ISSUE
03
FALL
2018

Seek

THE ROCKEFELLER UNIVERSITY

We've lived with it long enough

Inside the science that could finally end HIV

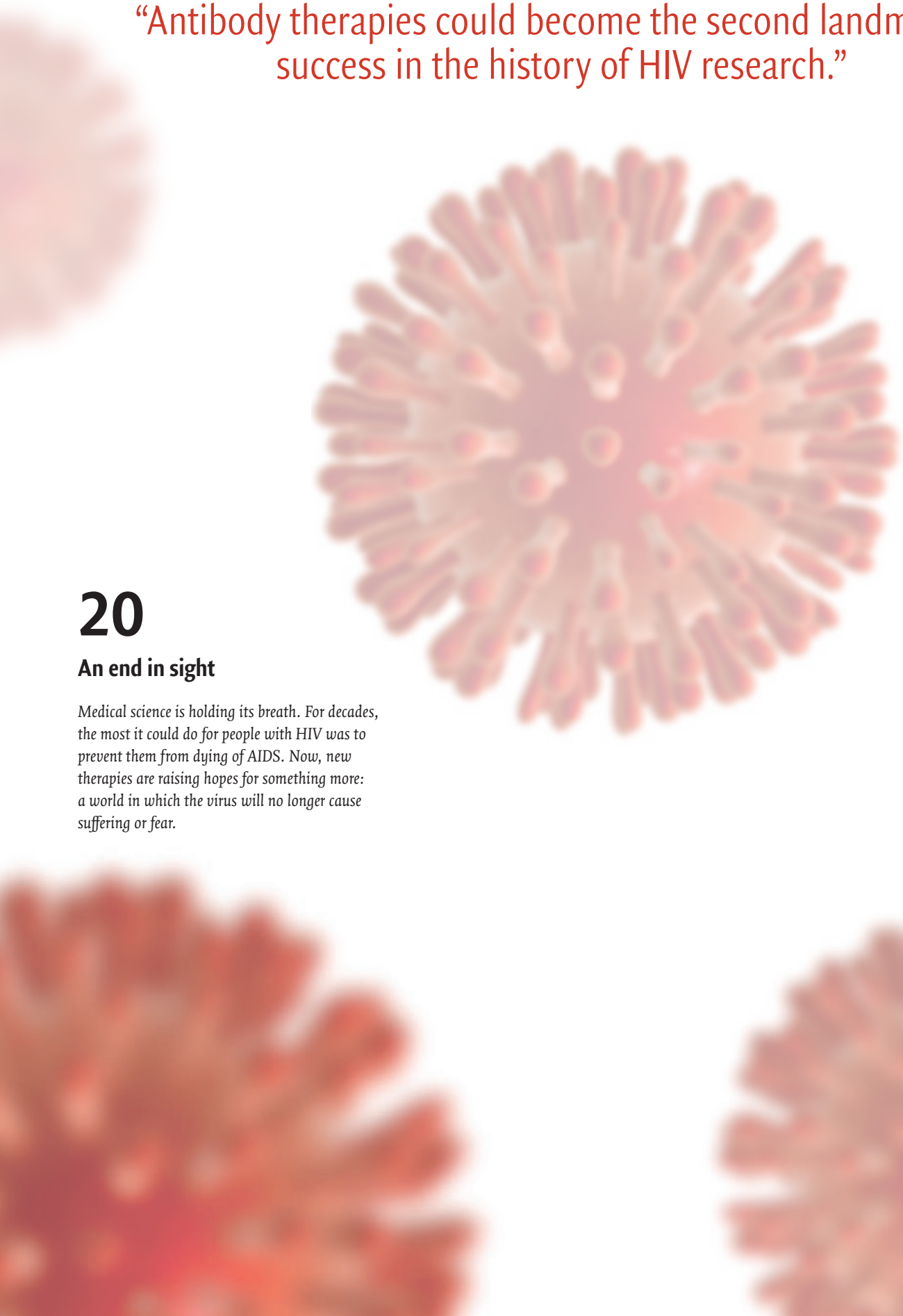
ALSO

Untangling Alzheimer's

Cells on camera

Günter Blobel

"Antibody therapies could become the second landmark success in the history of HIV research."



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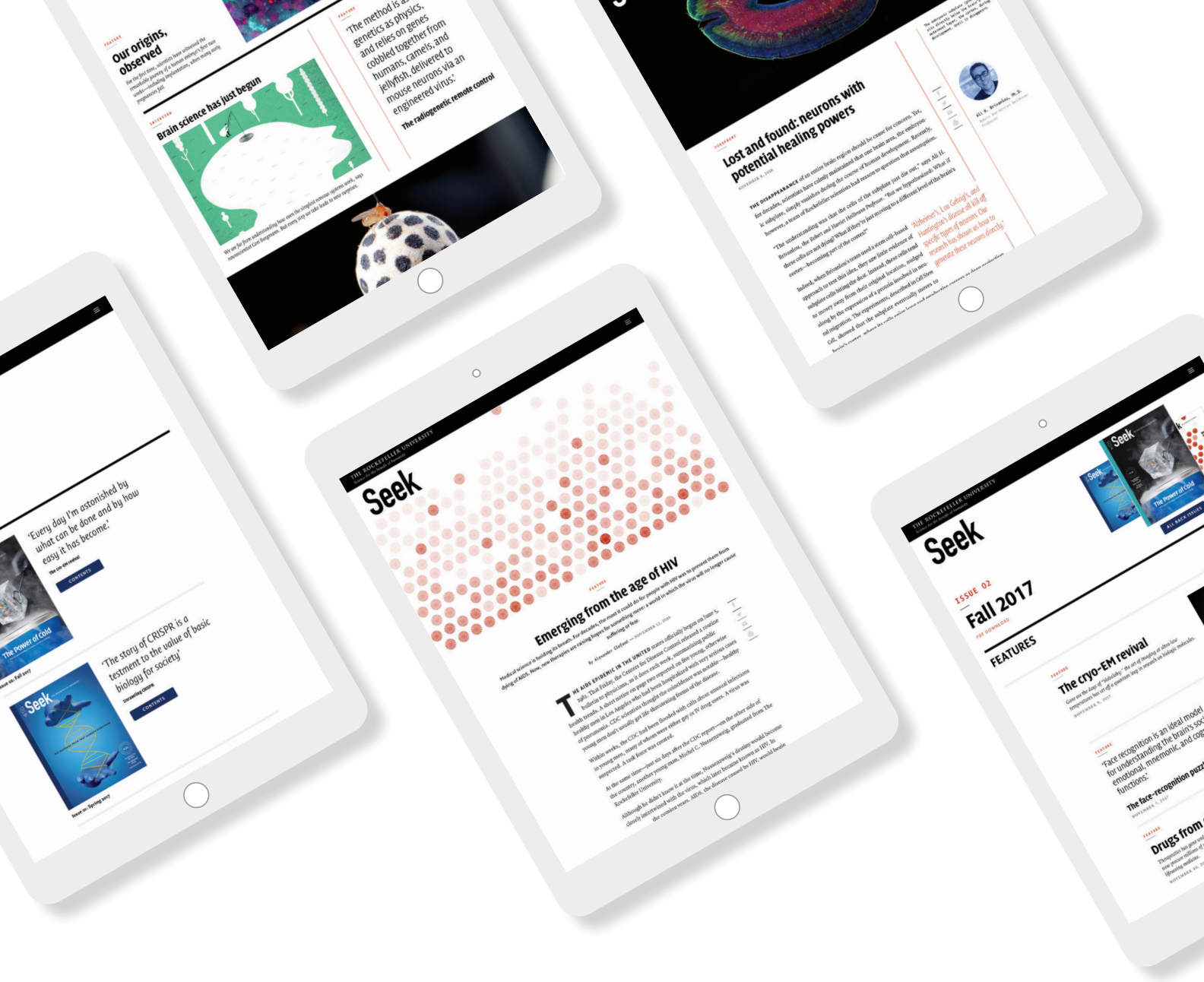
An end in sight

Medical science is holding its breath. For decades, the most it could do for people with HIV was to prevent them from dying of AIDS. Now, new therapies are raising hopes for something more: a world in which the virus will no longer cause suffering or fear.



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Seeing is believing

Scientists are blowing things up like never before. Here are five bio-imaging techniques ready to reveal biology's smallest secrets.

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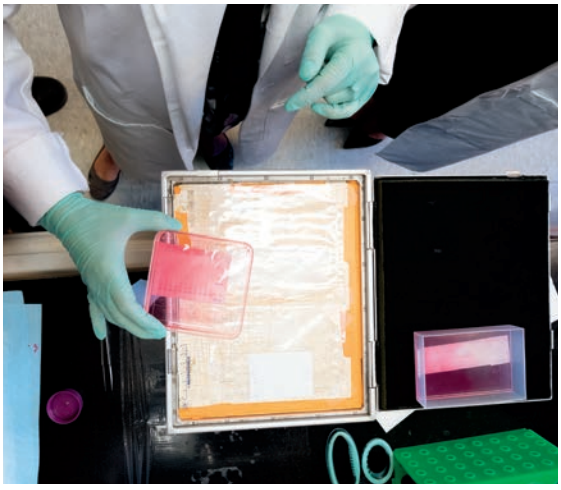

The long-neglected culprit of Alzheimer's

Despite decades of study, we know surprisingly little about why neurons fail and memories fade. One researcher is finding clues where few others have looked—in the brain's blood chemistry.

