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The magazine of Yale School of Medicine / yalemedicine.yale.edu

STRANGE BEDFELLOWS, GREAT SCIENCE

Yale researchers cross scientific boundaries to advance biomedical knowledge

Autumn 2017

Features

FRANK POOLE PHOTO

autumn 2017 departments

letter from the editor

Your editor bids farewell

This issue of *Yale Medicine* marks my last as editor. I have retired, effective September 29 of this year, almost 20 years after I started working as *Yale Medicine*'s first staff writer. When I started in 1998, only three other people worked on the magazine. Michael Fitzsousa, who was then the editor, now works in development. Cheryl Violante and Claire Bessinger have job titles that don't do justice to all they do that makes it possible to publish *Yale Medicine*.

My first big assignment was a feature article about the newly formed Center for Interdisciplinary Research on AIDS. My reporting took me from the streets of Hartford, where I shadowed outreach workers who were trying to penetrate drug networks, to laboratories at Yale, where scientists were seeking treatments for AIDS. Since then I've traveled to Russia and Uganda to cover international collaborations, reported on student efforts to save the Affordable Care Act, and overseen our special bicentennial edition, a photo-essay by six photographers who documented a week in the life of the School of Medicine.

Over these years, I've indulged in what makes journalism such a rewarding calling—the ability to approach remarkable people and talk to them about what they're doing. It's taken me into the labs, clinics, and classrooms here at Yale, and opened doors in New Haven and beyond.

As editor, I've had the pleasure—indeed, the joy—of working with talented writers and photographers who took on myriad assignments with energy and enthusiasm. Their efforts have made the magazine shine, and we've had the honor of winning silver and gold medals from the Council for Advancement and Support of Education (CASE). Along the way, the magazine and its writers and designers have garnered multiple individual awards, not only from CASE, but also from the Association of American Medical Colleges and the American Medical Writers Association.

In my mind, however, the greatest accolades have come from the people who make up the School of Medicine community—the students who told me an article in the magazine tipped the scales and made them decide to study medicine here; the physician who asked that I put him in touch with students who had formed a clinic in Nepal so that he could learn from them how to make alumni service trips more sustainable; a request from Yale's Office of New Haven and State Affairs for 100 copies of our Spring issue on the medical school's relationship with the city.

It's been a glorious ride, and I thank all of those—too many to name—who have worked with me and from whom I have learned so much. The magazine has long played an important role in engaging and uniting the medical school community, and I am grateful and honored to have had a part to play.

Finally, I welcome Adrian Bonenberger as the new editor of *Yale Medicine*. Adrian, a Yale College graduate, comes to us from Ukraine, where he's been working as a freelance journalist. Previously, he served in the U.S. Army, leaving as a captain after two tours in Afghanistan. He's also a graduate of the Columbia University Graduate School of Journalism. I wish him well as he takes the reins of the magazine that has long served the School of Medicine community.

John Curtis, Yale Medicine*, 1998-2017*

SECOND OPINION
BY SIDNEY HARRIS

Send letters and news items to
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Please limit letters to 350 words and include a telephone number. Submissions may be edited for length.

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Editor
John Curtis

Contributing Editors
Robert Forman
Kathy Katella-Cofrancesco
Kathleen Raven

Senior Writers
William Hathaway
Ziba Kashef
Jill Max
Karen Peart
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Contributors
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Jeanna Canapari
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Art Director
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Elaine Alibrandi
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Anne Sommer

Mailing List Inquiries
Claire M. Bessinger
Communications Coordinator
Cheryl R. Violante
Website Coordinator

Printing
The Lane Press

Correspondence
Editor, *Yale Medicine*
1 Church Street, Suite 300
New Haven, CT 06510-3330
Telephone: 203-785-5824
Facsimile: 203-785-4327
Email: ymm@yale.edu
Yale Medicine is distributed to alumni, faculty, students, and friends of Yale School of Medicine.

Yale School of Medicine
Robert J. Alpern, M.D.
Dean and Ensign Professor of Medicine
Mary Hu
Associate Dean for Communications and Chief Communications Officer
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Abbreviations used in *Yale Medicine* include HS to denote the final year of residency for house staff, FW for the final year of a fellowship, and YNHH for Yale New Haven Hospital.

Yale SCHOOL OF MEDICINE

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Cultural heritage to the microbiome: research at West Campus

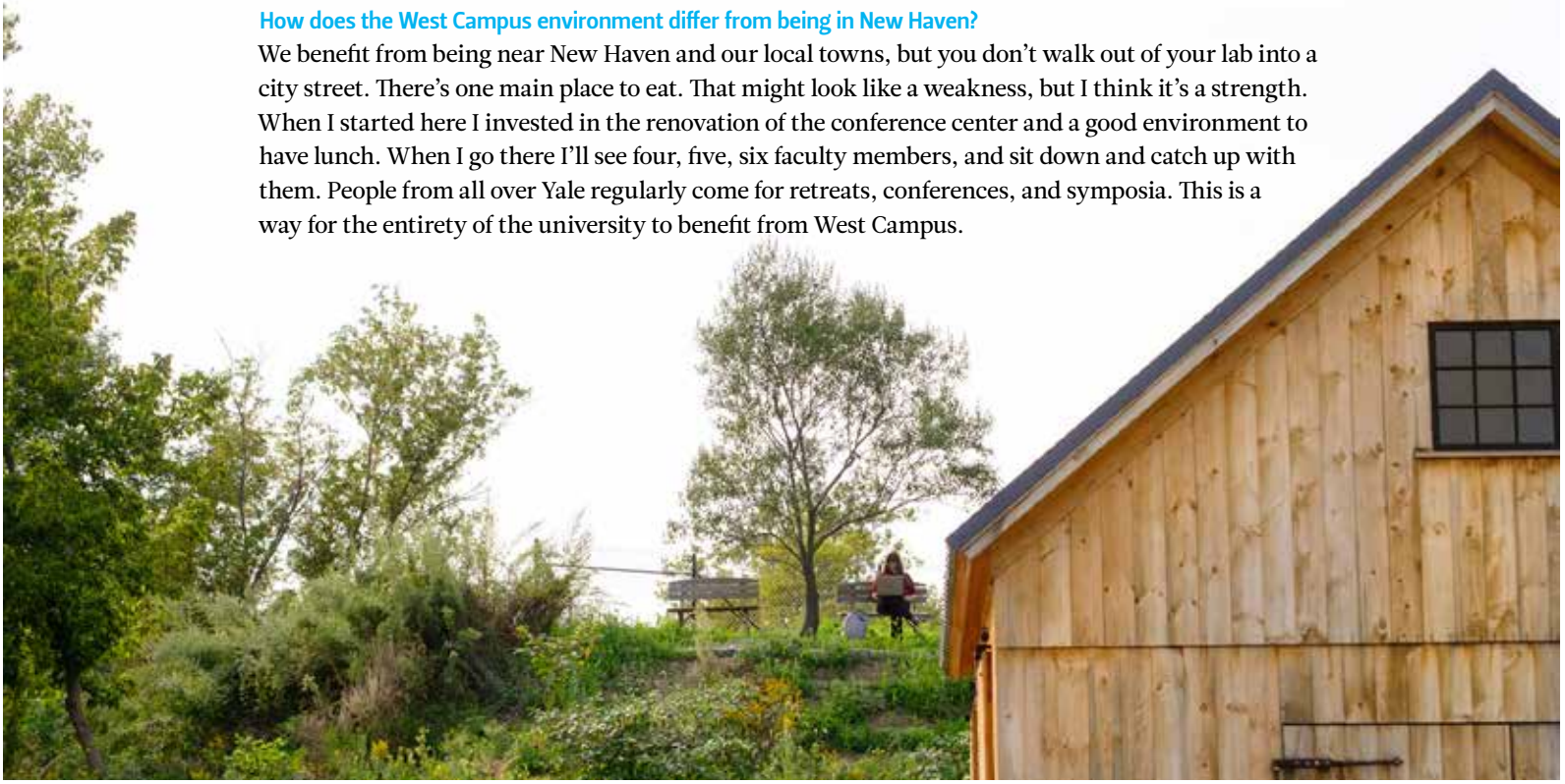
WHEN SCOTT A. STROBEL, PH.D., became vice president for West Campus Planning and Program Development in 2011, the 100-plus acres in West Haven and Orange had a work force of 84. Now, the population exceeds 1,500 across seven research institutes and the School of Nursing. At West Campus, the goal is to promote "collisional frequencies" that place researchers from different fields alongside one another. Strobel recently spoke with *Yale Medicine* about the vision for West Campus.

What is the vision for West Campus? We're trying to set up an incubator to bring together people from different departments who would never bump into one another. Then we have them focus on a common set of problems. They work in a common lab space, so engineers may be next to geneticists who are next to evolutionary biologists.

Was that the plan when Yale bought West Campus in 2007? Usually when you have a new building, you've planned it for years, so the day it's built you know exactly what's there. One day in October 2007, we didn't have the West Campus; then the next day we had 17 buildings and 1.5 million square feet of space. Now what are you going to do? The community started throwing out the biggest and brightest and best ideas. Michael Donoghue, who became the first vice president of West Campus, established the idea for interdisciplinary institutes with faculty from multiple departments.

How do those interactions work in practice? An interdisciplinary neighborhood will draw you in different directions than if you're sitting next to somebody who's in your field. You might say, "There's someone around the corner who can help me, so I'm going to give this crazy idea a shot."

How does the West Campus environment differ from being in New Haven? We benefit from being near New Haven and our local towns, but you don't walk out of your lab into a city street. There's one main place to eat. That might look like a weakness, but I think it's a strength. When I started here I invested in the renovation of the conference center and a good environment to have lunch. When I go there I'll see four, five, six faculty members, and sit down and catch up with them. People from all over Yale regularly come for retreats, conferences, and symposia. This is a way for the entirety of the university to benefit from West Campus.



FRANK POOLE PHOTO

Deans named to replace Carolyn Slayman

WITH THE PASSING OF CAROLYN W. SLAYMAN, PH.D., in December, the School of Medicine lost its first and only deputy dean for academic and scientific affairs. She served in that position for 22 years, as faculty throughout the school marveled at her influence and ability to keep up with advances in clinical and biomedical research during a time of significant expansion of clinical and basic science faculty. It was clear as well that she would be virtually impossible to replace. In light of the tremendous growth of the medical school as well as the increasing complexity of almost every aspect of academic medicine and research, her responsibilities have been divided among three deputy deanships that were filled in July.

Linda K. Bockenstedt, M.D., the Harold W. Jockers Professor of Medicine (Rheumatology), will serve as deputy dean for faculty affairs. Michael C. Crair, Ph.D., the William Ziegler III Professor of Neuroscience and professor of ophthalmology and visual science, will serve as deputy dean for scientific affairs (basic science departments). Brian R. Smith, M.D., chair and professor of laboratory medicine, of biomedical engineering, of medicine (hematology), and of pediatrics, will serve as deputy dean for scientific affairs (clinical departments).

"Our new deputy deans will work closely as a team to ensure that faculty receive the support they need to succeed and thrive," said Dean Robert J. Alpern, M.D., Ensign Professor of Medicine. "I'm confident that they will continue Carolyn's legacy admirably as they implement their collective vision on how to best support faculty."

The three deputy deans will draw upon their unique expertise in their new roles. Bockenstedt's experience includes serving as director for professional development and equity, a position created in 2006. She became associate dean for faculty development in 2014. Having worked closely with Slayman on faculty affairs, she had already taken on many of those responsibilities in the months leading to her new appointment.

"We've had an unprecedented number of requests for faculty positions from the departments since January," she said. "Ultimately, we want to help all faculty members understand their position at Yale along with the opportunities available to them, the appointments and promotions process, and faculty development, so they can be successful in their careers." She is committed to engaging the entire faculty so that they have a voice in the decisions that affect them.

Smith views his new position as an extension of his role as chair of laboratory medicine, in which he will continue to serve. He recently chaired the Ad Hoc Committee on the Clinician-Educator Track that is charged with clarifying and updating the track's criteria for promotion. He also chaired the Research

Committee of the Association of Pathology Chairs. The committee formulated a physician-scientist pathway that was certified by the American Board of Pathology in 2014, a process that helped prepare him for his position as deputy dean.

Smith acknowledges that the challenges he faced when he started his career more than three decades ago are greater, as both the competition for research funding and the necessity of mastering an ever-growing body of clinical knowledge have increased. "It used to be that you could live in a very small area of science and know all of it," he says. "Now you have to reach out across totally different disciplines, which is exciting but requires more work."

Crair served as deputy chair of the Department of Neuroscience and director of graduate studies for the department until his appointment as deputy dean. A team player who is often quicker to advocate for his colleagues than for himself, he is looking forward to making positive contributions on a larger scale. "I hope to help build the sciences, not just at the School of Medicine, but across the university," he said.

Crair's vision includes establishing an environment in which, despite the uncertainties of NIH funding, the school supports investigators at a baseline level that allows them to continue to do research even in the face of funding challenges. "As we get older we have more perspective, and it's easier to see past a couple

Three longtime faculty members have been named to take over the responsibilities of the late Carolyn Slayman, who served as deputy dean for academic and scientific affairs for more than 20 years. From left, Brian Smith will oversee scientific affairs for clinical departments. Linda Bockenstedt will take over faculty affairs. And Michael Crair will handle scientific affairs for basic science departments.

ROBERT LISAK PHOTO

ONLINE EXCLUSIVES

Kim Guy's story begins in 1966, the year she was born in a Connecticut juvenile detention center, and continues through foster care, a mother with mental health problems, and a father who died of a gunshot wound. Now she uses her own experiences with drug addiction to help others.

For more on Kim Guy, visit yalemedicine.yale.edu/guy

of years of fluctuations," he said. "But for our junior faculty, not knowing the future of research funding can be debilitating." He will also look for ways to increase diversity, noting that "we learn from those diverse views—in part shaped by diverse backgrounds—that bring a different perspective."

All three will continue to lead active research programs. Crair has developed optical imaging techniques to study neural development. He has made fundamental contributions to the understanding of neural activity in the developing brain and demonstrated that early spontaneous activity as the brain is forming is an essential part of normal brain development. He is currently exploring the mechanisms by which this activity is generated and how it shapes brain circuit development.

Smith conducts bench and clinical research on the interface between inflammation and coagulation, focusing on biomaterials and the pathophysiology of blood disorders caused by immune reactions. He also studies cellular immunotherapies. Bockenstedt is internationally recognized for her research on the host immune response to tickborne spirochetal infections. Her current research employs a systems biology approach to understand the diverse clinical manifestations of Lyme disease, and uses molecular profiling to identify host factors that determine the outcome of infection.

