '06, and her husband, Daniel, have welcomed their second child, Makeda.

2010s

Caitlin McMullen, M.D. '10, completed her otolaryngology residency at Montefiore, followed by a fellowship at the University of Toronto. She currently lives in Tampa, FL, and practices at the Moffitt Cancer Center as a head and neck surgical oncologist/reconstructive surgeon.

Rachel Shakked, M.D. '10, and her husband, **Michael Birns, M.D. '10**, moved to the Philadelphia area after completing their orthopedic surgery residencies and fellowships. Dr. Birns practices at Premier Orthopedics in Broomall, PA, and focuses on operative treatment of sports medicine conditions and athletes. Dr. Shakked works for the Rothman Institute with a focus on surgical care of foot and ankle conditions. They are happy to announce the birth of their first son, Ryan Archer, in July 2017. He is on his way to Einstein, Class of 2040!

Samuel Kallus, M.D. '11, completed his chief fellow year in gastroenterology at Georgetown University Hospital. He recently accepted a faculty position at George Washington University Hospital to work with medical students, residents and fellows.

Shira Koss, M.D. '12, completed her residency in otolaryngology–head and neck surgery at the New York Eye and Ear Infirmary of Mount Sinai. She is currently training as a fellow in laryngology at Emory University Hospital, specializing in vocal cord and trachea surgery and airway reconstruction. Next year she will head to Stanford University for a fellowship in the Stanford Biodesign Innovation Center, where she will work on medtech and healthtech innovations.

Stephen T. Constantine, M.D. '13, completed his residency in emergency medicine at the University of Chicago in 2016. In 2017, he moved to Charlotte, NC, to complete his fellowship in emergency medical services at Carolinas Medical Center, where he will stay on as a member of the faculty in the department of emergency medicine. He is now board certified in emergency medicine and subspecialty board certified in emergency medical services.

Nadira Ramkellawan, M.D. '13, and **Udit Rawat, M.D. '13**, married in August 2017. Dr. Rawat is currently finishing his radiology residency at the University of Virginia, and Dr. Ramkellawan completed her pediatric residency at Montefiore. She is in the second year of her pediatric emergency medicine fellowship at Inova Fairfax Hospital in Virginia.

Michael Szmyga, Ph.D. '13, has worked in the medical communications field since graduating from Einstein. He is currently a senior medical director with HealthLogix, a medical education company based in New Jersey. He lives in Astoria, Queens.

Dionna Williams, Ph.D. '14, accepted a position as an assistant professor in the department of molecular and comparative pathobiology at the Johns Hopkins University School of Medicine.

Michael Cooper, M.D. '15, married his wife, Beth, in November 2017, and honeymooned in Paris and the South of France. Beth currently works as an editorial recruiter at Hearst and Dr. Cooper has started the final year of his psychiatry residency at New York University, where he is a chief resident. They live in Brooklyn.

Evan Kyo Tamura, M.D. '16, is engaged to Christopher Allen, whom she met during her final year at Einstein. They live in Torrance, CA, where Dr. Tamura is finishing the final year in her family medicine residency at Harbor-UCLA Medical Center.

Aaron Weiss, M.D. '16, welcomed a daughter, Layla Elizabeth, this year.

A LOOK
BACK

Chanin at 40

The six-story Irwin S. and Sylvia Chanin Institute for Cancer Research was dedicated 40 years ago, on Nov. 15, 1978. The driving force behind its construction was Harry Eagle, M.D., Einstein's associate dean for scientific affairs at the time. He submitted grant proposals asking the National Cancer Institute to fund a facility devoted to the basic study of cancer, raising more than $10 million of the Chanin Building's $11.5 million cost. Dr. Eagle previously worked at the National Institutes of Health, where he developed Eagle's minimal essential medium—a mixture of amino acids, salts, glucose and vitamins that allowed animal cells to multiply in tissue culture. The breakthrough led to important research on cell metabolism, viruses and cancer. This 1977 photo of the nearly completed Chanin Building shows that it extends over part of the Forchheimer Building, is supported by a series of concrete columns and is adjacent to Robbins Auditorium. As was true 40 years ago, virtually all of the 200 scientists now working in Chanin are involved in some aspect of cancer research.

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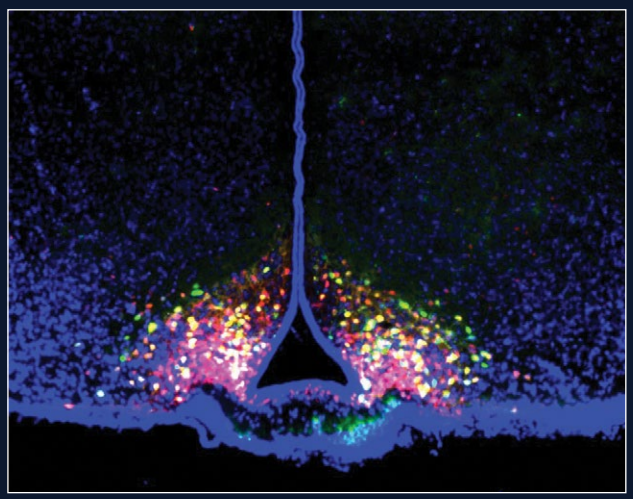

EINSTEIN IMAGE

A bundle of hypothalamic neurons called the arcuate nucleus (ARC) helps control food intake and metabolism. The ARC's pro-opiomelanocortin (POMC) neurons are particularly important; their *POMC* gene spawns peptides that powerfully inhibit food intake. Streamson Chua, M.D., Ph.D., a professor of medicine and in the Dominick P. Purpura Department of Neuroscience, studies *POMC* and other genes that regulate body weight and fat content. As shown in this image of a mouse hypothalamus, the ARC is adjacent to the pyramid-shaped third ventricle, a fluid-filled space in the brain. POMC neurons stained green/yellow are actively expressing the *POMC* gene; neurons stained red express an enzyme called Cre recombinase, which tags any cells that have ever expressed *POMC*. The image shows that many neurons express *POMC* during growth and development, but only a fraction develop into adult POMC-expressing neurons. A blue stain called DAPI, which binds to cell nuclei, colors other cells in the region. This image was made by Niloy Iqbal, an M.D./Ph.D. student co-mentored by Dr. Chua and Liang Zhu, M.D., Ph.D., a professor of developmental and molecular biology, of ophthalmology and visual sciences and of medicine.