"It looks like a little flower, and it has been photographed by thousands because it's so beautiful."

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Becoming a scientist

It took two years to get his sample, and three more to master his method. But by the end of his graduate training, Carlos Rico had nailed it: a new system to pinpoint candidate drugs.

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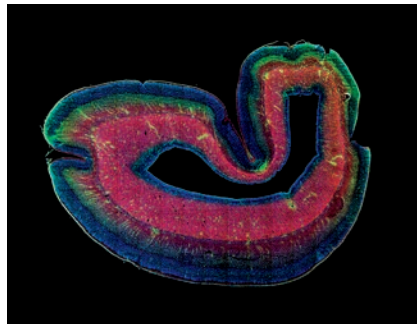
What can be done to cool the libidos of breeding mosquitos? From where did humans get their speech? **And how did scientists solve the mystery of the brain's missing subplate?**



ON THE BACK COVER

"The Rockefeller University" by Irena Gajic

LEFT TO RIGHT: ISTOCK; MARIO MORGADO; FRANK VERONSKY; LABORATORY OF STEM CELL BIOLOGY AND MOLECULAR EMBRYOLOGY / THE ROCKEFELLER UNIVERSITY

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Seek is published twice a year by the Office of Communications and Public Affairs.

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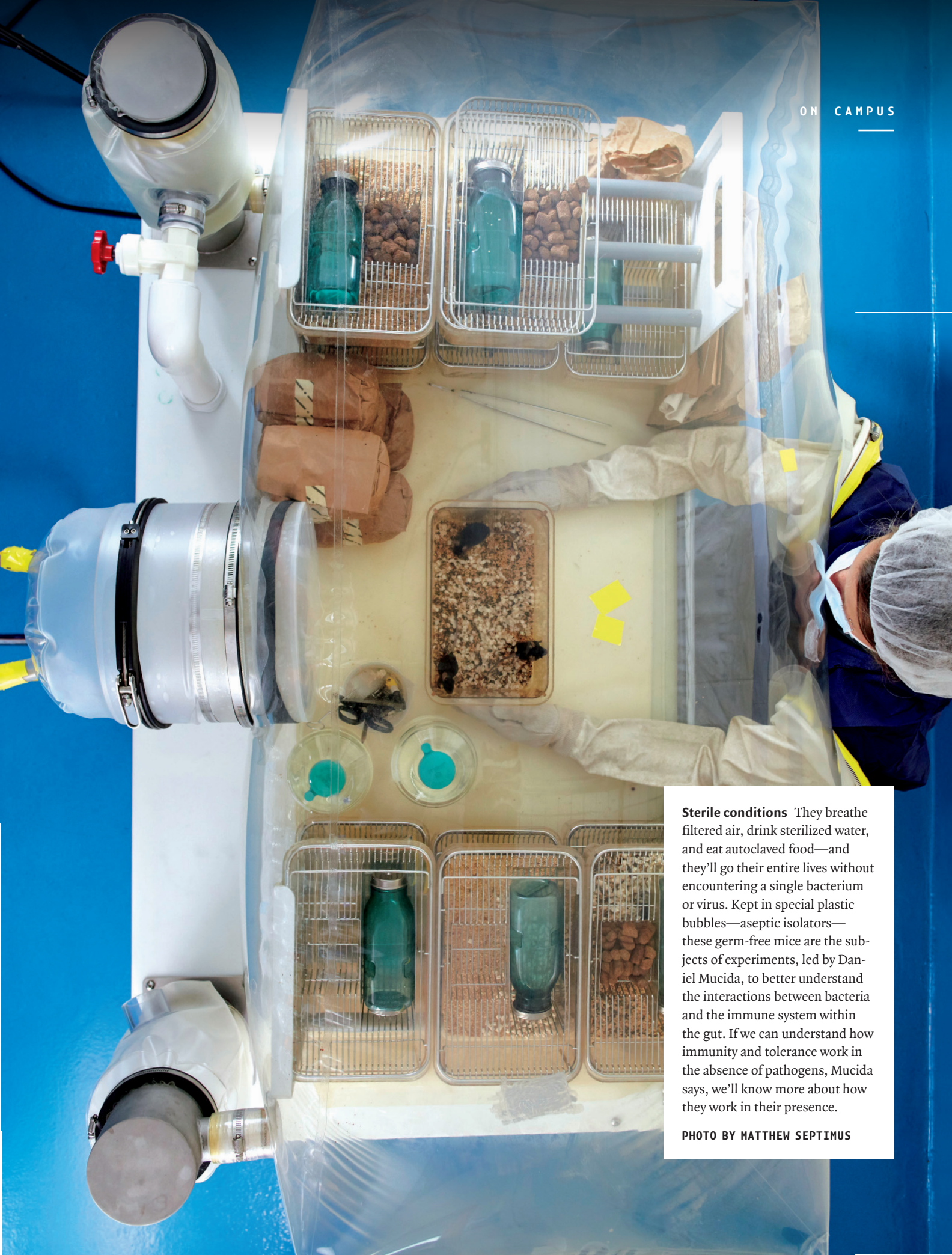
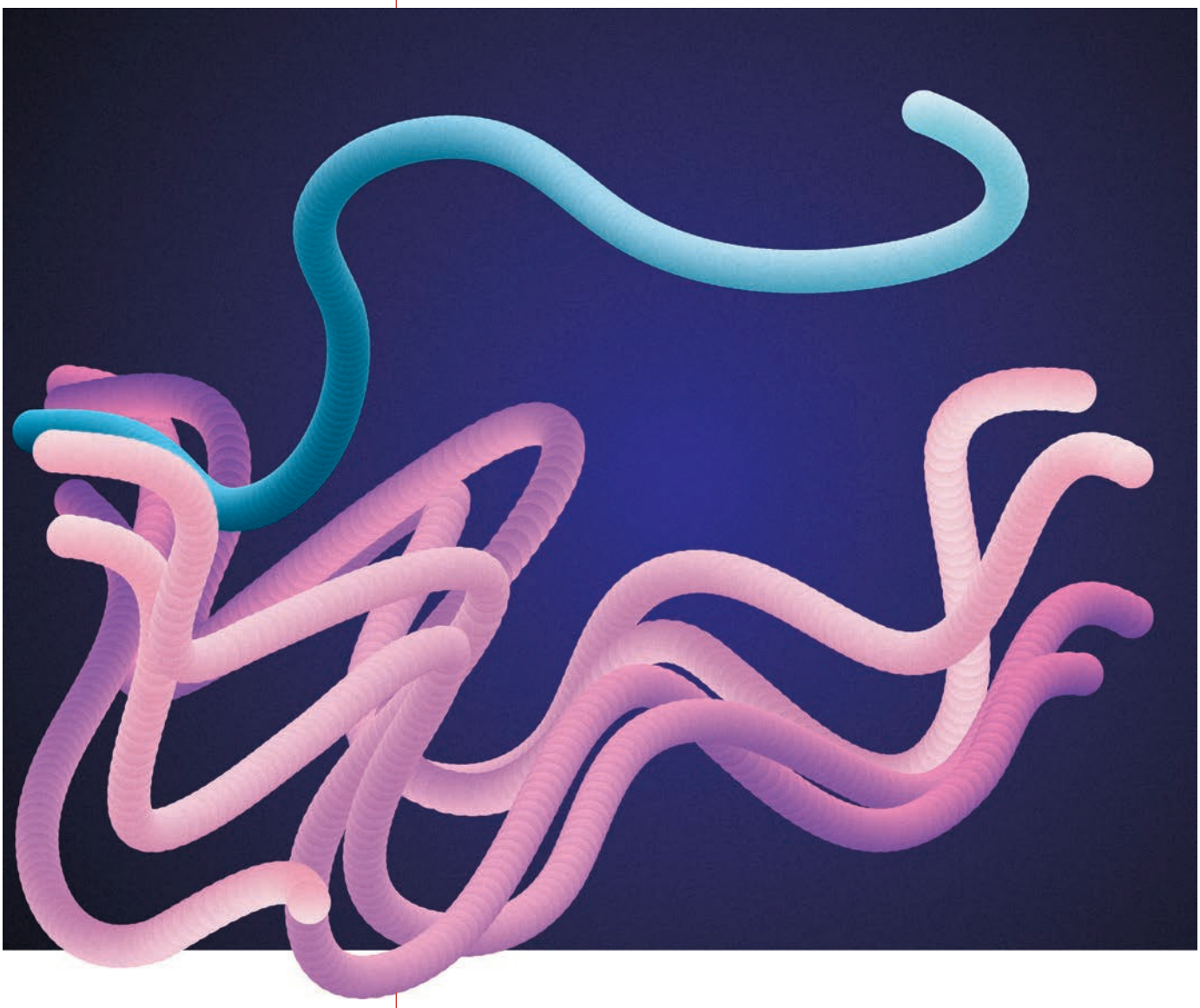


Sterile conditions They breathe filtered air, drink sterilized water, and eat autoclaved food—and they'll go their entire lives without encountering a single bacterium or virus. Kept in special plastic bubbles—aseptic isolators—these germ-free mice are the subjects of experiments, led by Daniel Mucida, to better understand the interactions between bacteria and the immune system within the gut. If we can understand how immunity and tolerance work in the absence of pathogens, Mucida says, we'll know more about how they work in their presence.