As deputy deans, the three professors are beginning to function as a unit as they work across departments to provide and support academic opportunities for faculty and promote an increased spirit of collaboration in the school's culture. They unanimously acknowledge that while Slayman's shoes are difficult to fill, they hope that their combined efforts and different perspectives will afford them broader reach as the school continues to grow. Reflecting on the legacy left by Slayman, Smith said, "I was fortunate to have her as a role model. Now we just have to think back and ask ourselves, 'What would Carolyn do?' "

—Jill Max

Navigating power structures in medicine

If you feared that colleagues at Guantanamo Bay might use your psychiatric care notes against your inmate patients, what would you do? After a natural disaster ravaged your hospital's resources and you overheard colleagues deciding who should live or die, would you speak up?

Sheri Fink, M.D., Ph.D., a Stanford University-trained physician, nonfiction author, and Pulitzer Prize-winning correspondent for *The New York Times*, described these scenarios based on interviews and research on the military prison in Cuba and the aftermath of Hurricane Katrina in New Orleans in 2005.

As keynote speaker at the 17th annual Power Day on May 12 in Harkness Auditorium, Fink observed that people can feel powerless in structures that they don't fully control. She referred to such physical structures as hospitals without clear evacuation plans, and to such institutional organizations as the military or medical field with deeply entrenched hierarchies. "One thing to take away today—you do have a lot of power."

Much of her talk described the moral dilemmas health professionals faced at Memorial Medical Center in New Orleans before and after Hurricane Katrina. Her 2013 award-winning book, *Five Days at Memorial: Life and Death in a Storm-Ravaged Hospital*, reconstructs each day of the tragedy, sometimes minute by minute. Nurses and doctors weathered the hurricane, only to face a larger crisis as the levees broke and the city was flooded. Memorial's backup generators, located in the hospital basement, eventually quit, leaving medical equipment, including life-saving ventilators, without power. Helicopter and boat evacuations faltered. Hospital staff—sleep-deprived, overworked, and exhausted—moved fragile patients up and down stairways, and passed them through a tunnel in a wall for access to the hospital's helipad. Without running water, such basic tasks as helping patients relieve themselves turned into laborious undertakings.

Pulitzer Prize-winning journalist Sheri Fink discussed issues of power that emerged at the military prison at Guantanamo Bay and a New Orleans hospital coping with the aftermath of Hurricane Katrina.

HAROLD SHAPIRO PHOTO

It's important to remember, Fink said, that at every step in every medical crisis, nurses and doctors have a choice. "Who do you save first when you know you could lose power at any moment? Who makes the choice? What will be the process of making the choice? Who's in the room making the choice?"

These concerns are related to a primary theme in Fink's book: how can doctors and nurses ensure that they provide care for patients when structures of command and order break down amid disrupted communications and severely limited resources?

At Memorial, health workers decided that the sickest patients—including those with do not resuscitate (DNR) orders—were those with the "least to lose" and should be evacuated last. A study published years later by the National Academy of Medicine concluded that using DNR orders "as a proxy for triage choice is not a good idea," Fink said, adding that in general, "it's hard enough to get people to think about end-of-life issues, and if patients do not trust how DNR will be used, they might not choose it."

In her talk, Fink highlighted the plight of Emmett Everett, a 380-pound patient who, on the morning of September 1, asked nurses if they were "ready to rock and roll" and begin his evacuation. By that evening, Everett and at least 16 other patients were dead, their bodies filled with high levels of morphine or the sedative midazolam—in some cases, both—according to toxicology reports and interviews Fink conducted with hospital staff.

With some patients—but not Everett—near death, the decision was made to inject the patients. Some doctors and nurses followed orders. At least one doctor spoke up, outraged that his colleagues would knowingly violate the Hippocratic Oath. Were the staff powerless to make another choice? No, Fink told the medical and nursing students. "I urge you throughout your careers to be aware and alive to the fact if something is uncomfortable," she said.

Originally conceived as an opportunity for nurses and doctors to examine the power in relationships between doctors and nurses and their patients, Power Day's focus has expanded more recently to examining power structures in which physicians and nurses operate. "Political, economic, social, cultural, and physical structures are decided, and then those structures affect medical care," said Nancy R. Angoff, M.Ed., M.P.H. '81, M.D. '90, HS '93, one of the founders of the event. She encouraged students to think about how power shapes structure and to examine how they can address these issues in the future. "Because you will encounter these situations—maybe even on Monday," she said.

—Kathleen Raven

»

New drugs to fight resistant bacteria

Earlier this year, Seth Herzon, Ph.D., professor of chemistry and member of Yale Cancer Center, found—quite inadvertently—an arresting opening slide for his lectures: an image of himself in the hospital with an infection he had picked up from a cat bite. "All right—here it is," he tells his audiences. "Here's why we need to do antibiotics."

There's no denying the medical need for new and better antibiotics—in 2013, the Centers for Disease Control and Prevention (CDC) reported that 23,000 Americans die of drug-resistant bacterial infections each year. Herzon worried he might be one of them when oral antibiotics failed against his infection.

ONLINE EXCLUSIVES

More than 150 people assembled around the steps of Sterling Hall of Medicine on an afternoon in June to support the Affordable Care Act of 2010 (ACA). Through a megaphone on the steps of the hall, speakers told tales from their own lives or the lives of loved ones about how repeal of the ACA could affect their health care or drive them into bankruptcy.

For more on ACA repeal, visit yalemedicine.yale.edu/aca

"My biggest fear was not death itself, but what would be on my tombstone if I died," he said. "It would be 'Herzon, '79–'17 (cat bite).' " Fortunately, his infection was cleared up with an IV antibiotic. Not everyone's is.

Our species has been in a continuous evolutionary arms race with bacterial pathogens for decades now, and they seem to be gaining the upper hand. Bacteria evolve at an alarming pace—some species can produce a new generation in half an hour—and can even exchange genetic information that confers defenses against our antibiotics. Today, some infectious bacteria have evolved such a degree of resistance that they've outpaced the production of fresh antibiotics.

Herzon's lab has recently developed a way to chemically produce pleuromutilin, a fungal antibiotic agent. It was isolated in the 1950s, but the means of creating it "from scratch" in the lab—an alluring possibility that would enable the production of many variations of the drug—had always posed a challenge to researchers.

"Bacteria can't find a way to evolve resistance to pleuromutilins without killing themselves," Herzon explained. The site that pleuromutilin binds to in pathogenic bacteria is essential for making proteins—and without proteins, the cells cannot survive. To this point, bacteria have not devised a way to evolve resistance without also injuring their own protein centers.

"We have a way now to access sites in pleuromutilin that were entirely inaccessible before," Herzon said. "And the structural data tell us if we modify these sites, we're going to get better antibiotics."

There are currently one pleuromutilin derivative approved to treat infections in humans, and two used for animals in the United States. Herzon's technique opens the possibility of developing many more to treat a broader range of bacterial species. Bacteria are classified as either Gram-positive or Gram-negative (more simply, as having one cell wall or two). Gram-negative bacteria are more difficult to treat, and the existing pleuromutilins fight only Gram-positive ones.

"There's some evidence that if we change the structure of pleuromutilin, we can get activity against Gram-negatives," Herzon said. "So that's what we're really going for."

The quest for novel antibiotics has fallen almost entirely onto universities' and philanthropies' shoulders. Big pharmaceutical companies are reluctant to invest in antibiotic treatments (despite the urgency), because even successful antibiotics offer a meager return on investment.

"We've got a unique opportunity here to make a dent in this problem using the chemistry that we've developed," Herzon said. "It's important work to do. Resistance to antibiotics has been in the literature for 30 years. People have been aware of it for 30 years—and it just keeps getting worse."

—*Natasha Strydhorst*

round up

a collection of recent scientific findings

EVOLUTIONARY TRADE-OFF: HAVING KIDS WILL BREAK YOUR HEART

Scientists have long wondered why coronary artery disease (CAD), which develops over a lifetime, has not been eliminated through natural selection. CAD starts in young adults, progressing over time to become life-threatening. Present in human populations for millennia, it is the leading cause of death worldwide. Scientists at Yale and other medical centers have now found that genes underlying CAD also contribute to reproductive success. A genomic analysis published last summer in *PLOS Genetics* suggests that natural selection has relatively recently preserved genes that contribute to the risk of coronary artery disease because they also contribute to better chances of having children. This evolutionary trade-off, said contributing author Stephen C. Stearns, Ph.D., the Edward P. Bass Professor of Ecology and Evolutionary Biology, shows that "babies can break your heart."

QUESTIONS ABOUT EARLY DETECTION

An analysis of breast cancer data has called into question prevailing beliefs about the value of early detection. The study, published June 8 in *The New England Journal of Medicine*, revealed that many small breast cancers have an excellent prognosis, not because they are caught early but because they are inherently slow-growing. Because these cancers often do not grow large enough to become significant within a patient's lifetime, early detection could lead to overdiagnosis, said the researchers at Yale Cancer Center. In contrast, they noted, large tumors that cause most breast cancer deaths can become intrusive before detection by screening mammography. "Our analysis explains both how mammography causes overdiagnosis and why it is not more effective in improving outcomes for our patients," said Donald R. Lannin, M.D., professor of surgery (oncology) and lead author of the paper. "More importantly, it questions some of our fundamental beliefs about the value of early detection."

PLAYING SPORTS WITH A DEFIBRILLATOR

Some young adults who have inherited heart conditions that put them at risk of sudden cardiac arrest require an implantable cardioverter defibrillator, or ICD. For years, the conventional wisdom—as well as professional society recommendations—was that these athletes should engage in no sport more strenuous than golf. Now a Yale study published in June in *Circulation* suggests that the risks are lower than previously thought. A team led by Rachel J. Lampert, M.D., professor of medicine (cardiology), enrolled more than 400 athletes with ICDs inside and outside the United States in a study to determine the risks of sports participation. Every six months over four years, the researchers checked in to see whether the athletes had had any adverse event while playing sports. While some did have shocks when their defibrillators detected an abnormal heart rhythm, none suffered the worst consequences—defibrillator failure, injury, or death. "We can't say all athletes with ICDs should do vigorous sports," said Lampert, "but our data imply that this can be an individualized decision between doctor and patient."

ISTOCKPHOTO.COM PHOTOS

STRANGE BEDFELLOWS, GREAT SCIENCE

Yale researchers cross scientific boundaries to advance biomedical knowledge

A DECADE AGO, when Yale purchased what is now known as West Campus from Bayer, the plan was to focus on cutting-edge science. The 450,000 square feet of lab space would be not spillover space, but a place that would foster a fresh approach to raise the visibility of science at Yale.

Now West Campus is home to no fewer than seven institutes covering cancer, nanobiology, microbial sciences, and more. "Our true aim," says Scott A. Strobel, Ph.D., the vice president for West Campus planning and program development, "is for true convergence in research."

To that end, West Campus is geared for research that crosses traditional boundaries. Biologists and chemists work with the Institute for the Preservation of Cultural Heritage to find ways to preserve ancient texts and scrolls. A molecular biologist and synthetic biologist team up to synthesize a type of protein. Nursing students learn about medicinal plants on an urban farm. Labs are located alongside labs in different fields—the hope is for interesting water cooler conversations. There's only one cafeteria for a reason—to encourage cross-disciplinary gatherings and conversations.

But interdisciplinary research has been going on for as long as physicians have turned to geneticists, biologists, and chemists for insights into the workings of the human body. And such research continues across the Yale campus. Radiologists work with biomedical engineers to tweak DNA and treat disease. Biomedical engineers work with dermatologists to develop a safer sunscreen.

In this issue of *Yale Medicine*, we celebrate science that stretches interdisciplinary boundaries throughout Yale and at West Campus as it celebrates its 10th anniversary.

FRANK POOLE PHOTO

HOW WEST CAMPUS IS FULFILLING ITS DREAM

Ten years ago Yale leaders envisioned a campus where biologists, chemists, physicists, oncologists, informatics experts, and scientists from other realms would share ideas, think big, and break new ground in medical research.

BY JENNY BLAIR, M.D. ’04 | FRANK POOLE PHOTOGRAPHY

Christopher Incarvito

The key to West Campus, says Chris Incarvito, is bringing people together in a space without walls. “When you talk, somebody’s going to hear. … But that’s a good thing.”

In early 2010, when Jesse Rinehart, Ph.D., then a young assistant professor, was setting up his lab on West Campus, the place was a ghost town. Parking was a snap. He usually found a spot right by the entrance.

These days, 1,700 people work and learn in the former pharmaceutical industrial park. Rinehart sometimes has to park a good 100 yards across campus from his lab. But as a researcher who thrives on chance encounters with colleagues—several of which have led to successful interdisciplinary projects—he couldn't be happier.

"We who came early, we imagined that we would fill the institutes with lots of exciting researchers and students and postdocs and all sorts of other people. That's actually happened," says Rinehart, who is now an associate professor of cellular and molecular physiology and a member of the Systems Biology Institute at West Campus. "The buildings are almost full everywhere you go. The labs and the floors are bustling with activity. There's just so much going on. It's really a vision as promised."

In the 10 years since Yale bought the entire 136-acre campus from Bayer for $109 million, West Campus has become a playground of sorts for researchers willing to work across disciplines. The vast campus increased Yale's footprint by 40 percent, adding 17 buildings, 450,000 square feet of laboratory space, and nearly 1 million square feet of warehouses, offices, a library, a day care, and more. After years of renovation, the place now offers what its leaders call a "high collisional frequency," prompting people to bump into one another, start talking about their research, and—ideally—work together to tackle the most complex problems in science.

Comprising seven research institutes spanning health, culture, energy and the environment, the Yale School of Nursing, multiple cores and centers with equipment to support research, a Landscape Lab for sustainability projects, and a conference center and cafeteria, West Campus now offers boundless opportunities for such collisions. The people ranging across its 136 acres come from all walks of academic life. Postdocs and PIs work in its open-plan labs. Ecologists study invasive species on the grounds. Nursing faculty conduct research in the school's biobehavioral lab while students study genomics and precision health there, then cross to its urban farm to cultivate and learn about medicinal plants. And everyone eats lunch together.

"Nursing as a STEM discipline is a science of human health ecology, supporting humans in the context of the many factors that influence wellness and disease. So to be ensconced in a literally rich research ecosystem like that on the Yale West Campus is powerful," says Ann E. Kurth, M.P.H., M.S.N. '90, Ph.D., dean and Linda Koch Lorimer Professor of Nursing.

"West Campus is an opportunity to do something different—no departmental structures and associated bureaucracy, no restrictions or mandates on where your scientific curiosity leads you," says John D. MacMicking, Ph.D., a Howard Hughes Medical Institute (HHMI) investigator and associate professor of microbial pathogenesis and of immunobiology who recently joined the Systems Biology Institute. "It's about bringing unlikely colleagues together to forge a common language and create a new lexicon."