PHOTO BY MATTHEW SEPTIMUS

Reported by Eva Kiesler, Caitlin Shure, and Zachary Veilleux.

FOREFRONT



INDIVIDUALITY

Why we need weirdos

ROUNDWORMS ARE NOT known for their personalities. But as it turns out, even microscopic organisms can have an independent streak.

Rockefeller's Cori Bargmann, the *Torsten N. Wiesel Professor*, has shown that genetically identical *C. elegans* worms, including those that have been raised in perfectly identical environments, can behave quite differently. In experiments published in *Cell*, her team used cameras to document every movement made by 50 worms searching for food. While most worms adhered to a standard foraging pattern, a few took the road less wiggled, departing significantly from the typical route. The scientists concluded that neural development involves a certain element of randomness—neither nature nor nurture completely determines behavior. (Read more about Bargmann's work in "Deep secrets," page 38.)

Illustration by Nathan Eames

DATA

The maximum speed of a *C. elegans* worm is approximately 0.4 millimeters per second.

They also found a way to influence worm eccentricity by tinkering with the animals' neurochemistry—specifically, by shutting off their serotonin production. Groups of *C. elegans* that lacked this chemical also lacked renegades: Every individual foraged the same way, in perfect synchrony.

Besides being boring, uniformity can be dangerous to a population. "From an evolutionary point of view, we can't have everyone going off the cliff all at once, like lemmings," says Bargmann. "Someone's got to be doing something different for a species to survive." ◎

JOHN ABBOTT

Tavazoie (right) is developing treatments to prevent the spread of cancer.

DRUG INCUBATOR

Bad news for cancer cells and their cronies

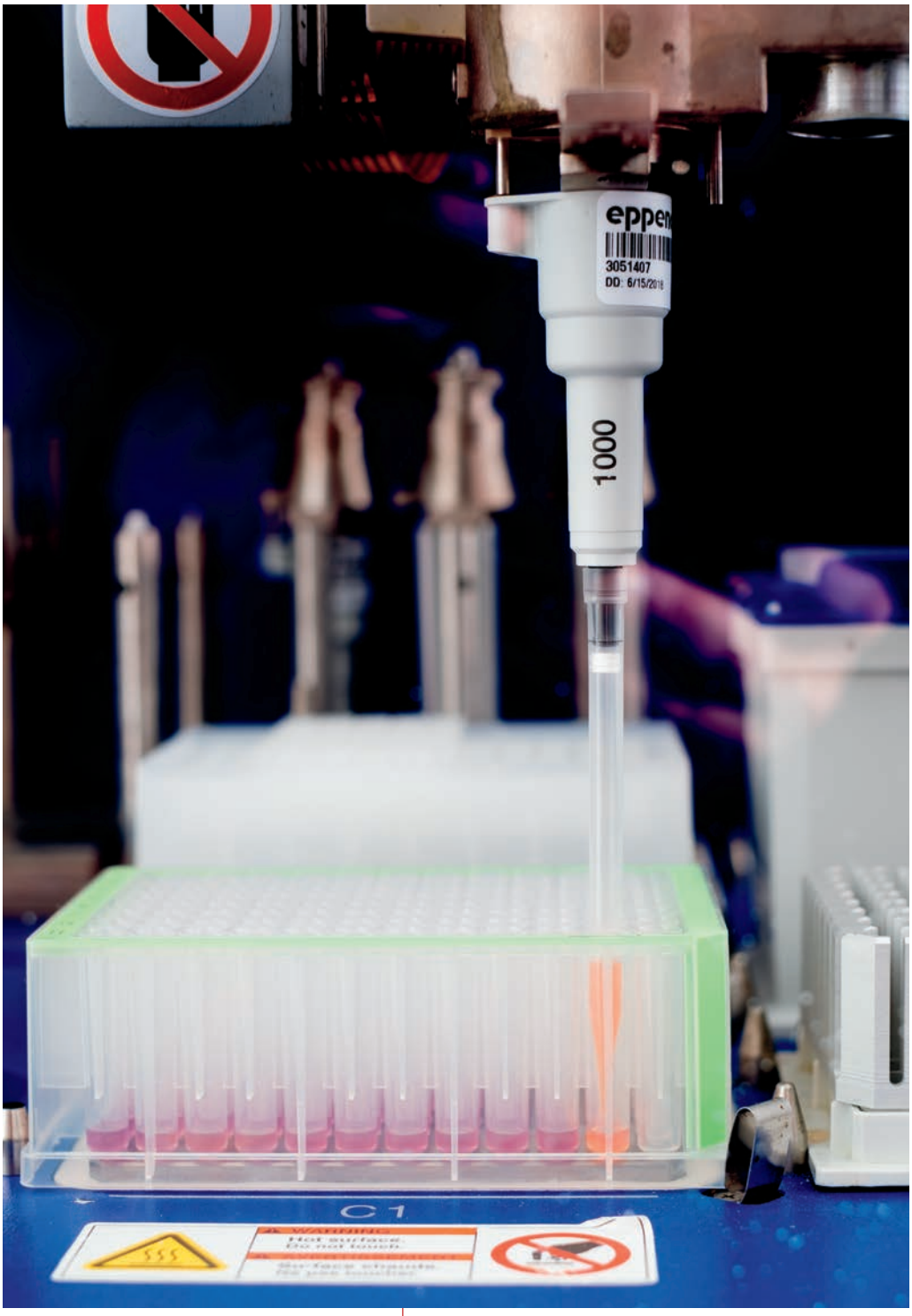
CANCER CELLS ARE notoriously stubborn. When not replicating uncontrollably, they evolve new tactics to pursue their tumorous tumult. In keeping with this reputation, these malign actors have not yet surrendered in the face of immunotherapy, a new class of treatment that aims to combat cancer using the body's own immune system.

Although researchers are optimistic about the future of immunotherapy, the treatment has yet to realize its potential—it currently works in only a slim minority of patients. One reason it often fails, it seems, is that cancer has found cellular allies within the immune system itself: tiny traitors known as myeloid-derived suppressor cells (MDSCs).

Cajoled by tumors, MDSCs stop other immune cells from doing their jobs, thereby protecting cancer cells and rendering immunotherapy ineffective. "We predicted that if we could find a way to kill MDSCs, it would lead to the activation of beneficial immune responses," says Rockefeller's Sohail Tavazoie, the *Leon Hess Professor*.

This calculation holds up, according to results from a recent study published in *Cell*. When Tavazoie's team used a drug to eliminate the problem cells in mice, the intervention reduced the animals' MDSC levels and boosted their immune powers. And the researchers obtained similarly promising results when they proceeded to test the drug, called RGX-104, in a small group of human subjects: Like the mice, human patients on RGX-104 experienced heightened immune activity as their MDSC counts fell.

Tavazoie and his colleagues will be launching a larger study to evaluate the drug's effectiveness against various forms of cancer. ◎



A robotic system used to process blood samples.

7 BILLION

Number of blood tests ordered by doctors in the U.S. every year.

DIAGNOSTICS

Bloodwork, working harder

FEW PEOPLE PARTICULARLY enjoy having blood vacuumed out of their veins. Still, we regularly submit to clinical blood tests because, we presume, the extracted sample will alert doctors to looming disease, risk factors, or other health changes.

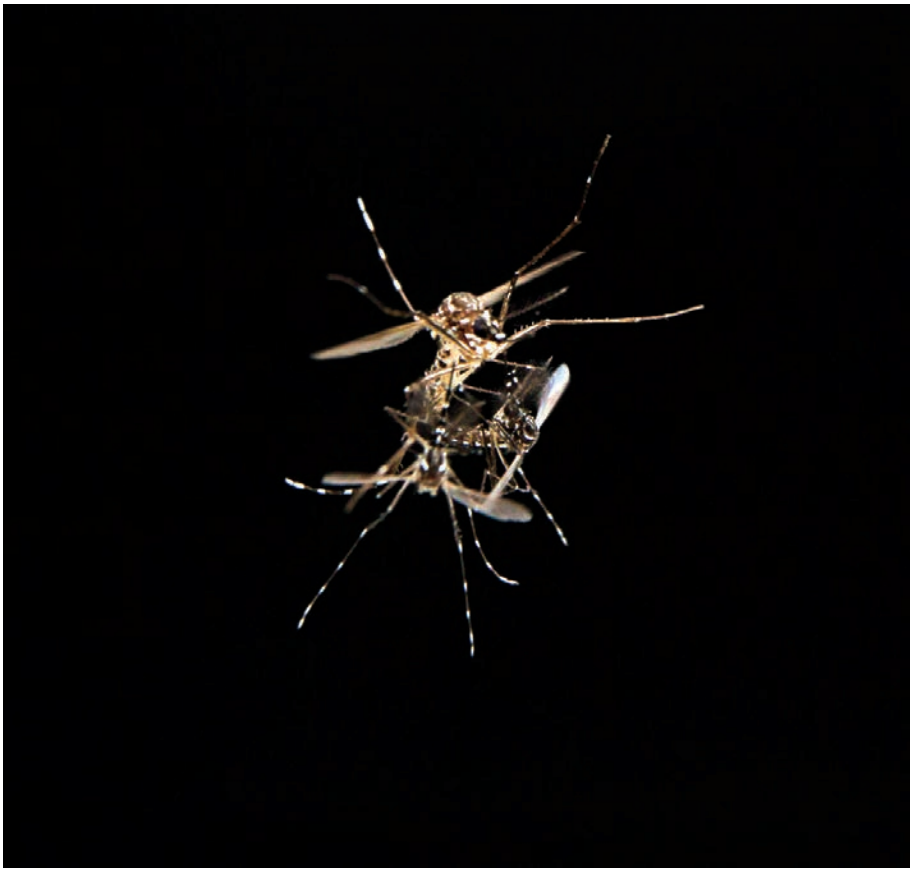
There's a lot that these tests can't tell us, however. Many medical conditions don't leave a chemical trace, or biomarker, in the blood—at least not one that conventional techniques can decipher. Researchers in the lab of Thomas Tuschl have therefore devised a new method that widens the net of information captured in a vial of blood.

The technique, detailed in the *Proceedings of the National Academy of Sciences*, involves isolating extracellular RNA, or exRNA, which cells throughout the body shed into the blood. These molecular scraps may betray medically significant details about the tissues they came from—for example, exRNA originating from the heart might be analyzed to determine the presence or progression of cardiac disease.

Tuschl and postdoctoral associate Klaas Max plan to further develop the strategy, which they hope will vastly expand the number biomarkers available for various medical uses. "This technique has enormous potential for detecting disease processes and discovering new abnormalities," Tuschl says. ◎

MARIO MORGADO

Less sex, fewer mosquitoes. Fewer mosquitoes, less disease.



Aedes aegypti mosquitoes mating in flight. The species transmits human diseases including Zika and yellow fever.

PEST CONTROL

This sexy protein may help reduce mosquito populations

MOSQUITO SEXUAL PARTNERS do not exchange sweet whispers or expensive jewelry. But male *aedes aegypti* mosquitoes do leave their mates with a parting gift—a protein known as HP-I. It may not be the most romantic of presents, but HP-I can leave a lasting impression: Transferred along with semen, the protein stays in the female's system for two hours following copulation.

Research associate Laura Duvall was curious about how HP-I affects the behavior of female mosquitoes. She and her colleagues in the lab of Leslie B. Vosshall, the *Robin Chemers Neustein Professor*, discovered that females receiving the protein from a mate will later spurn the advances of a second beau. If, however, a female copulates with a mutant male that doesn't make HP-I, she will happily entertain new suitors. The protein's function, the researchers concluded, is to discourage female promiscuity.

More than a peek into the sex lives of insects, this research, published in *Current Biology*, may ultimately yield public-health benefits, especially in regions affected by bug-borne illnesses such as malaria, dengue, and yellow fever. Since HP-I seems to curb females' sexual appetite, some version of this protein could potentially be used to limit the reproduction of mosquitoes and the diseases they spread. ◎

ALEX WILD

PRIMITIVE EXPRESSIONS

How we started speaking

MONKEYS DON'T TALK, but they excel at body language. Facial movements, such as the friendly lip smack, are especially expressive—and they may provide clues about the origins of human speech.

In a recent experiment, described in *Neuron*, Winrich Freiwald and his colleagues observed rhesus macaque monkeys as they watched videos of other monkeys, simulating face-to-face interaction. Brain scans showed that when the monkeys smacked their lips to engage with an on-screen peer, a particular brain region lit up. This part of the macaque brain resembles Broca's area, which is known to be involved in human speech—suggesting that verbal communication may have evolved from monkey mouth movements. ◎

DATA

Human speech may have arisen anytime between **50,000** and **2 million** years ago. It's hard to tell precisely since words don't fossilize.

The embryonic subplate (green) sits directly below the brain's outermost layer, the cortex, during development. Until it disappears.

DATA

A 12-week-old human embryo grows **15 million** new neurons per hour.

BRAIN SCAN

Lost and found: neurons with potential healing powers

THE DISAPPEARANCE of an entire brain region should be cause for concern. Yet, for decades, scientists have calmly maintained that one brain area, the embryonic subplate, simply vanishes during the course of human development. Recently, however, a team of Rockefeller scientists had reason to question that assumption.

"The understanding was that the cells of the subplate just die out," says Ali H. Brivanlou, the *Robert and Harriet Heilbrunn Professor*. "But we hypothesized: What if these cells are not dying? What if they're just moving to a different level of the brain's cortex—becoming *part* of the cortex?"

Indeed, when Brivanlou's team used a stem cell–based approach to test this idea, they saw little evidence of subplate cells biting the dust. Instead, these cells tend to mosey away from their original location, nudged along by the expression of a protein involved in neural migration. The experiments, described in *Cell Stem Cell*, showed that the subplate eventually moves to brain's cortex, where its cells enjoy long and productive careers as deep projection neurons, vital to a number of cognitive processes.

The researchers also found that, with some tinkering, they could prompt subplate-like stem cells to mature into projection neuron subtypes of their choosing—a technique that could potentially become a medical strategy to replace specialized neurons lost to neurodegenerative disease.

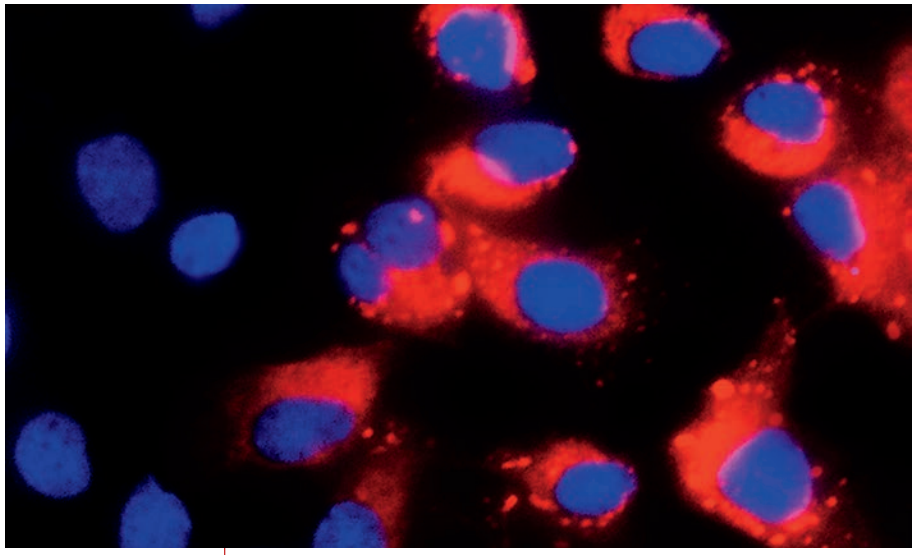
"Alzheimer's, Lou Gehrig's, and Huntington's disease all kill off specific types of deep projection neurons," says postdoctoral associate Zeeshan Ozair. "And our research has shown us how to generate these neurons directly." ◎

"Alzheimer's, Lou Gehrig's, and Huntington's disease all kill off specific types of neurons. Our research has shown us how to generate these neurons directly."

LABORATORY OF STEM CELL BIOLOGY AND MOLECULAR EMBRYOLOGY / THE ROCKEFELLER UNIVERSITY

BIO-DEFENSES

How to fight a virus? Ask the body's youngest cells



Stem cells lacking protective genes are vulnerable to attack by viruses such as dengue (red).

STEM CELLS ARE the most precious of the body's assets. Newly born and full of potential, they can grow up to be any other kind of cell—skin cell, heart cell, neuron. And, being rare and vital, stem cells receive thorough biological coddling. For example, the body has special mechanisms to protect them from the most dangerous viruses, making stem cells naturally immune to pathogens such as HIV and dengue.

"That just makes sense," says Rockefeller's Charles M. Rice, the *Maurice R. and Corinne P. Greenberg Professor in Virology*. "Because stem cells are pretty important, the body would want to be especially protective of them."

Recently, Rice's lab elucidated what this cellular caretaking entails: Stem cells constantly express antiviral genes, which help kick-start an immune response. By contrast, adult cells must employ these genes more prudently, switching them on only when a virus is around. These findings, described in *Cell*, help explain how juvenile cells stay safe, and may also lead to new insights into the defense mechanisms of older cells. ◎

LABORATORY OF VIROLOGY AND INFECTIOUS DISEASE / THE ROCKEFELLER UNIVERSITY

BAD HABITS

Addiction: It's all in your head

TOBACCO IS THE third hardest substance to quit, after cocaine and heroin. Yet smoking would be far less addictive if it weren't for Amigo1 neurons, a newly defined class of brain cells.

In fact, the brain has a built-in aversion to nicotine: When it detects the chemical, it sends a "yuck" message to a little-studied brain region known as the interpeduncular nucleus. In a recent study, published in the *Proceedings of the National Academy of Sciences*, Rockefeller researchers found that, in nicotine-addicted mice, Amigo1 neurons start to produce chemicals that dilute this message.

"If you are exposed to nicotine over a long period, you produce more of the signal-disrupting chemicals, and this desensitizes you," says Ines Ibañez-Tallon, a scientist in the laboratory of Nathaniel Heintz, the *James and Marilyn Simons Professor*. "That's why smokers keep smoking." ◎

Illustration by The Project Twins

Q&A

"I still feel the vibration"

In memory of Günter Blobel, 1936–2018

ONE OF THE MOST EXTRAORDINARY days of Günter Blobel's life was in December of 1974. Bundled up in the laboratory cold room, he spent hours attempting to divorce cells from their delicate membrane structures—something he had been trying to do, unsuccessfully, for almost two years. On this day, however, it happened: He was able to produce a viable membrane extract from dog pancreas and, for the first time, use this extract to simulate a biological process in a test tube.