As interdisciplinary as it can be

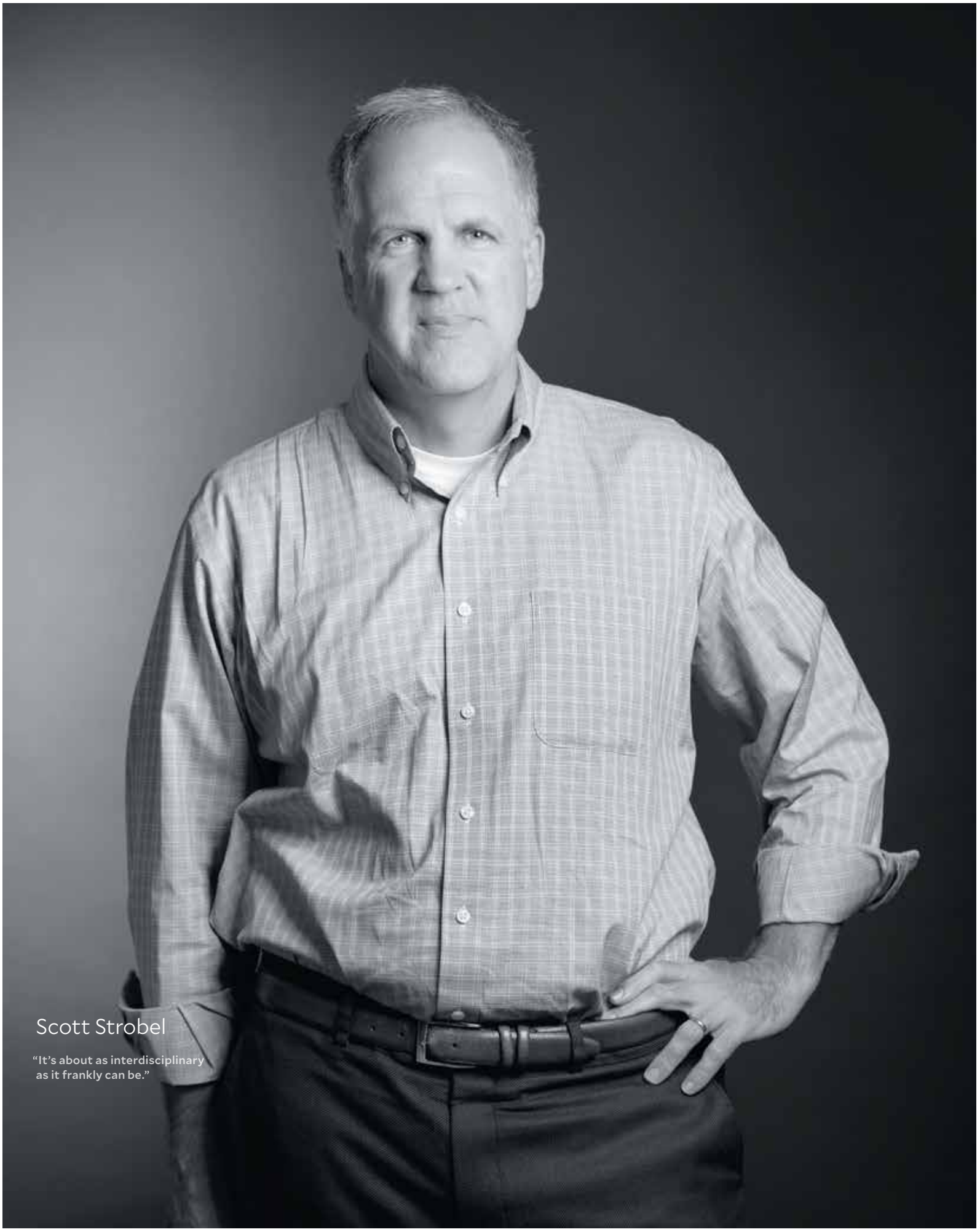
The interdisciplinary nature of West Campus was built into Yale's plans for the campus soon after the purchase, according to Robert J. Alpern, M.D., Ensign Professor of Medicine (Nephrology) and dean of the School of Medicine.

"A cancer biology institute was something that we thought about the first week after the purchase," Alpern recalls. Yale leaders were also enthusiastic early on about microbial diversity. And the campus happened to include a brand-new chemistry building.

So Yale made it happen. The Cancer Biology institute, the Microbial Sciences Institute, the Chemical Biology Institute, and the Systems Biology Institute were up and running by 2010. In 2011, three more opened in quick

Ann Kurth

"Nursing as a STEM discipline is a science of human health ecology. … So to be ensconced in a literally rich research ecosystem like that on the Yale West Campus is powerful."



Scott Strobel

"It's about as interdisciplinary as it frankly can be."

Scott Strobel

"Our goal is to be able to engage and support the mission of as many schools and departments as we can."

succession: the Nanobiology Institute in January, the Institute for the Preservation of Cultural Heritage (IPCH) in June, and the Energy Sciences Institute in September.

Each institute comprises a variety of researchers affiliated with various Yale departments. (The Systems Biology Institute, for example, includes faculty from biomedical engineering; ecology & evolutionary biology; immunobiology; microbial pathogenesis; physiology; genetics; molecular, cellular, and developmental biology; and physics.) Each researcher approaches the institute's central scientific questions from points of view born of very different training. And West Campus' open-plan renovated lab spaces mean they see a lot of one another.

"It's about as interdisciplinary as it can frankly be," says Scott A. Strobel, Ph.D., the Henry Ford II Professor of Molecular Biophysics and Biochemistry and vice president for West Campus planning and program development. He is also a member of the Chemical Biology Institute.

Needless to say, turning an industrial pharmaceutical campus into a massive center for academic research has taken a tremendous amount of work over the years.

"There were some spaces where we literally walked in, turned on the lights, and plugged in our instruments," Strobel recalls. "But there were some other spaces where it looked like a bomb had gone off inside. We had to rip everything out and start over."

Take Yale's largest building, the Collections Studies Center, for example. In this 462,000-square-foot, or over-10-acre behemoth, Bayer once churned out aspirin and Alka-Seltzer.

Today, 300,000 of its square feet house the collections of the Peabody Museum, the Yale University Art Gallery, and the Yale Center for British Art. It houses the IPCH, where conservators huddle over priceless works of art visible to hallway onlookers through generous windows. Nearby are labs of the Energy Sciences Institute's chemists, physicists, geologists, and engineers, as well as the hulking microscopes and spectrometers of the Materials Characterization Core.

In a sunny, open-plan common space where pill-pressing machines once stood, a scattering of tables and chairs stands ready to host conversations amongst the experts here.

"It's like going into a large mall—when you talk, somebody's going to hear. But that's a good thing," says Christopher Incarvito, Ph.D., director of research operations and technology at West Campus.

Renovations in this and other buildings across West Campus called for open laboratory floor plans, intriguing machinery in full view of passersby, smaller offices, and spaces that put students and faculty in closer proximity, according to Incarvito.

"People in general are more densely packed without a lot of walls. That's all that it takes—that and a place to write, a place to express yourself, a place to eat, and of course the willingness of scholars to come together," Incarvito says.

Something about being next door to somebody

This structure worked beautifully for Rinehart and Farren Isaacs, Ph.D., both of whom are part of the Systems Biology Institute. They met shortly after Isaacs joined the Institute in 2010.

At the time, Rinehart, a molecular biologist, was wrestling with a problem: how to get bacteria to scale up the synthesis of a particular type of protein.

"We had the product, we had the cellular machinery. We just didn't have a 'factory,' " Rinehart recalls. "It was an engineering technique that was showing a lot of promise, but there were a lot of challenges that nobody really had an answer to."

Along came Isaacs, an expert in synthetic biology. "If I'm being perfectly honest, an entire field that I was almost ignorant of," Rinehart says. They got to talking.

Isaacs was working on a genetically engineered bacterium. It turned out to work perfectly with the approach Rinehart's lab was using. It was "sheer luck," Rinehart says.

Right away, he recalls, "we were making dream molecules at scale, at purity, exactly as we had designed. It was this exact blend of two technologies from two different planets coming together in the same place." Within two years, the collaborators had published in *Science* and *Nature*.

"If I had not been at West Campus in systems biology working right next door to Farren, I don't think we would have realized what we've realized as collaborators," Rinehart says. "The design of the space, the location, the composition—it really matters. There's just something about being right next door to somebody."

A meeting of proteomics and ancient art

What happens when you introduce a proteomics expert to an art conservator? Insight into ancient animal husbandry. This encounter happened on West Campus when Brandon Gassaway, a graduate student in the Department of Cellular & Molecular Physiology and in the Systems Biology Institute, worked with Anikó Bezur, Ph.D., the Wallace S. Wilson Director of the Technical Studies Lab at the Institute for the Preservation of Cultural Heritage.

In collaboration with Yale University Art Gallery conservators Anne Gunnison and Irma Passeri, Bezur's group was studying a third-century wooden shield unearthed by a French-Yale team in 1935 at a site called Dura-Europos, a former Roman border outpost in what is now Syria. Decorated with paintings of scenes from the *Iliad*, the shield was made of poplar slats glued together. Bezur and her colleagues suspected that the adhesive and the paint's binder were made of animal protein, but their techniques didn't allow them to get more specific. Her team asked Jesse Rinehart, Ph.D., associate professor of cellular and molecular physiology, and Gassaway whether they could figure out what the ancient artisans used as adhesives. Using mass spectroscopy-based proteomics techniques and equipment in the West Campus Analytical Core, Gassaway found the telltale signature of three proteins in the adhesives. The verdict: cow's milk.

This finding was surprising, Bezur says—they were expecting a gelatin-based glue between the wood slats and egg in the paint—and they're looking to verify it with other techniques.

"My lab is very excited about being in an environment where there's so much biochemical and biological expertise," Bezur says. "In return, we're able to stretch the relevance of these tools not only to address medical questions but also to address questions that nurture the soul. Obviously, there are not that many lives that get saved by research on Roman shields, but … to be able to marshal new technologies to get at answers we couldn't even dream of before is really amazing. It allows us to be more responsible stewards of these treasures that speak to our shared human history."

—Jenny Blair, M.D. '04

Anikó Bezur

"We're able to stretch the relevance of biochemical and biological tools not only to address medical questions, but to address questions that also nurture the soul."

Jesse Rinehart

"The buildings are almost full everywhere you go. The labs and the floors are bustling with activity. There's just so much going on. It's really a vision as promised."

Jesse Rinehart

> "If I had not been at West Campus in systems biology working right next door to Farren, I don't think we would have realized what we've realized as collaborators."

[For more on their collaboration, see "A Fab Lab Collab," page 26.]

Over lunch and the computer

Two more planned elements of West Campus nurture its magical chance encounters, according to Strobel: the cores and the cafeteria.

The cores concentrate shared equipment. Like neighbors who agree to share a lawn mower, West Campus scientists share expensive tools that they might otherwise have kept to themselves. As they congregate at a microscope, spectroscope, or supercomputer, they talk to one another.

As for the cafeteria, it's a cheerful, busy place whose employees are famously warm. It's been completely renovated from its predecessor, which did not encourage patrons to linger. The West Campus cafeteria is the only place to eat lunch on campus, and that's on purpose, Strobel says.

"They're going to be drawn there for lunch, and as a result, there's going to be the opportunity for these kinds of conversations to occur," he says.

The cafeteria is part of a conference center that holds departmental retreats and seminars from throughout Yale. When faculty present their work, West Campus researchers can amble over and listen. Rinehart loves that.

"You're constantly getting exposed to all these different fields," Rinehart says. "We intersect so deeply with chemistry, with physics, with medicine, with basic biology, with evolution. You're hitting these major categories in depth and breadth that's just not typically seen on the other major centers on campus."

A decade after its purchase, the transformation of West Campus is almost complete, according to Strobel. The science is humming, and the campus plays host to many additional thought-provoking activities: conferences of the Yale Women Faculty Forum; architecture students' class on building a prefab house; agricultural experiments; summer camps; art installations; and police retreats, among many others. In the future, West Campus leaders plan to weave in faculty from more fields at Yale.

"Our goal is to be able to engage and support the mission of as many schools and departments as we can," Strobel says.

Reflecting on how the place has changed, Strobel recalls buying lunch at the campus' old Bayer-legacy cafeteria, Grab'n'Go, shortly after his appointment as vice president. The difference between then and now could stand in for the entire campus.

"Calling it the Grab'n'Go literally was the worst possible signal: come in, grab an old yucky sandwich, pay for it, and eat it at your desk. Two people would come in and grab a sandwich and leave, and it's like, 'This is the dreariest, saddest place. Is this ever going to be anything more than it is?'

"And now, the place is alive. It's just really exciting. It's been so fun to watch that transformation." */yale medicine*

Jenny Blair, M.D. '04, a freelance writer based in Montpelier, Vt., has written frequently for Yale Medicine.

BIOMEDICAL ENGINEERING MEETS RADIOLOGY MEETS GENETICS

A new tool for gene editing offers new approaches to prevent disease.

BY NATASHA STRYDHORST | MAYA SZATAI ILLUSTRATION

Adele Ricciardi navigates the corridors and stairways of the Hunter Building with practiced ease. The School of Medicine has come to feel like home after six years spent in its labs and classrooms.

"When I came to medical school, I wanted to find research that was translational, bridging the gaps between basic science and medicine," Ricciardi says. There's no doubt she's found it at the School of Medicine. Ricciardi spends her days in three different labs, bridging gaps and translating research across campus—and disciplines—in the pursuit of her M.D./Ph.D. degrees.

Ricciardi's work is necessarily multifaceted. In the landscape of medical research in general, and at the School of Medicine in particular, the junctions of traditionally disparate fields are yielding prolific harvests. Collaborative research among Ricciardi's home-base labs has produced a gene-editing tool more precise than the much-lauded CRISPR/Cas9, developed a nanoscopic vehicle to deliver it, and identified genetic ailments that it might alleviate. The tool, triple helix, was developed in the lab of Peter M. Glazer, M.D. '87, Ph.D. '87, HS '91, FW '91, chair and Robert E. Hunter Professor of Therapeutic Radiology, and professor of genetics. Triple helix is the fruit of a collaboration that goes back nearly a decade.

In 2009, Joanna Chin, M.D. '10, Ph.D. '10, presented her research on triple helix at an annual M.D./Ph.D. retreat. The DNA-editing tool was promising, but ferrying it safely into cells was proving a seemingly intractable challenge. Fortuitously, the nearby poster of Nicole Ali McNeer, M.D. '14, Ph.D. '14, illustrated the development of nanoparticles that could deliver complex molecules—like DNA—right to the heart of cells. Each quickly realized that the other's project solved a problem in her own: Chin had an editing tool without a delivery vehicle, while McNeer's nanoparticles were ferries in want of a payload.

Mark Saltzman

> "Peter [Glazer] and I have very little overlap in terms of our scientific disciplines, but as a team we could make progress on problems that neither one of us could easily do alone."

"Everybody realized this was a perfect synergism," says Glazer, who was Chin's principal investigator. In the eight years since Chin and McNeer's serendipitous meeting, the synergism has expanded to produce numerous papers and involve many more researchers. "It's been a tremendously productive collaboration," says W. Mark Saltzman, Ph.D., the Goizueta Foundation Professor of Biomedical and Chemical Engineering, and professor of cellular and molecular physiology, who was McNeer's principal investigator.