DATA

Blobel donated his Nobel Prize money for the rebuilding of the **Frauenkirche,** a baroque Lutheran church, and for the building of a new synagogue in Dresden.

The process was related to protein trafficking, a system that enables cells to organize billions of proteins so that each ends up in the right membrane-walled nook—those whose job it is to package DNA are ferried to the cell nucleus, for example, while proteins tasked with producing energy are sent off to mitochondria, the cell's internal powerhouses. Blobel imagined that the system relied on each protein carrying a virtual zip code, a sequence that signals its destination.

It was a controversial idea that Blobel had arrived at somewhat intuitively. To prove it, he needed a persuasive assay, a way to break apart a cell's protein-trafficking machinery and then reassemble its still-operational components in order to pinpoint which component does what. The 1974 membrane-manipulation exercise was a first step in developing this method, and although it didn't yield much useful data in and of itself, the very fact that it had worked was a landmark.

"Günter's work laid the foundation for the modern field of molecular cell biology," says Richard P. Lifton, Rockefeller's president. With his new methods to dissect cellular phenomena, Blobel helped set in motion a new phase in the study of life and disease, forever changing how biologists ask questions and seek answers.

In addition, his trailblazing insights into protein trafficking had far-reaching practical implications. "It led to important insights into normal physiology and numerous diseases," says Sanford M. Simon, a Rockefeller colleague who once trained with Blobel, "and it helped launch new fields of biotechnology, such as methods to produce human proteins in other organisms."

Blobel, who died on February 18, was the recipient of many prestigious awards, though he liked to point out that no prize—not even the Nobel, with which he was honored in 1999—could compare with the thrill of science itself. "It's very nice, and everybody claps, and you get a medal you can hang on the wall," he laughingly told us last year. "But it's not the equivalent excitement that you have when you discover the thing. That is why I am still in science—because I still feel the vibration of a new discovery."

We conducted over four hours of interviews with Blobel in 2017, as part of an oral history project. Here are a few highlights:

On cellular evolution and the nuclear pore complex: The arrival of the nucleus is one of the most important

Illustration by HelloVon

advances in the three and a half billion years of cellular evolution. The first two billion years were fairly boring, you could say. There were single cells, similar to our bacteria. But then, taking the genetic material and putting it into the nucleus, that was a very big revolution. It allowed the DNA to grow and be protected. But, it made it necessary to communicate between the nucleus and the cytoplasm.

You cannot just put it in a little capsule and say, here you are. There has to be bidirectional traffic. And the organelle that does it is called the nuclear pore complex. It looks like a little flower with eight petals, and has been photographed by thousands because it's so beautiful. It has been looked at and electron-microscoped for 20 years.

"Science is the only human endeavor that is for the entire mankind."

On witnessing the 1945 bombing of the historic city of Dresden, at age nine:
We came in with this car that my older brother was driving, and suddenly I saw all of these towers, and the cupola of the Frauenkirche, and I was absolutely enchanted. I've always remained attached to this city, because I saw it in a completely intact way. A couple of days later, we were at the farm of relatives about 30 or 40 miles away from Dresden, and we saw the planes that came, and the bombing started about nine o'clock. We went out and looked, and the entire sky was red. Then I saw the city again when we tried to go back to Silesia, and it was just rubble.

On being a scientist:
Science is the only human endeavor that is for the entire mankind. Music or cultures are local, but the formula for water is the same in China as it is somewhere else. So it's the only cultural pursuit of mankind, I think, that is universal.

Scientists should go out more, and should interact with the public, because the public doesn't know the absolute beauty of science. I find it most fascinating that we, as we sit here, represent three and a half billion years of continuous cell division—of eternal life, if you wish.

To watch these and other clips visit go.rockefeller.edu/oralhistory. ◎

LABORATORY OF CELLULAR AND STRUCTURAL BIOLOGY

DATA

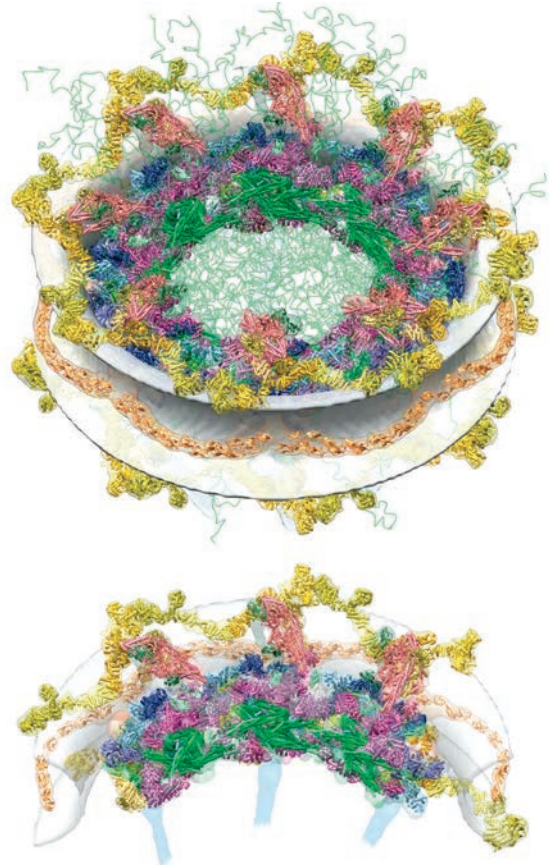
Blobel's lab discovered several components of the **nuclear pore complex** and elucidated the process by which molecules move through it.

INTRACELLULAR ARCHITECTURE

A molecular behemoth, meticulously mapped

IT'S HARD TO THINK of a more grandiose molecular fabrication than the nuclear pore complex, an ornate portal connecting a cell's inner and outer compartments. The pore complex occupied a special place in the heart and mind of the late Günter Blobel, who spent decades of his life scrutinizing it (read more in "I can still feel the vibration," left). Presumably, Blobel would have been thrilled to hear the news reported in *Nature* in March, just a month after his passing, of Rockefeller scientists issuing the first complete blueprint of the massive structure.

It took scientists in the labs of Michael P. Rout and Brian T. Chait more than 20 years, and a medley of methods, to study the 552 components of the pore complex in yeast, and figure out how they all fit together. "In the end, we used everything we could lay our hands on, brought the results together, and integrated them into a single structure," says Chait, who is the *Camille and Henry Dreyfus Professor*. ◎



A long-anticipated map showing how the 552 pieces of the nuclear pore complex fit together.

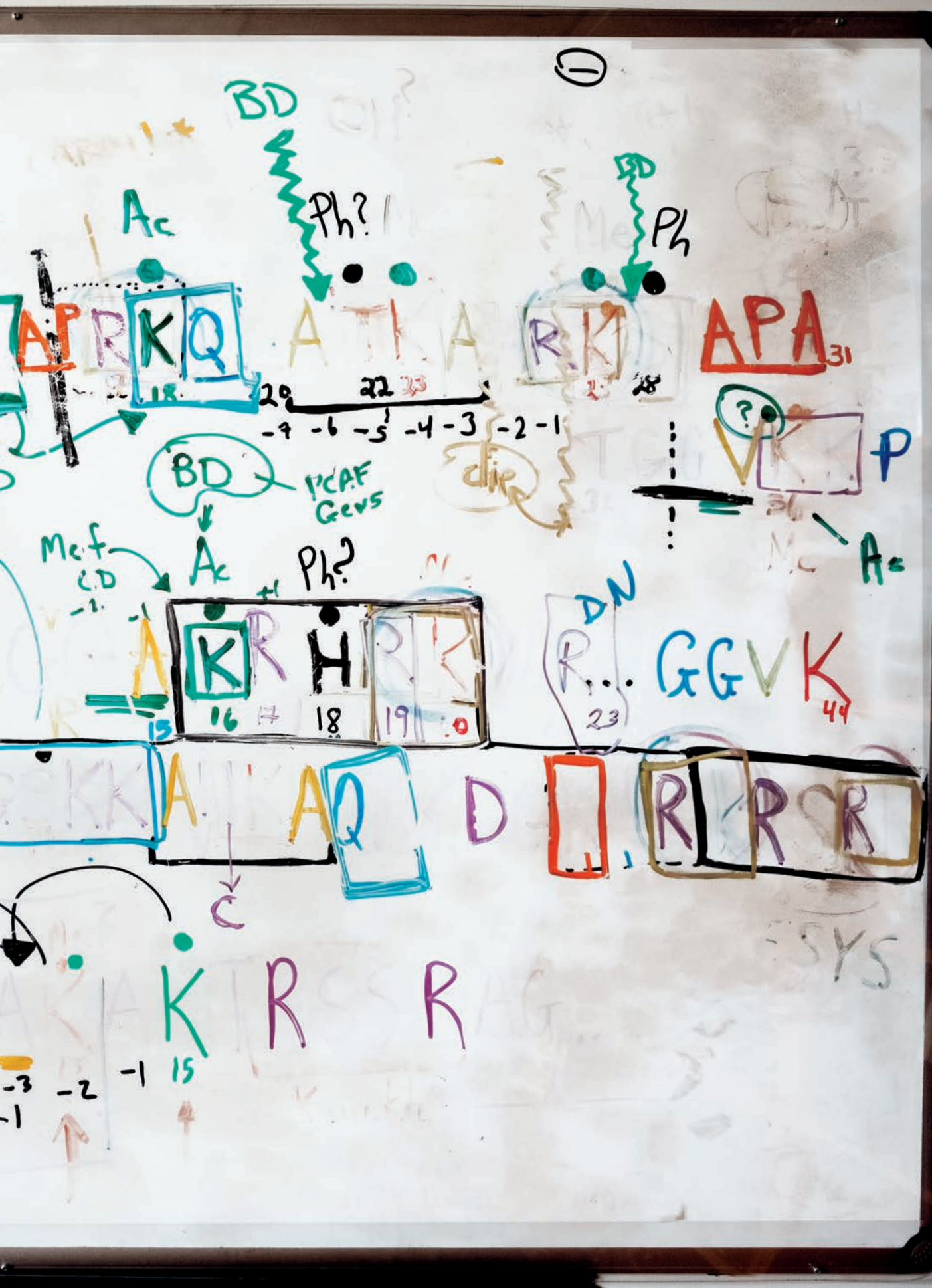
A Lasker in the making

WHEN C. DAVID ALLIS MOVED to Rockefeller from the University of Virginia in 2003, he brought a few ideas with him. In his first Rockefeller "chalk talk," Allis laid out the details of his histone code hypothesis, which suggested an entirely new way of thinking about genes that eventually would inform almost every field in biology.