Elias Quijano, an M.D./Ph.D. student, also works in the labs of both Glazer and Saltzman. Initially an English major at Yale College, after a class with Saltzman, Quijano became a biomedical engineering major, and later Saltzman's lab manager. He's now involved in the triple helix research, but that class he took as an undergraduate sparked his interest in biomedical engineering and medicine.

"It really came from seeing that first example of how science could enter clinical medicine," he says, "and how a clinical need could drive the scientific process itself. I think seeing that interplay—seeing that dance between science and medicine—was something that really attracted me to the field."

Like Quijano, Ricciardi works on basic science in the labs of both Saltzman and Glazer, refining nanoparticles and the genetic payload for them to deliver. She gets her clinical fix in the lab of David H. Stitelman, M.D., assistant professor of surgery (pediatrics). "I had an interest in engineering," Ricciardi says, "because I thought it married well with medicine." The union means she can "apply science in a very human way"—a prospect eliciting such excitement that it gives her goose bumps. At this stage, the applied science is operating in mouse models, but the human implications are palpable.

"If you can essentially cure a disease, or eliminate the symptoms of a disease with very few off-target effects—I think there's a huge unmet need there," Ricciardi says.

Triple helix in action

Ricciardi strides down a final corridor and pulls out her ID to unlock the Glazer lab. After greeting lab mates and consulting one of several hefty lab notebooks to check the DNA concentrations in her upcoming experiment, Ricciardi glances at the current research subject: F8 571. To an outside observer peering into the enclosure, the scurrying creature is an ostensibly average mouse. On the molecular level, however, something is dangerously amiss: a single point mutation in the mouse's DNA codes for a rare but injurious blood disorder, thalassemia. The condition is characterized by weak, quickly expiring red blood cells and resulting anemia. The tantalizingly minuscule genetic error and its outsize consequences are fueling the efforts to rewrite the code—not only for this mouse or this disorder but for such notorious conditions as cystic fibrosis and sickle cell anemia in human patients.

The genetic revision begins with a DNA analog (peptide nucleic acid, or PNA). Encased in a nanoparticle, the PNA gains access to cells' DNA—and the disease-causing mutation in it. Guided by its sequence, which will seek out its match in the DNA, the engineered PNA snakes alongside and around the snippet of erroneous DNA, gently dislodging and taking the place of its partner strand. Binding to either side of the DNA, this

new filament distorts the classic ladder-like helix to form a temporary triple helix: PNA-DNA-PNA. This aberrant arrangement sets off warning bells in the cell's machinery. The perturbed cell senses the distended bulge in its genetic makeup—much as you would a pebble in your shoe, Glazer says. The conspicuous arrangement spurs the cell's repair mechanisms, which hasten to slip a pristine piece of donor DNA (also delivered by the nanoparticle) into the damaged gene, repairing the initial mutation.

Triple helix has been used to correct the thalassemia-causing mutation in a mouse model. "We cured mice of anemia," Glazer says. "We did four injections of nanoparticles, and 30 days later, they were cured." The technology is less active than the common gene-editing CRISPR/Cas9—repairing about 5 percent of target cells, while CRISPR will act in 30 to 50 percent. However, the off-target effects (creating unwanted mutations elsewhere in the genome) are also much lower in triple helix than in CRISPR—10,000- to 100,000-fold lower. "I think people will improve the CRISPR nuclease to make it a little bit less promiscuous—but we're already there," Glazer says. "I think we have fewer off-target effects than CRISPR will ever be able to get to." Glazer expects triple helix to be in a clinical trial within two years.

"We're now at a stage where we've had advancements in PNA design and advancements in drug delivery converging," Quijano says. "We're getting to a place where both technologies are ready for clinical translation."

A dystopian future?

For many, the prospect of human gene editing raises the unsettling specter of a dystopian world in which elites create custom children with enhanced mental or physical agility—or even purely aesthetic characteristics such as a specific eye or hair color.

"I have very distinct memories of being in my high school biology class, and them wheeling in the TV on the cart and watching *Gattaca*," says Ricciardi. The 1997 film starring Ethan Hawke portrays a future world in which genetically engineered children excel, while natural ones come up against continuous prejudice. The work coming out of the Glazer and Saltzman labs has a more virtuous goal. "We are not trying to introduce favorable characteristics such as improved intelligence or athletic ability or musical prowess. What we're trying to do is eliminate the burden of disease in children," Ricciardi says. "There are kids with genetic disorders who will be going to doctors' appointments for the rest of their lives. They're going to be taking chronic expensive therapies to help ameliorate the symptoms of their disease. And if we can do anything to lessen that burden on patients, families, and the health care system—that's what the goal of our therapies is."

"The most exciting aspect of it is seeing how these molecules can be applied clinically, and seeing the potential for curing human disease," Quijano says.

Saltzman has been pursuing interdisciplinary research since his graduate school days, studying chemical engineering and then medical engineering to become a biomedical engineer. Immersion in the two worlds of engineering and medicine, he says, paved the way to being a collaborative scientist. "So much of it is about understanding the culture and understanding the language that people use," he says.

"Many easy problems have been solved, so the problems we're working on now are much harder. That's why many of them involve collaborative teams of people—often people with different kinds of expertise," Saltzman says. So-called easy problems have their questions and answers in the same discipline, whereas hard problems draw both from multiple fields. "Peter [Glazer] and I have very little overlap in terms of our scientific disciplines, but as a team we could make progress on problems that neither one of us could easily do alone," Saltzman says.

Glazer and Saltzman's collaboration has been prolific—producing papers, patents, and partnerships—and it's now becoming prototypical. Yale, Saltzman says, is "a sprawling university—intellectually—but a pretty compact university, and one where community is really valued. It's big enough that there are all sorts of different people here—with all different sorts of expertise—but it's small enough that they're not all that hard to find." A multidisciplinary environment is, perhaps paradoxically, where such researchers as Quijano, Ricciardi, Saltzman, and Glazer are finding their niche.

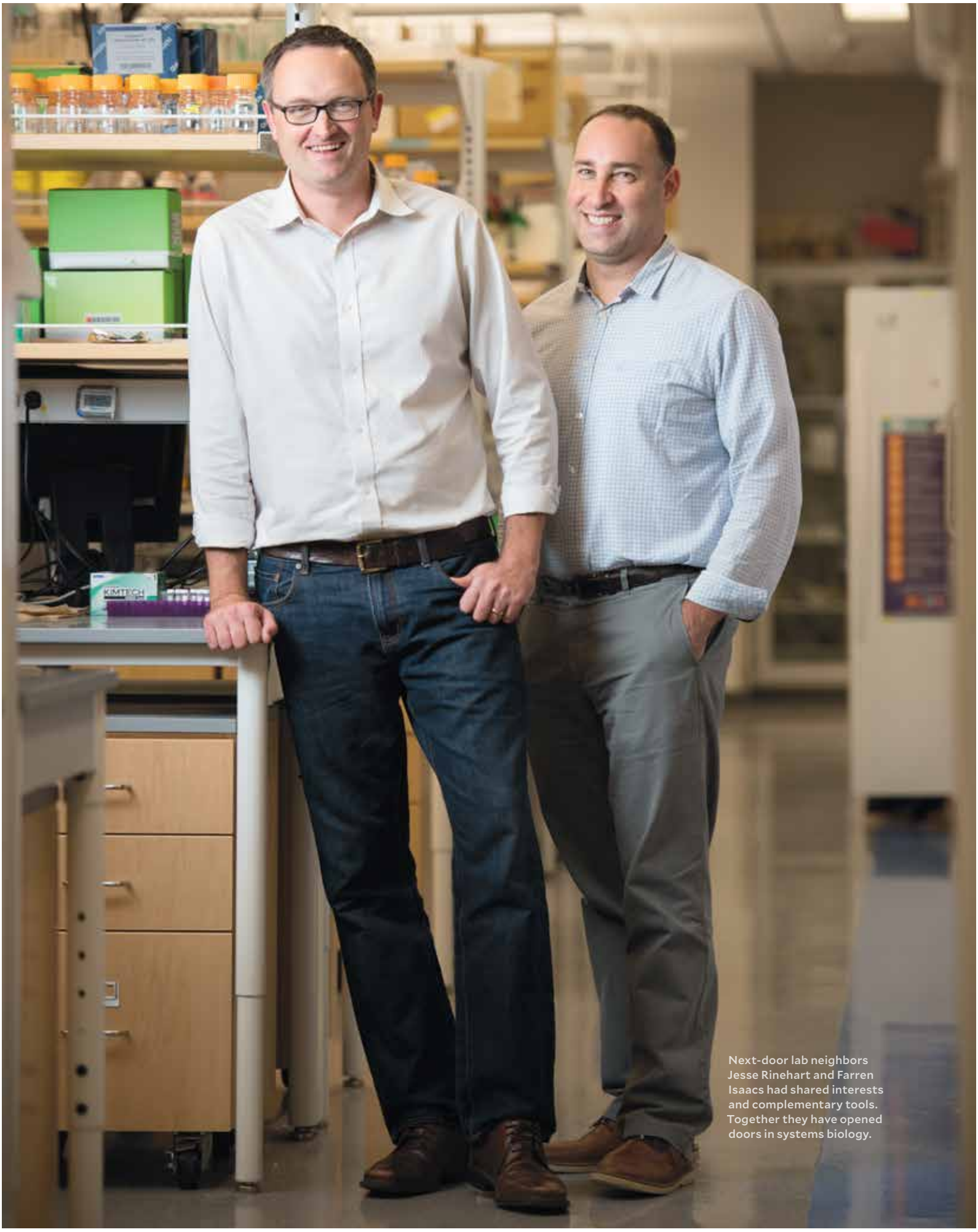
"It's just essential for me to collaborate with people," Saltzman says. "I couldn't be competitive if I didn't." *yale medicine*

Natasha Strydhorst was Yale Medicine*'s summer writing intern in 2017.*

A FAB LAB COLLAB

Jesse Rinehart had a protein he wanted to fabricate in bacteria; Farren Isaacs had the perfect bacterial factory. Isaacs moved into the lab next door to Rinehart's, and the rest is history.

BY ASHLEY P. TAYLOR | FRANK POOLE PHOTOGRAPHY



Next-door lab neighbors Jesse Rinehart and Farren Isaacs had shared interests and complementary tools. Together they have opened doors in systems biology.

It was 2010 and Jesse Rinehart's first day as the head of his own lab and a faculty member at Yale's West Campus when an email requested his presence at a meeting to discuss a new recruit—a scientist whom the Systems Biology Institute hoped to lure to West Campus to start a lab. As soon as Rinehart saw what Farren Isaacs, M.S., Ph.D., was working on, he became very excited. "I was like, 'Oh, my god, I hope this guy comes,' " Rinehart says. Isaacs' current work, he saw, held the solution to a problem that he faced in his own research.

Rinehart, M.S. '99, Ph.D., '04, associate professor of cellular and molecular physiology, studies how phosphorylation—the addition of a phosphate chemical group to proteins and other molecules—changes the way cells behave. Phosphorylation is critical for many cellular functions—along with dephosphorylation, it can turn enzymes and receptors "on" and "off"—and in humans there are an estimated 230,000 phosphorylation sites. Phosphorylation is the cell's most common tool for regulating protein function and passing on signals. It may sound like the nitty-gritty, but it affects human health in a big way: phosphorylation defects can cause high blood pressure, the spread of cancer, and other medical problems.

At the time he started his job on West Campus, Rinehart had developed a bacterial system for adding phosphate groups to proteins to study their effects. But his system didn't work very well in the bacteria that he was using. "We had invented this amazing manufacturing process that was going to change the world, but we didn't have the right factory," Rinehart says. "We were forced to make this in our garage with crappy materials and things that barely worked." In Isaacs' unpublished work, Rinehart saw that he had created a bacterial strain that would be the perfect manufacturing plant. "All we had to do was install our technology into this factory, and all of our problems would be solved," Rinehart says.

That's essentially what happened. As soon as Isaacs, now an associate professor of molecular, cellular, and developmental biology, accepted Yale's offer and moved into the lab next door to Rinehart's, they set to work building Rinehart's phosphorylated proteins in Isaacs' bacteria. "Not only did we have exciting, very complementary research programs, but we started at the same time, we were right next door to each other, we were similar in mind and spirit and scientific method—it was just a really, really good match," Rinehart says. Now they are using their bacterial factories to develop treatments for glioblastoma. Specifically, they are making large amounts of a protein that becomes active when phosphorylated and causes brain tumors to spread. The researchers can then screen for drugs that would *inhibit* that protein and stop tumors in their tracks.

Changing the genetic code

Rinehart has sought in his research to understand what happens when a protein gets phosphorylated. "How does it change the properties of the proteins? Does it make them more active? Does it turn them off like a switch?" Of particular interest to him is phosphorylation of the amino acid serine, one of the 20 amino acids that make up proteins. Serine phosphorylation is the most frequently used signal in the cellular communications that control most physiological processes. The simplest way to study phosphorylation's effects on protein function would be to make two versions of the protein, one phosphorylated, one not, and compare their activities. But there was no easy way to alter a protein's phosphorylation status.

Given what we know about the genetic code, however, it was fairly easy to alter a protein's amino acid sequence: genes, made of DNA, encode proteins, and, on a smaller scale, three-letter stretches of DNA called codons code for amino acids. To find out how one amino acid affects a protein, scientists can add or delete its codon. Rinehart used this approach to figure out a way to study phosphorylation in bacteria. Only to do it, he had to expand the genetic code to include a new amino acid that was already phosphorylated, plus its corresponding codon. With an expanded genetic code that included phosphorylated serine, or phosphoserine, Rinehart reasoned, he could program a phosphate group into a protein by adding its codon into that protein's gene.

Putting this approach into practice was not without its hurdles. All the DNA codons already encoded other things—amino acids or stop signals, which tell the cell's protein production machinery to release the finished protein. Luckily for Rinehart, the genetic code is redundant: more than one codon represents each amino acid, and the same goes for the stop signal. Rinehart used a stop codon called the amber stop codon to encode phosphoserine. The bacterial cell would still have other stop codons that could signal "stop."

Rinehart also had difficulties at the protein production level. To make a protein, a gene—essentially a series of codons—is copied into a messenger RNA. The messenger RNA, also a collection of codons, travels to the cell's protein production machine, where transfer RNA matches the codons and amino acids in a process called translation.

To make sure that the amber stop codon would encode phosphoserine, Rinehart needed transfer RNAs that were attached to phosphoserine and would recognize the codon. While working on his doctoral dissertation, he worked closely with a team that discovered a protein that attaches phosphoserine to transfer RNAs, and by 2011, he had developed a translation system that inserted phosphoserine wherever the amber stop codon appeared. Sounds great, right? But exciting as it was, Rinehart says, there was also "a major, major problem."

The bacterial cell had competing systems that translated the amber stop codon in different ways. The bacterial cell recognized it as a signal to stop translating and release the finished protein; Rinehart's transfer RNAs recognized it as a signal to insert phosphoserine. That competition rendered the technology weak, Rinehart says. "We could make the proteins we wanted, but there were very low levels; it was almost trace amounts."

Rinehart was attacking that problem when Isaacs arrived with a bacterium he had created that solved the problem. In his bacterial strain, Isaacs had replaced the amber stop codon with another stop codon throughout the entire genome and deleted the factor that recognized it as meaning "stop." The amber stop codon took on a new meaning—not "stop," but "insert phosphoserine."

"We could easily take our genetically recoded organisms and his phosphoserine system and bring them together, and start to produce custom-designed phosphorylated amino acids, phosphorylated proteins," Isaacs says. As they reported in a 2013 paper published in *Science*, the system worked well: in their bacteria, wherever the amber stop codon occurred in RNA, the cell translated it as phosphoserine in the resulting protein. This system would later allow them to study how phosphorylation of a specific protein causes brain cancer to spread, and to look for drugs that, by blocking phosphorylation, may be able to stop the cancer's progress.

Rinehart and Isaacs decided to study a kinase, a protein that, when active causes brain tumors to spread. And it becomes active, they found, when it is phosphorylated. Their approach appears counterintuitive. Rather than inhibiting phosphorylation, they first used their bacterial factories to generate large amounts of the phosphorylated active kinase. Then they screened for drugs that would inhibit not only that kinase, but also, they hoped, cancer's spread. They've found some candidate treatments that prevent the cancers from migrating in a tissue-culture dish. Now they are testing these candidate drugs in mice implanted with human brain tumors. They hope that in the future, such a compound could prolong human lives.

"It's a great collaboration," Isaacs says. "We have developed a great environment to do this work that really lies at the interface of multiple disciplines, and I think that's really allowed us to sort of do things and achieve things in our science that independently we wouldn't have been able to do. And that's precisely what science is about and what collaboration in science is about." */yale medicine*

Ashley P. Taylor is a frequent contributor to Yale Medicine.

A CATASTROPHE IN THE BRAIN

Clinicians at the Child Study Center worked with experts in genetics, neuroimaging, and eye tracking to understand what causes childhood disintegrative disorder, a rare form of autism.

BY RACHEL HORSTING | MAYA SZATAI ILLUSTRATION

Dylan started life as a typical baby, meeting his milestones for walking, talking, and other markers of normal development. In a home video from when Dylan was about 3, he climbs, bursting with energy, on the couch and pretends to read aloud from a picture book. His conversation is animated as he talks about the book with his father, who is recording, and he speaks in full sentences. In kindergarten, his parents noticed some language delays, and Dylan received special education support, but his mother, Kim Covell, saw him as "just a quirky kid."

That changed at the end of third grade. Dylan entered a period of intense anxiety that lasted nearly six months. In a video from this phase, he frantically paces his living room, shaking his hands, scratching his shoulders, repeating over and over, "I'm upset. … I don't like it. … oowww, it hurts. … I'm scared." He scratches under his shirt, giving the impression he wants to crawl out of his skin. "He cried all the time," Covell recalls. "I'm convinced when he was looking at me, he was seeing a distorted version of me." As this phase of terror ended, Dylan started new, dangerous behaviors. He jumped from high places and darted into the road. He developed tics and licked surfaces. Then he slowly ceased talking, began to lose vocabulary, and used simpler sentences. When his scores on his developmental evaluations dropped in every single area, his family convinced his school to get him evaluated at the Yale Child Study Center (YCSC).

In advance of the visit, Covell shared the videos of Dylan at the ages of 3 and 8 with clinicians at the YCSC. A final video shows him sitting limply in front of a puzzle, staring around the room. Occasionally, he picks up a piece and shows it to the camera before setting it back down. He does not speak. Minutes after the video ended, Fred R. Volkmar, M.D., the Irving B. Harris Professor in the Child Study Center and professor of psychology, and Alexander Westphal, M.D., HS '11, Ph.D. '12, FW '12, assistant professor of psychiatry in the YCSC, broke the news: her son had childhood disintegrative disorder (CDD).

The diagnosis offered little comfort. "It put a name to it, but it didn't really help," Covell says. What the family learned was terrifying: there is no treatment for CDD, and Dylan will likely need special services and support for his entire life. But in those first few years, Covell says, things were OK. "It was challenging—he lost a lot of speech and some of the joy, but he was still involved in the family." From fifth through 10th grade, the family worked with the public school system to get Dylan the support and accommodation he needed. Covell said it was especially difficult to get the schools to understand Dylan's new reality. "He's different from your typical kid with autism."

As a result of years of advocacy, Covell, an assistant editor for the Press News Group in Southampton, N.Y., started a summer camp specifically tailored for kids on the autism spectrum, pairing them with typically developing peers. Now, she figures she has seen just about every variety of autism. This exposure, however, makes her uncomfortable putting Dylan's experience and her family's challenges on the same spectrum. "I have friends whose kids have autism and are going to college. My kid can't wash his hair. It's not only hard to think of those as the same thing; it's absurd."

The mystery of what is really going on with her son has kept her connected to Yale, and committed

to participating in any research that might help scientists better understand autism and CDD.

A rare and devastating disorder

CDD, which affects between one and two children in 100,000, was first identified in 1908. It is also known as Heller's syndrome, for the Austrian educator Theodor Heller, who identified the disorder 35 years before autism was first described. Westphal, one of the doctors involved with Dylan's case, describes CDD as what happens when normal kids suddenly develop autism. They lose acquired language; motor, social, and play skills; and frequently bladder and bowel control. The loss often follows a period of such psychiatric disturbances as hallucinations and anxiety, similar to Dylan's six-month period of terror. In 2013, CDD, then a distinct disorder, was incorporated into autism spectrum disorder (ASD) in *DSM-5*, the *Diagnostic and Statistical Manual of Mental Disorders* used by psychologists and psychiatrists. This reclassification has diminished awareness of the disorder, making it harder for families to find information and researchers to secure grant money.

This *DSM-5* reclassification is a mistake, according to Abha Gupta, M.D., Ph.D., FW '07, assistant professor of pediatrics, who became interested in CDD during her fellowship at Yale. Although people with CDD meet the full criteria for autism—characterized by difficulties in social communication and restricted, repetitive patterns of behavior—the clinical history of the disorder is different. It is distinguished by its late onset—starting any time between the ages of 2 and 10—and involves dramatic regression and severe impairment.

YCSC faculty have researched CDD for more than 20 years, starting with Volkmar, the center's former director. Through word of mouth, families affected by CDD referred one another to the YCSC for evaluation, building up a community of families like Dylan's that are committed to seeking answers for a condition that has no treatment.

In addition to the desire to understand a mysterious and devastating disorder, the interest in studying CDD comes partly from what it could say about all of autism, says Westphal. The conventional wisdom on autism is that it is a developmental disorder existing from the beginning and that different individuals are affected by atypical development in various areas of communication and social learning to differing degrees, hence, its description as a spectrum disorder.

But Westphal describes CDD as more of a global catastrophe in the brain—low-functioning autism by a different pathway. "That's significant because it may illustrate that not all people with low-functioning autism have the same kind of autism as people with high levels of function."

Gupta and Westphal were two of the lead researchers on a team composed of geneticists, clinicians, neuroimaging experts, and eye-tracking scientists to perform a neurogenetic analysis of CDD. They identified genetic mutations associated with it, mapped its pattern of abnormal brain activity through functional magnetic resonance imaging (fMRI), and charted its social activity through eye tracking. In every area, patients with CDD were compared to those with autism, both with intellectual disability and without, and to typically developing controls. The team hoped these data could help them understand what happens in the brains of kids like Dylan, and how similar it is to more common subtypes of autism.

The genetic analyses showed important differences between CDD and most forms of autism. Not only were different genes involved, but so were the brain regions where these genes were active. The genes most likely to be involved in CDD were expressed strongly in non-neocortical regions of the brain, which help control eye movements and attention to social information. ASD genes are more strongly expressed in neocortical regions. Another analysis showed that the pattern of expression of potential CDD genes had the most similarity to autism cases with a history of regression, suggesting that regression might have a distinctive genetic pattern. The symptoms seen in CDD, this finding suggests, are likely caused by a genetic mechanism in the brain different from most other subtypes of autism.

The team used non-sedated fMRI to see patterns of brain activity when the research participants looked at images of emotional faces (a social stimulus) and houses (a neutral stimulus). The study also, for the first time, included patients with intellectual disabilities in addition to their autism—a group that is

underrepresented in imaging studies because it is difficult to get these patients to cooperate with the study protocols.

The CDD cohort had an abnormal pattern of activity in nonneocortical brain regions when viewing faces versus houses, a departure from the abnormal pattern that people with high-functioning autism exhibit. The low-functioning group had a pattern between those of the CDD and high-functioning autism groups.

The researchers also found a surprising convergence between the genetic and neuroimaging tests—the regions that were abnormally overactive in people with CDD were the same regions where CDD candidate genes are most active.

Eye-tracking studies record what research participants look at when shown pictures or videos. When viewing faces, most of us look at the eyes, while high-functioning individuals with autism split their time between the mouth and eyes. This difference is thought to explain some social skills deficits found in people with ASD. Because people with CDD are more severely affected than average, Gupta expected to find an abnormal eye-tracking pattern. Instead, she found that people with CDD focused on the same things as typically developing people did. "They also favored the eyes when viewing faces," Gupta says.

The clinical observations, genetic analyses, and imaging and eye-tracking data converged in several areas. First, the genes that are most likely to be involved in CDD are very active in the same areas that are overactive when people with CDD looked at faces. Along with this abnormal overactivity came increased attention to the eyes. The researchers speculate that because CDD surfaces after prolonged normal development, the neural circuits that control attention to faces may be preserved. If so, then whatever is happening in the brain during the regression in CDD does not change how the brain processes faces. Why the preservation of some neural circuits is still accompanied by the severe behavioral symptoms of CDD remains a mystery.

A distinct disorder

Studies like this, says Westphal, are notable and should push a rethinking of the definition of autism. He favors modeling it as "a converging constellation," in which multiple pathways meet to present similar symptoms. "For me, CDD is so much at the center," says Westphal. "It's the canary in the coal mine, marking the possibility that gradual developmental accounts do not explain all forms of autism."

The distinction has clinical implications. With a CDD diagnosis, the initial push is to hunt for a reversible cause. If the patient is diagnosed with autism and intellectual disability instead, that hunt never happens. "This means we may be missing a whole world of possible treatments for kids on the low-functioning end," says Westphal.

Pamela Ventola, Ph.D., FW '08, assistant professor in the YCSC, helped lead the team that evaluated the research participants. She believes that this study supports her hunch that CDD is its own entity. In other research, she has predicted the effectiveness of a particular treatment based on brain images of patients. CDD "feels very different, clinically," she says. Even though many of the behavioral features are the same as those of autism after the regression has passed, Ventola thinks the results suggest that CDD may be an entity distinct from ASD. "This interdisciplinary research is really the key—none of these methods alone would have given these results," she says.

James C. McPartland, Ph.D., an associate professor in the YCSC who wasn't involved in this study, is skeptical about abandoning the spectrum model for kids who also have intellectual disability or severe regression. Previous attempts to define subtypes based on clinical evaluations were unreliable and inconsistent, he says, something that does families and patients no favors. And he points out that the sample of 17 participants with CDD is still relatively small. It is impossible to figure out the degree of heterogeneity that exists in CDD. "The reason we stay with the spectrum is because we haven't found anything better."

Dylan's story continues

Dylan continued to lose speech skills. Two years ago, at 16, he was diagnosed with catatonia, a disorder characterized by stupor, mutism, loss of motor skills, and periods of hyperactivity that can be combative and destructive. Dylan has since started in a boarding school that specializes in autism and has experience

Alexander Westphal and Abha Gupta led a research team that studied childhood disintegrative disorder. Their findings on the disorder, they say, should push a rethinking of the definition of autism.

HAROLD SHAPIRO PHOTO

working with students who have catatonia. After over a year of working with him, they have found a communication system for him. Covell describes it as an "old-school" picture system—laminated icons. Many kids use iPads to communicate using pictures, but Dylan's unpredictable behavior—he can become destructive when frustrated—makes that impractical. He can stay in the school until he is 21, and there is no clear answer for what will be best for him after that.

For Kim Covell, the most elusive mystery is the sense, shared by many people who have loved ones with CDD, that the old Dylan is still in there somewhere. He becomes verbal when he gets agitated, but he refers to people and events in his pre-CDD past—teachers from preschool, classmates, things he did with his family. "There's something—it's there," Covell says. "But it's not." */yale medicine*

Rachel Horsting is the director of communications for the Yale Child Study Center.

MELANOMA, HOOVES, AND THE UTERUS

BY ASHLEY P. TAYLOR | VSHIVKOVA IMAGE

Melanoma is often fatal in humans, particularly when it metastasizes, spreading from the skin to other tissues. Yet Lipizzaner stallions, the famed Viennese show horses, frequently develop skin cancer with no ill effects, in large part because the cancer tends not to spread in these horses. Since hearing about the melanoma-resistant horses, Günter P. Wagner, Ph.D., an Austrian native himself, has been trying to understand why. The answer, he found, relates to the evolution of mammalian pregnancy.

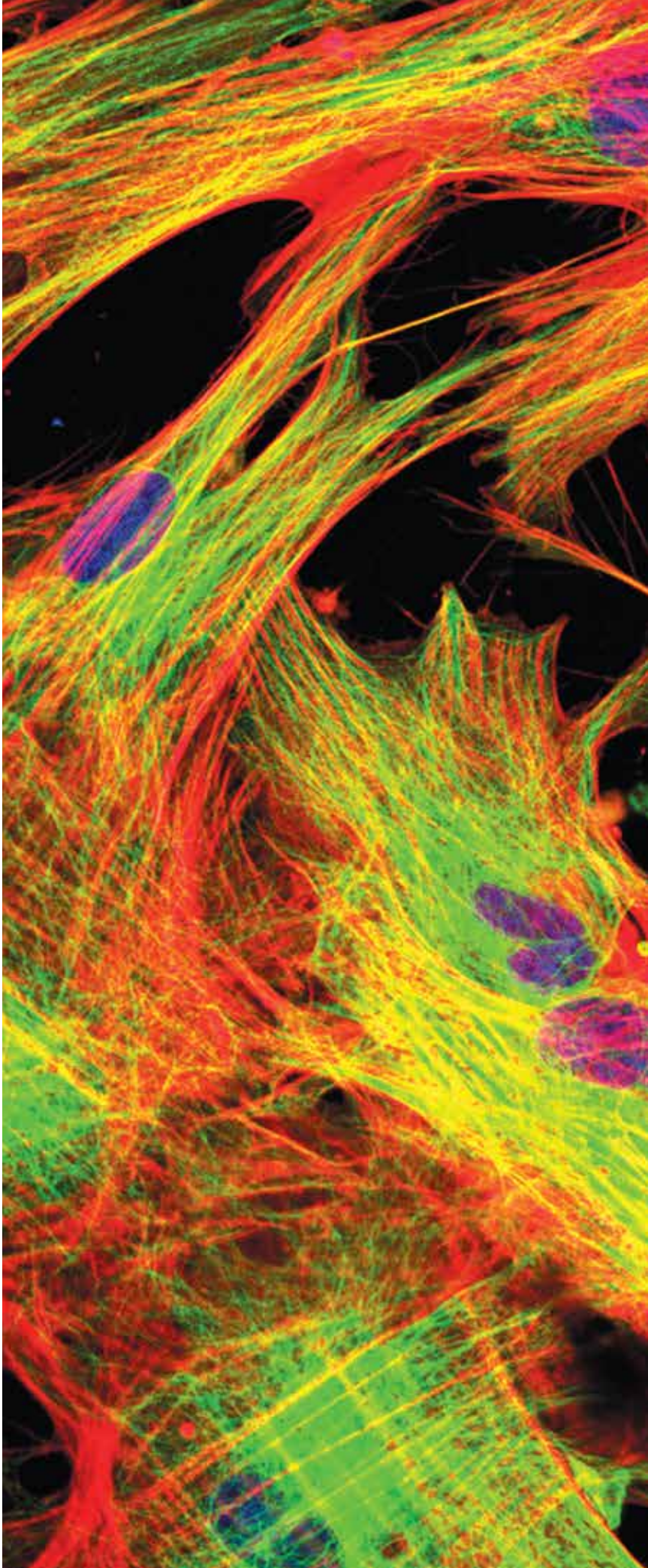
In many mammals, including humans, says Wagner, the fetus, via its sac-like placenta, invades the wall of the uterus, or implants, in much the same way that cancer metastasizes and invades new tissues. The hoofed mammals in which skin cancer does not metastasize—including horses, cows, and pigs—are also those species in which the fetus does not implant, and Wagner believes that this is no coincidence.