Histones—proteins that glom together to form spools around which DNA is wound—control access to specific sections of the genome. The focus of Allis's work is on histone "tails," which hang off the spools like loose pieces of thread. Over the years, his lab mapped dozens of proteins that make up those tails, and methodically recorded how they respond to specific enzymes to turn genes on or off. Through his research, Allis, who is the *Joy and Jack Fishman Professor,* has been able to confirm and refine his initial theory of gene expression; moreover, he has drawn connections between the proteins that manage histone modifications and specific diseases including heart disease, autism, and cancer. This fall, Allis received an Albert Lasker Basic Medical Research Award, one of the most prestigious honors in science, for his work.

The 15-year-old whiteboard notes from that original talk, now preserved behind Plexiglas to prevent smudging, still hang in his office.

MARIO MORGADO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Scientists rarely run out of ideas. More often, they have the opposite problem: too many leads, not enough time. Meet the graduate whose solution was a smarter way to audition molecules for drugs.

Carlos Rico

By Alexandra MacWade

EVERYWHERE HE LOOKED, Carlos Rico saw titration curves. When he stepped outside for a walk, he'd spot them in the arches of iron gates or within an intricate pattern on someone's clothing. A tree branch bent in just the right way would make him stop. "I was carrying what was on my mind everywhere I went," he says.

Rico, then a graduate student, was determined to find a way to produce pristine batches of CCR5, a protein that helps HIV attack human cells. On a typical day, he would spend hours in the lab trying to coax CCR5 into a purified form, anticipating the curve that would indicate success. And late into the night, he would sit at his computer, doggedly plotting his titration curves and calculating equilibrium dissociation constants—values that, with a bit of luck, might teach him something new about the protein's proclivity to interact with small molecules.

Rico's hope was that, if he could isolate CCR5 in sufficient quantities, he'd be able to study it in ways that would otherwise not be possible. This was the key to his graduate thesis and potentially an important step in the development of antiviral drugs: CCR5, situated on the rim of human white blood cells, can help provide a foothold for HIV, allowing the virus its first opportunity to get through a cell's outer membrane and infect it.

If realized, Rico's method would make it possible to quickly sift through a long list of HIV drug candidates, vetting each for pharmacological fitness. Compounds that excelled in these and other lab tests would then have a chance to graduate to animal testing, clinical trials, and—hypothetically—become real-world drugs with the power to protect people from one of the biggest public-health problems on the planet.

But none of this would come to pass unless Rico produced an immaculate extract of his protein and got it to interact with other molecules important in his experiments. Until then, he was unlikely to attain anything besides wishful thinking.

A NOT-INSIGNIFICANT chunk of Rico's childhood was spent in his grandmother's attic in León, Mexico, tinkering with two cherished chemistry sets—gifts from his father, Hector.

Beyond his delight in watching ingredients react, the science projects made him feel closer to Hector, who had left Mexico for California when Rico was six. Working at a dairy manufacturer near Los Angeles to support the family, Hector rarely had opportunities to return to León. So Rico and his younger brother were looked after by their mother and grandmother.

Rico struggled with his father's absence, and after six years apart, the family made a risky decision: Rico, with his mother and brother, would attempt to enter the United States to join Hector. It was a decision that would ultimately open the door for Rico to pursue his love for chemistry at the highest level.

But first, they had to cross the border. Unlike Rico's father, who had come to the U.S. on a work visa, the rest of the family didn't have legal documentation, so they hired a *coyote* to help them cross the border. Under the coyote's guidance, they first traveled to Tijuana, where Rico and his brother were separated from their mother. The boys were instructed to stay in a hotel with a small group of strangers preparing to make the trip. After about a week, the group boarded

Photography by Frank Veronsky

a truck headed for San Diego. Rico's mother arrived a week later.

The crossing went relatively smoothly, and if the episode was nerve-racking for his parents, Rico didn't experience it that way. "I think I didn't fully understand what was happening," he says. "It wasn't until I was much older that I realized how dangerous this journey was, and how much my dad and mom had sacrificed for us to make it across the border."

Once in L.A., Rico was relieved to be reunited with Hector, who later attained U.S. citizenship for himself and for the rest of the family. But he suffered culture shock. He didn't know any English when he first arrived, and he missed his small León neighborhood, where, unlike in L.A., nearly everyone he met was friendly and kids would play soccer in the streets until late in the afternoon. Eventually, Rico found solace in his studies—both in high school and at Hamilton College, where he earned a scholarship and majored in chemical physics.

Although he did well in school, it wasn't until after joining Rockefeller that he finally began to feel genuinely at home, connecting easily with his classmates. "They were all in love with the science they were doing," he says.

He completed three rotations, one each at Rockefeller, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medicine. When it was time to pick a lab and choose a thesis project, Rico knew exactly what to look for: a complex chemistry endeavor, and preferably one that could be applied to the treatment of human diseases. He wanted a project he could get lost in.

He found it, soon enough, in Thomas P. Sakmar's laboratory.

CELLS ARE RATHER squirmy in interacting with their environment. The world outside is, after all, awash with dangerous pathogens and poisons. But clamming up is not an option, either—a cell needs to carefully read its surroundings and communicate with other cells. As a sensible compromise, evolution gave cells thousands of antennae for picking up external signals. Many of these antennae, including CCR5, belong to a vast "superfamily" of so-called G protein coupled receptors that Sakmar, Rico's thesis mentor, has spent close to three decades investigating.

> If realized, Rico's method would make it possible to quickly sift through a long list of HIV drug candidates, vetting each for pharmacological fitness.

More than one-third of all modern drugs work by binding with a G protein coupled receptor, usually to compete against a particular outside signal, or ligand. The idea is that if the drug uses up all the cells' receptors, there's no place left for the ligand. When Rico joined Sakmar's lab, he knew that one of the biggest challenges for drug discovery is to find a substance whose receptor interaction is so snug that the ligand stands little chance of delivering its message—the snugger the fit, the more likely the drug will be effective, especially in low doses.

Rico was inspired by colleagues in Switzerland who had created hundreds of different compounds that bound to CCR5, the white blood cell receptor that sometimes gets hijacked by invading HIV viruses. All these compounds were variations on a natural ligand, called RANTES, and their affinity for the receptor varied. From this panel, the Swiss team had selected a strong candidate and used it to

Rico, who graduated this spring, is now a microscopy specialist in the university's bioimaging facility.

develop a topical HIV prophylactic. The drug was already showing promise—among other things, it had been found to protect monkeys from infection with a simian version of HIV (for more on new HIV therapies, see "Emerging from the age of HIV," page 20).

Rico wondered about the rest of the RANTES ligands. There were still hundreds of molecules that hadn't been tested, some of which might work even better than the one under investigation. But no one could possibly have the time and resources to sort through the panel one by one, analyzing each compound's molecular structure and testing its pharmacological properties.

Then again, if someone could come up with a strategy to run many of these experiments side by side, the work could be done quickly and cheaply. With the encouragement of Sakmar and Thomas Huber, a molecular biologist and research assistant professor in the lab, Rico asked the Swiss team for access to their panel.

The first thing Rico had to do was isolate and purify CCR5 away from cells. This was a particularly challenging step, because he had to ensure that the protein would remain active and intact after its exposure to the detergent used to wash the rest of the cell away. After two years of trial and error, he finally got it: a pure, functional, full-length version of CCR5 with no aggregates or cellular contaminants that might complicate the experiments.

Next, Rico had to figure out the most nimble way to detect and measure the receptor's interactions with the RANTES molecules. Nobody had tried to do this before with purified receptors, and Rico decided to use a detection method called fluorescence cross-correlation spectroscopy, or FCCS. It is a finicky technique, but it would give Rico a clear visual signal, direct confirmation that the receptor was binding to the molecules. No one at Rockefeller, however—and, in fact, few people anywhere—actually knew how to perform FCCS. And most labs didn't have the necessary equipment.