"If we investigate in cows or horses or pigs or whatever and see how they keep out invasive cell types—either the trophoblast, the placenta, or cancer cells—we may learn how to treat or contain or make less aggressive cancers in humans," Wagner says.

Wagner, the Alison Richard Professor of Ecology and Evolutionary Biology, with a secondary appointment in the Department of Obstetrics, Gynecology and Reproductive Sciences, established his lab at Yale in 1991 in the biology department at 165 Prospect Street. When West Campus opened 10 years ago, Wagner was the first investigator to move his lab to the new enclave, which promised myriad interdisciplinary opportunities. As a member of West Campus' Systems Biology Institute and the new Cancer Systems Biology @Yale program, which bring together researchers from different disciplines to work on common problems, Wagner draws on the diverse expertise of his collaborators as he explores the pregnancy-cancer link.

Other researchers had proposed that throughout the evolution of pregnancy, the aggressiveness of the fetus from a given species, like the strength of a bulldozer, determined the extent to which it invaded the uterus. Humans, for example, have invasive pregnancies: the fetus burrows into the lining of the uterine wall. Horses, cows, and pigs, on the other hand, have noninvasive pregnancies: the fetus contacts the uterine wall but does not burrow through it. Cow, pig, and horse fetuses, therefore, should be less aggressive than human ones. Wagner, however, says that the fetuses of hoofed mammals do not invade the uterine wall "not because the fetus became less aggressive; it's because the mother found a way of keeping [the fetus] out." It's less the force of the invading fetus and more that of the uterus opposing the invasion that determines how far the fetus gets.

In collaboration with Andre Levchenko, Ph.D., director of the Systems Biology Institute and the John C. Malone Professor of Biomedical Engineering, the Wagner and Levchenko labs demonstrated how the uterine lining, the endometrium, fights the invading fetus. To simulate fetal invasion, the researchers set up placental cells to move along tiny grooves fabricated in the Levchenko lab as they pass through endometrial cells. Following the so-called nanogrooves, each one about 400 nanometers wide—about one-hundredth the width of a human hair—the cells move in a straight line, and researchers can easily measure their invasive progress. "That's the basis for us being able to measure different rates of invasion that are going on," Wagner explains. The result? Human placental cells travel farther through human endometrial cells than they do



Fibroblasts appear in both the skin and the womb. They may hold clues as to why horses, cows, and pigs resist melanoma.

through bovine endometrial cells—cow cells are resisting the invasion.

The skin cells of pigs, cows, and horses, Wagner hypothesized, resisted melanoma metastasis in the same way that their wombs resisted fetal invasion. But what defenses could the skin and the uterus share? Both the endometrium and the skin contain cells called fibroblasts, and throughout the evolution of mammals, Wagner found, the fibroblasts in these two locations evolved together, such that as the uterus began to resist fetal implantation, so the skin began to resist melanoma metastasis. Nanogroove experiments supported the hypothesis: skin fibroblasts from cows resist melanoma invasion better than those from humans.

In experiments with bovine melanoma cells, Wagner collaborates with another West Campus researcher, Sidi Chen, Ph.D., assistant professor of genetics in the Integrated Science and Technology Center. Cow melanoma cells are hard to come by, so "we have to make them ourselves," Wagner says. Chen uses gene editing techniques to rewrite the genetic code of cow melanocytes and make them cancerous. "Our goal is to grow healthy melanocytes in the lab, and then we ask Chen to make them into tumor cells so that we can study cow melanoma cells," Wagner says.

To see whether human skin fibroblasts could be coaxed to resist invading melanoma, Wagner, in collaboration with the Levchenko lab, is modifying human skin fibroblasts to make them more like fibroblasts from cows. So far, modified human cells are better able to resist melanoma invasion than their unmodified counterparts. "This is still preliminary, but promising," says Wagner. *yale medicine*

Ashley P. Taylor is a writer based in Brooklyn, N.Y.

PUTTING THE PRECISE IN PRECISION MEDICINE

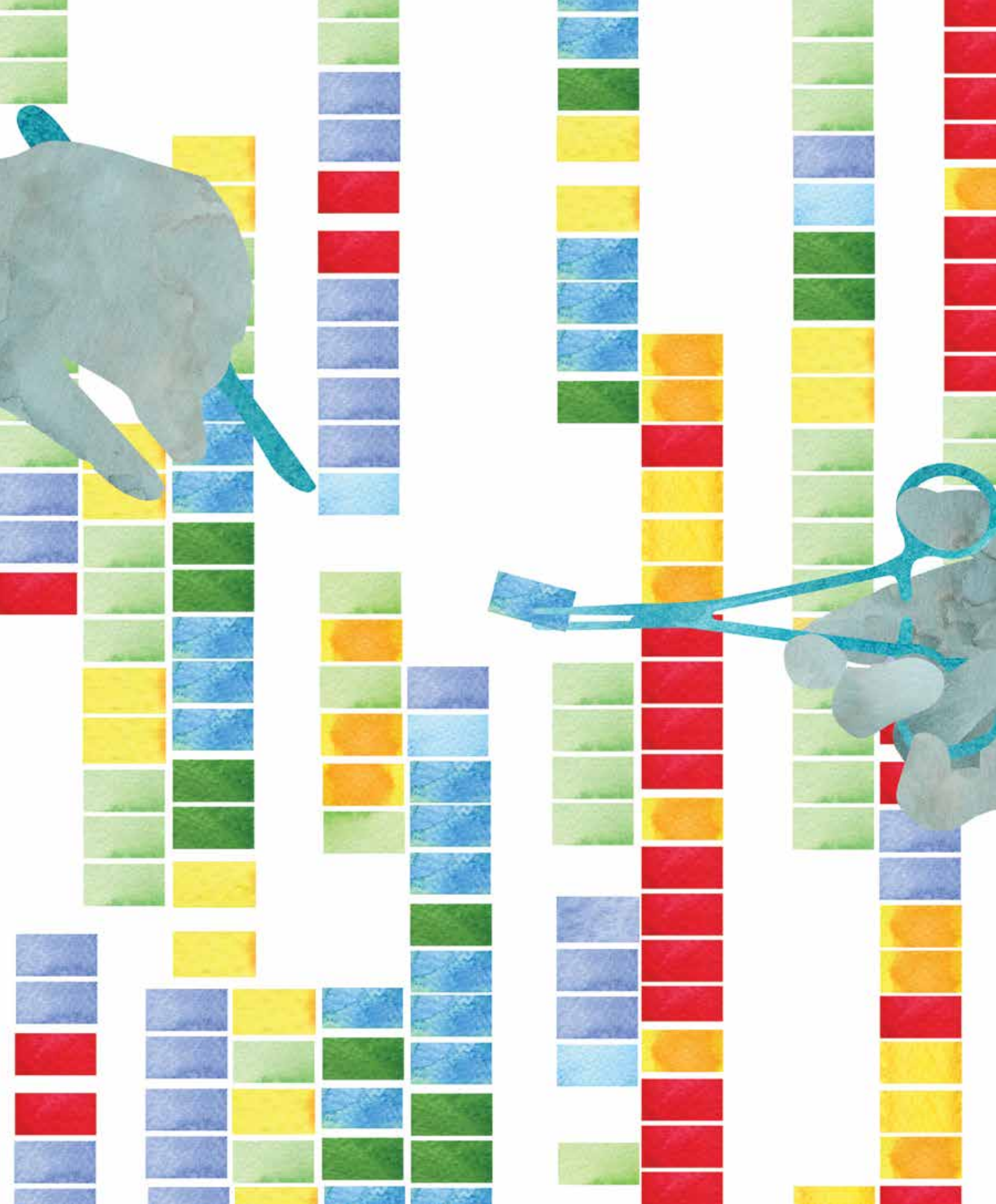
Exome sequencing allows scientists and clinicians to zero in on the mutations responsible for a disparate array of ailments.

BY BRUCE FELLMAN | MAYA SZATAI ILLUSTRATION

About eight years ago, a doctor in Turkey examined a 5-month-old boy for "failure to thrive and dehydration." Paradoxically, his diapers were wet, so the medical team was inclined to suspect Bartter syndrome, a congenital kidney defect which is manageable if caught early. But the standard treatments weren't working. Baffled, the doctors sent the infant's blood sample to Yale for a sophisticated analysis then under development called exome sequencing.

While the Human Genome Project and related work had looked at the entire genetic code and generated an unruly amount of data, exome sequencing detailed only the region of the genome—about 1 percent—that codes for proteins. The technique was pioneered by School of Medicine researchers Shrikant M. Mane, Ph.D., director of the Yale Center for Genome Analysis (YCGA), and Richard P. Lifton, M.D., Ph.D., former chair of genetics who's now president of Rockefeller University, and their colleagues. Exome sequencing, says Mane, "gives you just about everything you need for diagnostic purposes, and quickly we knew this wasn't a kidney problem. The doctors had been barking up the wrong tree."

Exome sequencing revealed a mutation in gene *SLC26A3*, which leads to a condition called congenital chloride diarrhea. While the condition can't be altered, prompt salt replacement therapy helped bring the baby back from the brink. "This was the first use of the exome sequencing technique as a diagnostic tool," says Mane, who delights in explaining that his



uncle in India underwent whole-exome analysis—and when Mane was trying to figure out the source of his own recent mysterious malaise, he also undertook the sequencing equivalent of a selfie. "Now, the whole world is using it."

Since a seminal paper on this case appeared in 2009 in the *Proceedings of the National Academy of Sciences*, Mane and his colleagues have employed exome sequencing to zero in on the exact mutations responsible for a disparate array of ailments from severe brain malformations to unusual kinds of melanomas. The technique is rapidly becoming a key component in the toolkit that health care workers and researchers are using to achieve a long-standing dream: precision medicine.

In a presentation last February to the Connecticut Commission on Economic Competitiveness and the state legislature's Commerce Committee, Dean Robert J. Alpern, M.D., Ensign Professor of Medicine, explained that precision medicine uses "a patient's genomic information, environment, and lifestyle to assess a person's risks for disease and to develop more effective and targeted treatment plans and therapies." Doctors will be able to probe a patient's DNA to determine in advance what will and won't help an individual, rather than the general population. "Ideally, we'll also be able to develop an alternative therapy that worked for the non-responders," says Alpern. "This is true precision medicine, and while today it has had some applications, for many conditions it remains a dream. But it is a dream that will soon be realized."

Perhaps paradoxically, becoming more precise has required School of Medicine researchers and physicians alike to adopt an ever broader, more interdisciplinary approach to their work. Not only are investigators in the basic medical sciences, from pathologists and cell biologists to immunologists, collaborating with an array of front-line clinicians, but they're also sharing an array of new tools and working closely with investigators throughout the entire university, from physicists and chemists to mathematicians and computer scientists, to lay the groundwork for the move to a new kind of medicine.

One way this is being achieved is through the YCGA, a joint endeavor among the university, the School of Medicine, and Yale New Haven Hospital. Established in 2009, the YCGA opened its new headquarters on West Campus in May and is using the highest of high-tech genome sequencers and computers to investigate the genetics of rare inherited diseases, uncover mutations that can help doctors diagnose ailments, and—this is the ultimate hope—discover individualized ways to deal with often baffling, even intractable, situations.

A multimillion-dollar array of state-of-the-art machinery and analysis equipment has been critical in bringing costs within reason. Mane noted that the Human Genome Project, the federal effort to sequence the complete genetic code, took some 10 years and $3 billion to complete; it was wrapped up in 2003. Yale geneticist Jonathan M. Rothberg, Ph.D. '91, FW '93, invented high-throughput sequencers that reduced the time considerably and lowered the cost of sequencing a human genome to about $1 million—subsequent technologies have dropped this expense to a few days of analysis time and a "mere" $1,000. Sequence only the exome, says Mane, and the work could be done in close to real time for approximately $275—about the cost of a routine office visit. "That's why this revolution is starting to take place," says Mane. "Sequencing has become so cheap that we're poised to take a quantum leap in our ability to use it routinely."

There are, however, roadblocks—some technical or institutional, others structural or philosophical—that will have to be addressed. Among them is the challenge of locating a mutational needle in the genetic haystack. "It has become relatively easy to sequence a genome, but it's still very hard to determine the genetic cause of a disease," says Mane. Part of the reason for the difficulty comes from the fundamental but surprising insight provided by the Human Genome Project: we simply don't have that many genes.

"We used to believe that it was one gene, one protein, so if there were 100,000 proteins, there had to be 100,000 genes," Mane says. "But we now know that we have only about a quarter of that number. In fact, we have fewer genes than a rice plant."

The smaller number, however, makes life harder, not easier, for researchers, since those 20,000 genes are expert multitaskers, which makes identifying all their responsibilities especially challenging. Uncovering

which mutation leads to what ailment requires sequencing numerous individuals and keeping the YCGA's pair of NovaSeq 6000s and related machinery working overtime. Building such genetic profiles and sorting the good from the bad also requires the analysis of an almost unfathomable amount of data and the development of new techniques to mine and protect them. That is the mandate of a newly formed entity called the Yale Center for Biomedical Data Science.

Center co-director Mark B. Gerstein, Ph.D., the Albert L. Williams Professor of Biomedical Informatics, explains that succeeding with what researchers term "Big Data" requires "real thought about standards, the uniform collection of data, the distribution of samples, and the presentation and packaging of results." After three years of planning, Gerstein and co-director Hongyu Zhao, Ph.D., a geneticist and the Ira V. Hiscock Professor of Biostatistics, have assembled a kind of central clearinghouse for research and development of these issues, particularly cloud computing and privacy, as well as for education and bridge-building collaboration on university, national, and international levels. "Our mission is really about connecting and coordinating the people and resources already here, and becoming a way to recruit the scientists we want to attract in the future for the Big Data initiatives we want to participate in," says Gerstein. "We expect the center to have a very broad impact."

Tamar S. Gendler, Ph.D., dean of Yale's Faculty of Arts and Sciences, the Vincent J. Scully Professor of Philosophy, and professor of psychology and cognitive sciences, concurs. At the university, she explains, data science encompasses three interlocking circles that range from the most abstract—pure mathematics—to the most applied, the clinical. "What's exciting is the often unexpected ways that the math informs the physics, which informs the chemistry and the biology and the clinical work," says Gendler, pointing to the work of Ronald R. Coifman, Ph.D., the Phillips Professor of Mathematics. His fundamental insights enabled precise information organization methods, which, due to a collaboration with Frederick J. Sigworth, Ph.D. '79, professor of cellular and molecular physiology, of biomedical engineering, and of molecular biophysics and biochemistry, led to remarkable enhancements in the images produced by the cryo-electron microscope. Those images can reveal the basic structure of molecules that may be important in understanding diseases and developing targeted therapies. "This device allows atomic structures to be determined from a smaller number of molecules—a millionfold smaller—compared to the more traditional method of X-ray crystallography. And the ability to obtain atomic structures with cryo-EM happened quickly—about five years from the initial theoretical math to an actual insertion into a scientific tool," says Gendler.

Steven H. Kleinstein, Ph.D., associate professor of pathology, is using the cutting-edge sequencing tools to better understand how the immune system responds to pathogenic challenge, as well as to uncover the roots of autoimmune disorders like myasthenia gravis. Kleinstein targets the body's 100 billion B cells, a key component of the immune system, to discover the characteristics that enable each cell's antibody receptors to recognize and fight off pathogens. "This is a powerful technique that lets us understand the dynamics of the process," says Kleinstein. "We can use these data to reconstruct a person's unique immunological history. This helps us understand the processes that led to a disease, or may eventually help us design better vaccines that can leverage an individual's current immune state to get the exact response we want. Receptor sequencing is already being used as a personalized biomarker for certain kinds of tumors and can detect, with much greater sensitivity than established methods like flow cytometry, if the disease is coming back. This kind of precision medicine is no longer a pie-in-the-sky idea. We're going to get there." */yale medicine*

Bruce Fellman is a writer in North Stonington, Conn.

A NEW TOOL AGAINST CANCER

BY JEANNA CANAPARI | MAYA SZATAI ILLUSTRATION

When two experts in their fields get together and combine their labs, incredible things happen. W. Mark Saltzman, Ph.D., the Goizueta Foundation Professor of Biomedical and Chemical Engineering, and his team designed "sticky particles": nanoparticles that were bioadhesive and stuck to the surface of the skin. Combining this discovery with the expertise of Michael Girardi, M.D. '92, HS '97, FW '97, professor of dermatology, the two used those sticky properties to create a sunscreen that blocks any toxins in the sunscreen from soaking through the skin and entering the bloodstream.

Then they realized that they could take the technology further. "We discovered that this adhesive property that adheres the nanoparticles to the skin also makes them attractive to tumor cells," says Saltzman. Based on Saltzman's previous success with a similar method to treat models of ovarian and other types of cancer, the team created a system that could adhere chemotherapeutic agents to tumors to treat skin cancer. While the team is still figuring out why these particles are attracted to tumor cells, the potential is obvious.

As the collaboration continues, so do the discoveries: "We can keep expanding the technology in the lab," says Girardi, "and see what else it can be used for." But there are limits to what even super labs like Saltzman's and Girardi's can do. "You can't, in a Yale lab, start developing a product," Girardi notes.

Now, a new grant is poised to do just that and help them take their double discovery from the lab into the marketplace. With funding from the Blavatnik Family Foundation, Girardi and Saltzman seek to close the gap between the technology they have developed in the lab and the commercial world, where sunscreen can be sold to consumers and treatment can reach cancer patients via prescription.

The purpose of the grant, which is in the range of $100,000 to $300,000, is to give Girardi and Saltzman the resources to bring their technology to the manufacturing stage, a critical step in getting it ultimately to consumers and patients. The demonstration of manufacturing at a larger scale will open the door to licensing the technology or to beginning a start-up for advancing both applications of the technology to market.

While Girardi and Saltzman can develop these products in the lab at a small scale, "there are questions surrounding how to make this cost-effective, and do it at a large scale, so that's a very important step to bring this technology to the real world," says Girardi. Through the grant, they will engage a contract research organization to help them prepare to scale up the technology and perform preclinical testing to answer such crucial questions for potential investors as quantifiable efficacy and levels of toxicity. There is a great deal of overlap, Girardi says, between how the sunscreen and skin cancer treatment would be developed, scaled up, and manufactured, but there are some fundamental differences. "There are different levels of tolerable toxicity and sterility in preparation in each of those, not to mention the active ingredients are different," Girardi says.

"It is difficult to translate research work into a commercial venture," says Saltzman. "Venture capitalists or commercial partners want to see certain kinds of development results that are difficult for academic labs to accomplish. ... The goal of the Blavatnik Family Foundation is to provide dollars that are explicitly for this purpose."

As they prepare to engage with industry, Girardi and Saltzman continue to hone the technology they have developed. The sunscreen was first developed

with the agent padimate O, which blocks only the sun's UVB rays. The new version now uses a combination of agents to achieve broad-spectrum coverage, to block not only UVB rays, but harmful UVA rays as well. The team is working on even further uses for the platform. "One of the most exciting aspects of a platform technology is the capacity to expand it in other directions," Girardi says.

Both researchers say the disparate nature of their backgrounds makes such a breakthrough possible. "One of the things that makes it impactful is that our areas of expertise are so different, but we communicate well together," says Saltzman, "so we can do things that neither of us could easily do alone." */yale medicine*

Jeanna Canapari is a writer in Guilford, Conn.

Old specimens yield new clues to disease

A reunion visit leads to a search for genetic clues to a brain disorder

By Natasha Strydhorst

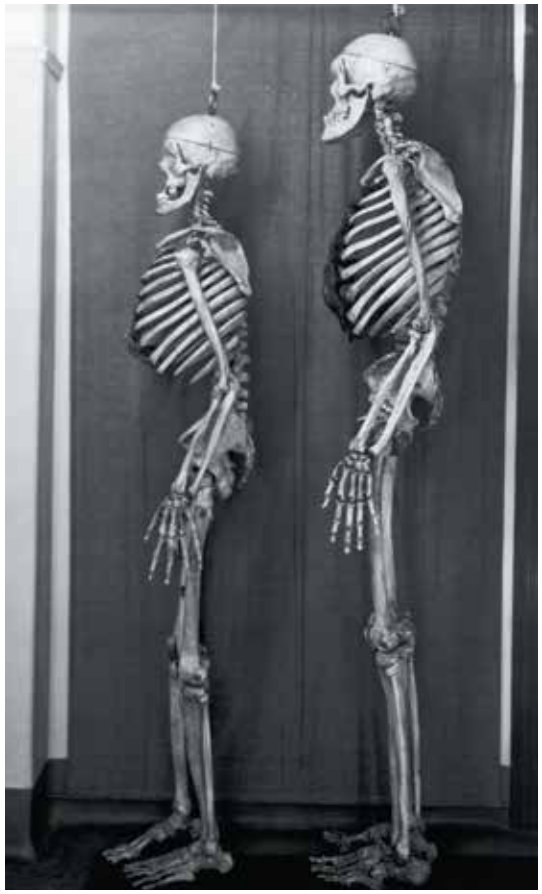
Four years ago, when Maya Lodish, M.D. '03, and her young daughter visited the Cushing Center for a scavenger hunt at Lodish's class reunion, both were struck by the unfamiliar, even eerie setting—and its contents. Soft warm lighting illuminated hundreds of jars containing brains and tumors excised in the last century by Harvey Cushing, M.D.

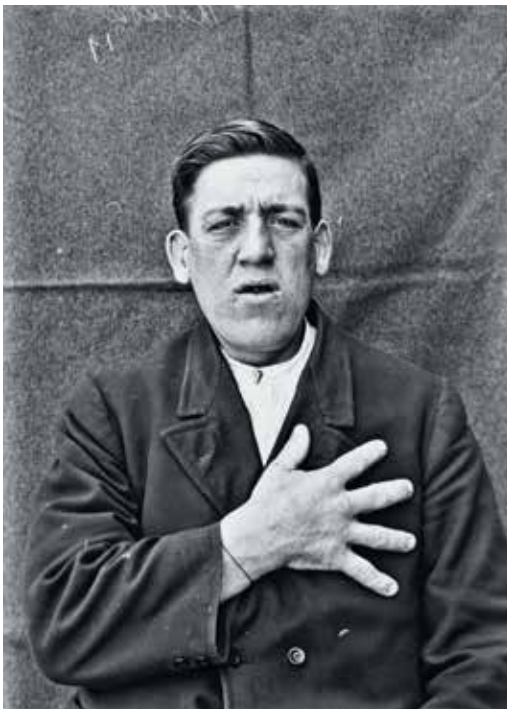
Known as America's father of successful neurosurgery, Cushing introduced practices a century ago that reduced an 80 percent mortality rate to 8 percent, according to Dennis D. Spencer, M.D., the Harvey and Kate Cushing Professor of Neurosurgery and former chair of the Department of Neurosurgery. Cushing also procured many, many brains for future research.

Today, those brains, which once gathered dust in a basement storeroom at the medical school, have received fresh formalin—and offer a renewed avenue for research. On seeing the specimens, Lodish wondered whether any DNA survived in the preserved tissues—and whether it might reveal genetic links connecting Cushing's patients with contemporary pituitary diseases.

"I can't express enough how important genetics is," Lodish said. "It goes hand in hand with the care of the patient." Investigating the genes of long-deceased patients is "contributing to understanding the genetics of disease," Spencer said. He and Lodish sought out a medical student to take up the investigation as a thesis topic. The undertaking was a natural fit for Cynthia Tsay, who studied the history of medicine during her undergraduate years at Yale.

"It was her dream-come-true project," Lodish said. In the early stages of the project, Tsay and Lodish were flipping through Cushing's clinical notes when they came across an intriguing patient. Today known simply as G.B.S., his photograph from Cushing's autopsy report looked familiar to Lodish, one of the few people who regularly sees patients





OPPOSITE Neurosurgeon Dennis Spencer examines a specimen from the Cushing Tumor Registry selected by Maya Lodish and Cynthia Tsay for their study. Although this patient sample did not appear in the final paper, it was identified as coming from a patient of interest.

FAR LEFT A brain specimen and clinical notes from a patient known as G.B.S., in left in photo, yielded clues to the disorder called Carney complex. The disorder was traced to the patient's genetic code. The larger skeleton was from another patient and used for comparison in the study.

LEFT The patient known as G.B.S. suffered from acromegaly, the result of a pituitary tumor secreting excess growth hormone.

with the smattering of freckle-like pigmentation that could indicate a rare disorder called Carney complex. Symptoms vary, but G.B.S. was a patient with a pituitary tumor secreting excess growth hormone, resulting in a condition called acromegaly.

"It was a fortuitous discovery," Tsay said, "because all the pieces lined up." The patient's photograph and records from a century ago could be matched to his brain specimen preserved in the Cushing Center. It fell to Tsay to line up the most challenging piece—the genetic code.

"Cynthia worked *tirelessly* in the lab," Lodish said, "trying to isolate DNA from these samples." The effort paid off in a posthumous diagnosis for G.B.S.: Carney complex was indeed written in his genetic code. Could she go back in time, Tsay would have a great deal to tell Cushing about his former patient. But Cushing would also have a great deal to tell current doctors about the link between environmental factors and disease.

"Cushing would find out where you came from, what your work was, what your background was," said Terry Dagradi, the Cushing Center coordinator who orchestrated the cataloging of Cushing's images and records for the project. "You had to just get to the details of people's lives and see if there was a hint of something that you could put together."

An inherent fascination with brains in jars enthralled Cushing in the 1900s, Lodish and her daughter in 2013, and continues to fascinate today's visitors to the Cushing Center. "It does really spark the interest of younger people," Lodish said.

Dagradi recalls an architect's young daughter visiting the center, peering up at the specimens, and wondering out loud whether they were still thinking. "It was this very sweet little moment," she said. "And you think, 'Oh—they're not thinking, but they're still telling us stuff.'"

TERRY DAGRADI PHOTOS

M.D./Ph.D. student wins Soros Fellowship

SINCE HE ARRIVED IN NEW YORK CITY IN 2006 as a 16-year-old immigrant from Suriname, Lorenzo R. Sewanan has packed in what looks like a lifetime of experiences. Sewanan, who is in his sixth year of the M.D.–Ph.D. Program, worked on a team that has designed prize-winning firefighting robots. He's volunteered with Curtin Volunteers, a student-led service group, in indigenous communities in Western Australia, where he worked on educational initiatives and community service in mining towns. He's won an international poetry prize and been interviewed by *The New Yorker*. And this engineer-poet-physician-in-training can fix a mean batch of yuca (cassava) fries.

This year, Sewanan won a Paul & Daisy Soros Fellowship for New Americans, a two-year $90,000 educational grant. He was one of just 30 immigrants nationwide to receive an award that drew 1,775 applications.

"I feel lucky," Sewanan said. "I really appreciate getting to stand as a placeholder for all the great work that immigrants of all kinds are doing, trying to give back to American society."

Sewanan was born to Guyanese parents in Suriname, a former Dutch colony in South America; the family's ancestors were among a 20th-century diaspora that left India for what was then known as British Guyana to become indentured laborers. He and his younger sister Amanda grew up in Paramaribo speaking English and Dutch; their parents sold clothes, jewelry, and cosmetics in a small shop. After Lorenzo finished the 11th grade, the family immigrated to the United States. He completed high school at a public school in Jamaica, Queens.

That may sound like a painful transition, but it wasn't bad. In Suriname, Sewanan explained, people from neighboring Guyana were subject to discrimination after fleeing political turmoil in the 70s and 80s.

"You get made fun of a lot for speaking Dutch with a Guyanese accent, or for speaking English, for instance," he said. "When I moved to the States, I felt more at home. … Everyone was an immigrant from somewhere in that area of Queens."

Lorenzo Sewanan writes poetry, has built robots, and has been interviewed by *The New Yorker*. Now he's in his sixth year of the M.D.–Ph.D. Program, studying the human heart.

Lorenzo Sewanan //

"The heart is one of the most mechanical organs—it's so beautiful, and the purest version of biomechanics that we can get."