"Rockefeller has the setup and was the perfect place for me to do this," Rico says. He spent countless hours at the university's Bio-Imaging Resource Center, teaching himself how to master the painstaking technique, and then getting it to work on his CCR5 extract. All in all, the endeavor cost him three additional years, but it turned out to be time well spent. In the end, Rico was able to use his new method to better understand how different RANTES analogues interact with the receptor—why some bind more tightly or loosely than others, for example, and why still others do not bind to the receptor at all—information that will inform future drug discovery efforts. The experiments were a success, and, more importantly, the methodology was proven. Others could now pick up where Rico left off.

"Ultimately, Carlos's strategy allows you to screen a large number of drug candidates, in this case those that could be useful in preventing HIV, and learn about their biology and learn about their pharmacology in a quantitative way," says Sakmar, who is the *Richard M. and Isabel P. Furlaud Professor* and a Rockefeller senior physician. "This wasn't possible before."

Last year, Rico completed his Ph.D. and became a microscopy specialist in the Bio-Imaging Resource Center, where he trains researchers in microscopy techniques, including those he perfected during his graduate studies. But he's not finished with his education. He intends to go to medical school to study psychiatry, a field he is drawn to in part because studies have shown that G protein coupled receptors play a role in many psychiatric disorders.

Even as he looks ahead, Rico likes to think back to the moment when his experiments first began to yield results. "I was just so happy," he says. For a long time after proving that his method worked, he'd still occasionally daydream about titration curves. "It's how you know you're spending too much time in the lab," he jokes.

Sakmar sees it a little differently. "When you're continually processing information in the back of your mind, that's a really good sign," he says. "That's a sign of a good scientist." ◎

Emerging from the age of HIV

By Alexander Gelfand

First, it was a death sentence.

Then, a life sentence.

The next step: ridding the world of the virus once and for all.

THE AIDS EPIDEMIC IN THE UNITED states officially began on June 5, 1981. That Friday, the Centers for Disease Control released a routine bulletin to physicians, as it does each week, summarizing public health trends. A short notice on page two reported on five young, otherwise healthy men in Los Angeles who had been hospitalized with very serious cases of pneumonia. CDC scientists thought the coincidence was notable—healthy young men don't usually get life-threatening forms of the disease.

Within weeks, the CDC had been flooded with calls about unusual infections in young men, many of whom were either gay or IV drug users. A virus was suspected. A task force was created.

At the same time—just six days after the CDC report—on the other side of the country, another young man, Michel C. Nussenzweig, graduated from The Rockefeller University.

Although he didn't know it at the time, Nussenzweig's destiny would become closely intertwined with the virus, which later became known as HIV. In the coming years, AIDS, the disease caused by HIV, would begin ravaging communities in the U.S. and around the world, and some of the best minds in medicine would struggle to bring it under control. Eventually, HIV's power to enfeeble immune systems would be recognized as one of the gravest health problems of our time—and Nussenzweig would dedicate his career to solving it.

But at the time, he had other plans, and none of them involved HIV.

IT WAS A SINGLE, SEEMINGLY MUNDANE DECISION THAT shifted the course of Nussenzweig's work.

A physician-scientist, he trained as an immunologist at Rockefeller while attending medical school and went on to a residency in infectious disease in the mid 1980s, a time when the field was shaken by the burgeoning AIDS epidemic. He later returned to Rockefeller to start his own immunology research program. By the turn of the millennium, Nussenzweig was deeply involved in detailed studies of white blood cells called B lymphocytes and the antibodies they produce—molecules that help the immune system recognize invaders, such as bacteria and viruses, as foreigners.

As part of this work, he developed a method for replicating antibody genes that he believed would allow researchers to better understand why immune defenses sometimes fail. And this was where fate, if you believe in that sort of thing, intervened.

He needed a virus on which he could test his new protocol: something that would provoke an immune response and cajole the B cells he was interested in to produce antibodies. He could have chosen anything.

"We had to pick a pathogen, so we picked HIV," Nussenzweig recalls. "Frankly, I didn't think it was going to be very interesting."

But in the years that followed, the antibody response that HIV provoked among Nussenzweig's B cells, and that he was able to explore using his novel techniques, proved to be interesting in the extreme. Some of these antibodies turned out to have unique and unexpected properties—unexpected enough to prompt Nussenzweig to embark on a steady line of research into the specific interactions between HIV and B cells. By 2008, he had begun to see the possibility of devising new strategies to combat the virus. And before long, much of the activity in his lab was dedicated to that goal: He ran experiments to test those strategies, added clinical researchers to his team, and initiated trials with human subjects.

Although Nussenzweig's approach is still in its infancy, there's no denying that it shows tremendous promise. In fact, his work with HIV, along with converging work from several other labs at Rockefeller, may be bringing us closer to an AIDS cure than we have ever been. Their research has breathed new life into a line of inquiry that had once been abandoned in the face of repeated failure: using antibodies to treat, prevent, and possibly even cure HIV infection. And it has led to novel tools for combating other deadly viruses, such as Zika and Ebola, as well.

IF ANTIBODY THERAPIES LIVE UP TO THEIR PROMISE, they could become the second landmark success in the history of HIV research. The first occurred in the mid-1990s, when David Ho, scientific director of the Aaron Diamond AIDS Research Center (ADARC), a Rockefeller affiliate, established treatments based on multiple antiretroviral drugs to control HIV—a strategy that came to be known as combination, or cocktail, therapy.

"The eighties and early nineties were brutal," says Martin Markowitz, ADARC's clinical director. "I'm a gay man, and all my friends were dying of AIDS. I was a doctor by day, a nurse by night, and a mourner by weekend."

Then, seemingly overnight, the arrival of antiretrovirals transformed the disease from a death sentence to a chronic condition. It gave millions the opportunity to live with the disease rather than perish from it (today 37 million people are HIV-positive worldwide, one million in the U.S.).

"It was a miracle," Markowitz says.

Over the past few decades, these drugs have only improved. Modern antiretroviral drugs—many of which were first tested at The Rockefeller University Hospital in collaboration with ADARC—can suppress the virus in HIV-positive patients with exceptional efficacy, allowing them to live out a near-normal life span. The drugs are also much less toxic than they used to be, and can even be used to prevent infection in the first place.

But as revolutionary as they are, antiretrovirals are far from perfect. They must be taken in pill form each and every day. They cause side effects ranging from nausea to kidney damage. And, for many of the people who need them most, they're nowhere to be found.

Huge numbers of people who can and should be taking antiretrovirals aren't—either because they don't have access to them or because obtaining them involves stigma or even danger. In some parts of sub-Saharan Africa, for example, which is home to nearly 70 percent of all infected people and where combination therapy can now be had for less

Michel C. Nussenzweig, the Zanvil A. Cohn and Ralph M. Steinman Professor.

than a dollar a day, many women who test positive for the virus are subjected to discrimination and violence. In the U.S., associations between AIDS, homosexuality, and drug abuse have similar consequences. As a result, only 30 percent of HIV-positive individuals around the globe actually receive antiretroviral therapy.

The bottom line: More than 30 years after HIV was identified as the cause of AIDS, there is no vaccine and no way to completely clear the virus from an infected person. Although we've come a long way, we still can't claim victory over the virus.

TYPICALLY, IT TAKES THE immune system two to three weeks to generate antibodies capable of tackling a virus. But HIV isn't like other viruses.

For one thing, the virus actively targets the immune system itself. Through various mechanisms—many of them uncovered by Paul Bieniasz, who has spent years exploring how HIV broaches the body's defenses—the virus invades T lymphocytes, a class of white blood cell that plays a crucial role in organizing the body's immune response. Evading their built-in antiviral defenses, HIV reprograms the T cells' DNA, hijacks their internal machinery, and replicates at breakneck speed—killing the infected cells and laying waste to the immune system in the process.

To make matters worse, HIV mutates at an incredible rate: As soon as the immune system generates an antibody with the ability to neutralize the virus, a new and different strain pops up. That same gift for mutation allows the virus to quickly develop

Photography by Allison Michael Orenstein

Marina Caskey, assistant professor of clinical investigation.

resistance against individual drugs, which is why combinations of multiple antiretroviral medications are needed to keep it in check.

As this cat-and-mouse game continues, the immune system is gradually destroyed, and the patient progresses to full-blown AIDS. Even if the amount of virus in a person's blood is pushed below detectable levels by antiretroviral therapy, HIV's ability to integrate itself into the DNA of its host cells allows it to lurk in the body's tissues. This reservoir of virus represents a lifelong threat: stop treatment, and the infection will come raging back, sometimes stronger than before—a phenomenon known as viral rebound.

Yet curiously enough, occasional cases of HIV are far less menacing. A tiny proportion of infected people—roughly one percent—produce antibodies that neutralize multiple strains of the virus and help the immune system outmaneuver it. But they only begin manufacturing these broadly neutralizing antibodies—which scientists like to call bNAbs, pronounced "bee-nabbs"—after two to four years of infection.

In the late 1990s, researchers explored several ways of using such antibodies, harvested from the lucky one percent, to either treat or prevent HIV. One strategy was to transfer the proteins to test subjects who lacked them with the hope of boosting these individuals' immune systems—much as modern forms of cancer immunotherapy work by enhancing patients' ability to kill or suppress their own mutating cells. Another strategy was to develop vaccines that would naturally prompt the immune system to produce broadly neutralizing antibodies in people who are at risk of HIV infection.

But these early attempts failed: The bNAbs that researchers were able to identify, using the techniques available at the time, weren't potent enough to kill the virus.