The next stop was harder for an immigrant from Suriname: affluent, mostly white Trinity College in Connecticut. "Fitting in was tough," he recalls. He majored in physics and engineering (hence the robots), with a minor in writing and rhetoric. Sewanan also worked as an EMT, mentored students in a "Physics in Science Fiction" class, and studied abroad in Perth.

When he was a sophomore, a workshop on reflective writing and literature in medicine launched his interest in the medical humanities. Once he read physician-author Abraham Verghese's memoir *My Own Country*—"an incredible journey"—he knew he wanted to explore medicine.

Drawn to Yale in part because of its robust medical humanities program, Sewanan kept writing.

JOHN CURTIS PHOTO

ONLINE EXCLUSIVE

When Esther Choo, M.D. '01, tweeted about her emergency room encounters with white nationalists, she never expected her story to go viral. In the wake of the incidents in Charlottesville, her thread led to a live interview on CNN and an article in the *Washington Post*.

For more on Esther Choo, visit yalemedicine.yale.edu/choo

He co-founded a health professions literary journal, *Murmurs*. In 2013, he won the Marguerite Rush Lerner Award for poetry, as well as the Yale UCL Collaborative Poetry Competition. The latter award landed him in *The New Yorker*, where he appeared in a "Talk of the Town" story called "Poet, M.D."

When Sewanan isn't writing poetry, he's righting wrongs. In 2013, Sewanan co-founded Students for a Better Healthcare System, in which medical students held teach-ins in New Haven about health care access after the passage of the Affordable Care Act (ACA). For their efforts, the students received a 2015 Yale University Seton Elm-Ivy Award.

For Sewanan, such activism is partly personal: prior to the ACA's 2010 passage, he had family and friends who struggled with spending caps, restrictions for preexisting conditions, and losing health insurance. "It was very obvious that this was stuff we should try to help people with," he said.

In 2015, Sewanan joined the Integrative Cardiac Biomechanics Lab of biomedical engineering professor Stuart Campbell, Ph.D. They're working to grow new tissues made with stem cells from patients with cardiomyopathy. These tissues can increase understanding of the disease and possibly lead to new therapies.

"The heart is one of the most mechanical organs—it's so beautiful, and the purest version of biomechanics that we can get," he said. "I also just love the idea of cardiology from a poetic sense as well. It's very poetic to fix people's hearts. ... not to be too corny."

In his spare time, Sewanan enjoys reading, writing, exploring the outdoors, and tasting craft beers. And he likes to cook.

"I'm known for my yuca fries," he said. "I love making stuff that reminds me of home."

—Jenny Blair, M.D. '04

A diagnosis of the health care system

Robert M. "Robbie" Pearl, M.D. '72, recalls the days nearly 15 years ago that changed his life—and ended his father's. A series of medical miscommunications resulted in a medical error that a few years later in 2003 would lead to the premature death of his father, Jack. Myriad specialists tended to his father during this last hospital stay, each recommending a different operation. Once the family concluded that no additional treatment would lead to the quality of life his father would want, Pearl said, they declined further aggressive procedures and the physicians stopped coming.

"There's no CPT code for compassion," Pearl said.

Now Pearl is on a mission to return compassion, expand prevention, and reduce medical errors in American medical practice. Pearl, who for 18 years was CEO of Permanente Medical Group and is now chair of the Council of Accountable Physician Practices, recently published his first book, *Mistreated: Why We Think We're Getting Good Health Care—and Why We're Usually Wrong*.

"I've heard fiction writers talk about the characters coming alive, but I think it's just as true for nonfiction," Pearl said. Not just characters, but memories, experiences, and convictions demand to be narrated—and the reasons for writing "start bubbling over." His father's death and his observations as a physician and CEO of Permanente solidified his conviction: there's something rotten in the system of health care in this country.

After training at Stanford, Pearl began his career as a plastic and reconstructive surgeon, enthralled with the specialty's capacity to redirect the trajectory of patients' lives. "Plastic surgery is the rebuilding of life, not just the correction of disease," Pearl said.

Health, he believes, needs to be the focus of modern medical care. In contrast, medical practice in America was fixated primarily on correcting disease rather than preventing it in the first place. "I think that in many ways I've spent my entire career wanting to change American medicine, and this book has opened a new chapter," Pearl said.

He describes medicine as an industry operating two centuries in the past. The

fee-for-service structure of payment resembles that used among the scattered British population of the 19th century, and paper-and-pencil record keeping belongs in the 20th century, Pearl said. America's health care system is "as destined to fail as the economy of England was before the Industrial Revolution," he said. "What we need is a new revolution—a revolution that's going to change the structure, and change economics, and change the technology." According to Pearl, the structure of American health care is not integrated, but fragmented along specialty lines, with poor communication and patients falling through the cracks. A legion of specialists treated his father, he recalled, each assuming his father had received an essential vaccine following his spleen removal, and none administering it.

In *Mistreated*, Pearl uses neurophysiological research to show how context shifts perception and changes behavior. For example, physicians—particularly specialists—need to communicate with those in other disciplines, he said. "When care is integrated, you see everyone as being on the same team as you. As a result, you're going to collaborate with them. You're going to cooperate. You're going to coordinate. You're going to interact," he said. "And as patients, most people assume that it's happening in the health care they receive, but often it's not."

Events in his personal and professional life led Robert Pearl to write a book about what he believes is wrong with the American health care system.

Robert Pearl //

"There's no CPT code for compassion."

Pearl points to his experience at the School of Medicine as a contrast to this structural weakness. "My classmates were not my competitors. They were my partners," he said. "It was the best environment I could have been in to understand collegiality and the power that it can have." That same atmosphere is one that, as CEO, Pearl strove to incorporate into Permanente Medical Group. His integrative approach extends to his own combined pursuits of medicine, management, and writing. He authors a health care and business column on Forbes.com, and serves on the faculty of Stanford's medical and business schools. He has also spent eight years as Stanford's plastic surgery residency director, training future physicians. "What I tell all of them about their future is that it's going to be multiple careers," Pearl said.

The route to better health care, Pearl said, begins with acknowledging medicine's shortcomings—and addressing them through a model of integrated, preventive, and compassionate care. This vision echoes the philosophy of Sidney R. Garfield, M.D., who co-founded Kaiser Permanente in 1945: "We need a health care system—not a disease system."

—*Natasha Strydhorst*

PHOTO COURTESY OF ROBERT PEARL

How Peter Schulam came to lead a center for innovative thinking

AS SCIENCE AND RESEARCH MOVE away from a narrow focus within a field and toward efforts across disciplines, a gift from an alumnus of the Yale College Class of 1986 aims to spur such collaborations by establishing a home for innovation. In May, Joseph C. Tsai, J.D. '90, co-founder and executive vice chair of Alibaba Group, the Chinese e-commerce company, made a donation through the Joe and Clara Tsai Foundation to support the construction and launch of the Tsai Center for Innovative Thinking at Yale (Tsai CITY). The 10,000-square-foot building, which will be located on Prospect Street near the School of Engineering & Applied Science, is slated to open in 2019, but the center's basic operations are up and running.

Peter G. Schulam, M.D., Ph.D., chair and professor of urology, is the inaugural faculty director of the center. No stranger to collaboration, in 2014 Schulam co-founded the Center for Biomedical Innovation and Technology (CBIT) with W. Mark Saltzman, Ph.D., the Goizueta Foundation Professor of Biomedical Engineering, professor of cellular and molecular physiology, and of chemical engineering, to encourage physicians, engineering and medical students, and patients to invent devices for health care gaps. The success of CBIT led to an invitation to serve as faculty director of Tsai CITY.

Schulam's collaborative experiences extend further back to his work as vice chair of urology at Ronald Reagan UCLA Medical Center. There he collaborated with architects and hospital administrators to design the hospital's second-floor surgical operating suites from the ground up.

A native of New Haven, Schulam came to Yale in 2012 to lead the newly formed Department of Urology at Yale New Haven Hospital. In the five years since, he has learned that persistence is the most powerful tool to bring projects to fruition. "Everyone has great ideas," he said. "Very few people have the resilience to keep going despite unfavorable headwinds."

What will Tsai CITY do? This center will coalesce all innovative activities throughout the Yale campus, and we already have quite a few. We have a number of ongoing innovative efforts including, to name a few, the Yale Entrepreneurial Institute, CBIT, the Office of Cooperative Research, the Center for Engineering Innovation & Design, the Center for Business and the Environment at Yale, the Social Innovation Lab at Dwight Hall, and InnovateHealth Yale. The idea is to support what others have done, and create connectivity to build a network. Each organization is like a single candle burning. If we bring all the candles together, then the lumen output will be much higher. It will be a place that gives students in all Yale schools a space to work on a new invention, a process improvement, or to increase the efficiency of technology that already exists.

How are innovation and interdisciplinary work intertwined? I once read about a concept that encompasses what we are trying to do: "Look for similarity in dissimilar things." It's really difficult to be innovative when you are with individuals in your same field. You want to shake it up. You have to be taken outside of your element and kind of repositioned to see new opportunities. And you also have to be willing to be spun a little bit. That is not necessarily comfortable, but the more we get our students to experience that, the more successful and uniquely educated they will be, and the greater the impact that students can have beyond Yale and New Haven.

What is a key ingredient for working well among disciplines? First, you have to be inclusive, not exclusive. Whoever wants to participate is welcome to get involved. A success metric for the center will not be the number of ventures created, but rather the engagement of the community. For example, how many people from how many different schools and programs are involved? The second idea we will emphasize is that innovation isn't about ownership. People want to say that an idea is theirs, but that creates a wall, and we need to think bigger.

Innovation often involves failure. What advice do you have for students on this? This isn't something you can give advice about. CITY will be a safe space for failure. It does not have a curricular component—nothing is being recorded. The only thing that matters is the eventual success. No one needs to know that a project went through 55 failures or reiterations before becoming a success. We aim to create an environment that will allow students and collaborators to experience that. There's nothing I can really say to students—they have to experience the process for themselves. We want failure and success to be part of their education here so they can take that with them into the world.

watch an interview with Peter Schulam at yalemedicine.yale.edu/schulam

TERRY DAGRADI PHOTO

To nominate a subject for Q&A, contact
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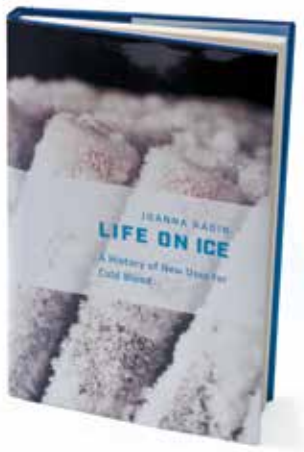

Life on Ice: A History of New Uses for Cold Blood

By Cathy Shufro

Many of us have donated tissue for research without knowing it, according to Joanna Radin, Ph.D., associate professor in the history of medicine. If we've had a blood test or biopsy, or given birth in a hospital, then frozen specimens from our bodies may live on in laboratory freezers—blood, biopsied tissue, a snippet of umbilical cord. As of 2015, there were an estimated 600 million frozen human tissue specimens in the United States, accumulating at the rate of 20 million per year. In a new scholarly history, *Life on Ice: A History of New Uses for Cold Blood*, Radin explores the terra incognita of the "invisible infrastructure" that preserves human tissue.

Many people have read about one such tissue sample, as recounted in the 2010 bestseller *The Immortal Life of Henrietta Lacks*. Author Rebecca Skloot describes how in 1951, before the advent of informed consent, a biologist at Johns Hopkins Hospital used cells taken from Lacks to establish an important cell line for cancer research. But Lacks is not unusual in having unwittingly donated her tissue to science. As Radin points out, "There are millions and millions of other samples, including maybe even your own."

She explores not only the practical challenges but also the spiritual and ethical quandaries that arise from preserving "latent life": Is frozen tissue alive or dead? Does the donor retain a claim to that tissue? "These are the kinds of questions that start to emerge when we pry open the freezer door," says Radin.

In a book rich with metaphor, Radin describes how the need for transfusions on World War II battlefields advanced cold storage. After the war, cattle breeders pushed forward cold technology by using liquid nitrogen to refrigerate sperm used by itinerant inseminators. In light of the atomic bombing of Hiroshima, biologists, geneticists, and epidemiologists began to worry about the health effects of radiation and chemical pollution. They reasoned that blood collected from remote places where "primitive" people lived, supposedly closer to nature, would serve as a baseline for knowledge about human health. These scientists "adopted the freezer as a time capsule that might prove useful in ways they could not even predict," says Radin. A writer for the popular *Life* magazine nonetheless did make a prediction, speculating in 1952 that "spermatozoa from exceptional males could be saved to fertilize females of the future."

Stored blood has indeed provided new information. For instance, blood collected in eastern Africa proved the hypothesis that the sickle cell trait evolved in response to the environment, as protection against malaria. In 1985, researchers from WHO found the first known trace of HIV-1 in human blood collected in the Congo in 1959.

But some donors have come to view the removal of blood from their communities as "biocolonialism." The Yanomami community in the Amazon region demanded that blood collected in the 1960s be returned, in part because the donors had no control over how their blood was used for research. "Science is not a god who knows what is best for everybody," a spokesperson told the press. While the community celebrated the return of 2,693 blood samples in 2015, Radin writes that for scientists, relinquishing the blood "was experienced as a loss of part of the vital legacy of science."

Writing her book, Radin says, "has made me think differently about the boundaries between being alive and being dead." When she goes to the Yale Health Center for a routine blood test, she says she thinks, "This material might outlive me. Does it become its own life form with its own lifespan?" And she recognizes that her blood has a different significance for her than it will if it goes into a laboratory freezer: "My concern about being sick or well is contributing to someone else's hope for a cure."

Send notices of new books to
Yale Medicine, 1 Church Street, Suite 300, New Haven, CT 06510 or email ymm@yale.edu

PHOTOS: THIS PAGE, TERRY DAGRADI; OPPOSITE, MAX JORDAN NGUEMENI TIAKO

Bonding through hiking

ON THE FIRST WEEKEND IN AUGUST, 30 incoming members of the Class of 2021 spent three days in the High Peaks Wilderness Area of the Adirondacks in New York as part of the annual Medical Outdoor Orientation Trip. In groups of six accompanied by two second-year team leaders, the students hiked along trails that ranged from easy—up to four miles a day—to more challenging routes of seven to 10 miles. During the hike, they carried their own sleeping bags and pads, cooking gear, bear canisters, and food—tortillas, cous cous, and cheese. The excursion often becomes a bonding experience that leads to lasting friendships. "When you're in the woods," said second-year student Libby Fairless, one of the organizers, "you have to drop any pretense. You're dirty, you stink, and you're tired."

At the trailhead, group leaders Lindsay Eysenbach (left) and Andrew White (right) and incoming students Sangwon Yun, Alexandra Junn, Michael Shang, Kristin Yu, Osama Ahmed, and Prerak Juthani took a leap in the air before their hike.

—John Curtis