For similar reasons, every attempt to develop a vaccine went off the rails.

As a result, researchers largely gave up on antibodies as a means of combating HIV—at least until Nussenzweig's fateful decision to employ the virus in his B cell experiments caused them to reconsider.

His breakthrough, developed with assistance from collaborators at the National Institutes of Health, was a highly effective means of fishing B cells out of people who had developed broadly neutralizing antibodies, combined with new cloning techniques that made it possible to isolate, analyze, and cultivate generations of highly potent BNAbs. Soon after Nussenzweig's breakthrough was reported, researchers elsewhere were using his techniques to identify additional bNAbs, and before long scientists throughout the field were diving back into antibody-related research.

After several failed attempts to devise an HIV vaccine, for example, Ho and his team at ADARC abandoned those efforts and instead decided to use the expertise they had gained engineering proteins to construct highly potent bNAbs in the lab.

The researchers have generated a library of close to 250 different antibodies, each with its own unique properties. Last year, they unveiled a custom-built bNAb, developed for preventive purposes, that neutralizes HIV by binding to two different targets: one on the virus, and another on the T cells upon which the virus preys.

Such bispecific antibodies effectively act like two antiviral weapons rolled into one, and this particular model has proven to be especially powerful: When tested in mice, the protein neutralized 99 percent of hundreds of viral strains. "It has exquisite activity against HIV," says Ho, who recently secured funding from the NIH to develop the antibody for treatment purposes and hopes to begin clinical trials with it next year.

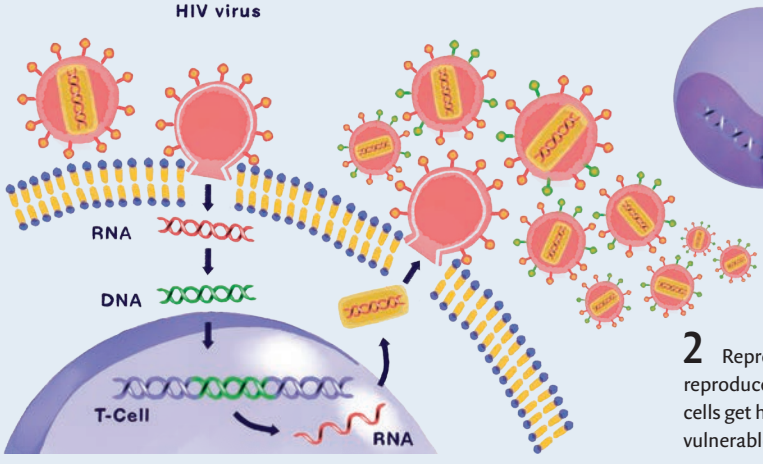
"Our mission is to come up with two bispecific antibodies that could be used as periodic therapy," he explains, laying out a scenario in which patients could be given an injection every couple of months, rather than consuming a daily menu of antiretroviral pills.

MEANWHILE, A DIFFERENT SET OF CLINICAL TRIALS is already under way with two of the bNAbs that Nussenzweig and his colleagues found in patients. And his lab work has yielded fresh insight into how an HIV vaccine might ultimately be engineered.

In a series of trials conducted at The Rockefeller University Hospital, Nussenzweig and his colleague Marina Caskey demonstrated that the most effective bNAbs they have so far laid hands on—one

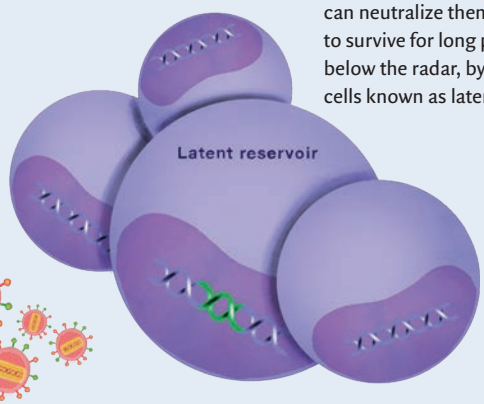
How HIV attacks

1 HIV is effective largely because of an enzyme called reverse transcriptase. Normally, DNA is transcribed into RNA. But reverse transcriptase allows retroviruses like HIV to invert this process. HIV converts its RNA genome into DNA and inserts it directly into the DNA of the immune T cells it infects.



2 Reprogrammed, the T cells are commandeered to help the virus reproduce and spread. As more and more of these critical immune cells get hijacked, the immune system weakens, leaving the body vulnerable to other infections.

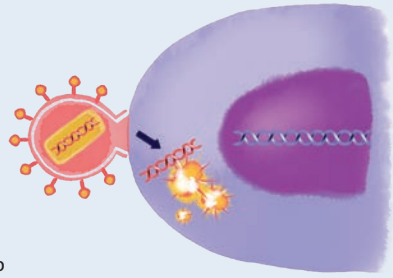
3 HIV uses several tricks to hide and persist. The surface of its particles are studded with receptors that mutate rapidly, preventing the body from generating antibodies that can neutralize them. HIV is also able to survive for long periods of time below the radar, by hiding in dormant cells known as latent reservoirs.

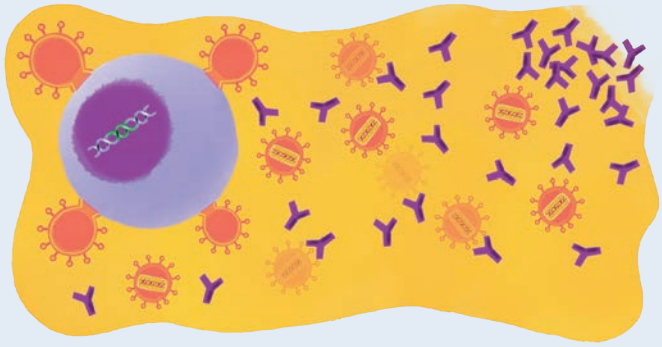


Illustrations by Kevin Whipple

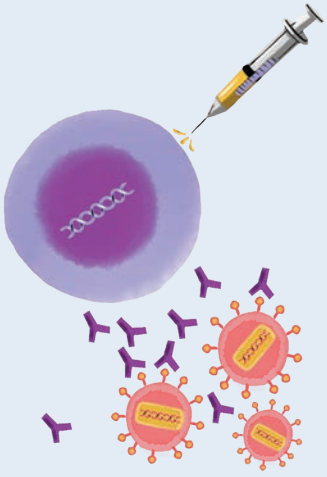
How scientists are fighting back

ANTIRETROVIRALS: Drugs that block the ability of HIV to replicate are known as antiretrovirals. By targeting reverse transcriptase, or other proteins that HIV needs to reproduce, they are highly effective at controlling the infection. But they cannot eradicate the virus completely—miss even a few doses and HIV resurges. Scientists are developing versions of these drugs that are much more potent—able to control the virus for two months or more with a single injected dose.





ANTIBODY THERAPY: A tiny proportion of HIV-positive people produce antibodies that are capable of recognizing HIV despite the virus's ability to mutate. These unusually effective antibodies, known as broadly neutralizing antibodies, are made by the body's B cells. Scientists have developed tools to extract B cells from these HIV-immune individuals and clone the antibodies they produce. By administering these cloned antibodies to other patients, they have had success in preventing and treating infection.



VACCINES: To manufacture antibodies, the body's immune system puts B cells through an iterative process of maturation and selection. Vaccines help to shortcut that process, effectively teaching those B cells how to produce neutralizing antibodies of their own. An effective HIV vaccine—cheap and easy to administer—would put an end to the HIV epidemic. But there are many hurdles, both practical and scientific, still to clear before it becomes a reality.

derived from the blood of an anonymous African woman, the other from an American who has visited Rockefeller to provide samples—can drive the amount of virus in the blood of HIV-positive patients below detectable levels, reducing the risk both of opportunistic infections and of sexual transmission.

Like the antiretroviral drugs that represent the current standard of care, these two antibodies, which go by the unglamorous names 10-1074 and 3BNC117, work best in combination. In work published just this fall in *Nature*, Caskey and Nussenzweig showed that the two antibodies together, administered three times over six weeks to patients who stopped antiretroviral therapy, surpressed the virus for an average of over five months.

Unlike current antiretroviral drugs, the antibodies continue to provide protection and treatment for weeks after they have been administered.

"And from what we can tell," says Caskey, "they have no major side effects."

Nussenzweig and Caskey are now testing versions of the antibodies that have been altered to make them last even longer. Like Ho, they would ideally like to create a single injection that would work for months at a time.

The protection conferred by fully formed antibodies does not last as long as the immunity granted by a vaccine that prompts the body to produce its own. But getting a shot once every few months, rather than taking a pill every day, should go a long way toward mitigating one of the biggest problems with antiretroviral therapy—the fact that many people who initiate the treatment have a difficult time adhering to it. It is a proposition that Nussenzweig and his team will test with a large-scale clinical trial in Africa sometime within the next year or two.

The trial will target young African women, a group that is at once highly vulnerable to infection and unlikely to seek help to prevent or treat it, in part due to the stigma associated with HIV and AIDS. To counter that stigma, trial participants will receive the antibodies in conjunction with a long-acting injectable contraceptive that is already widely accepted by African women.

Paul Bieniasz, head of the Laboratory of Retrovirology.

It is even possible that antibodies could offer a way to address the viral rebound problem.

According to Jeffrey V. Ravetch, the *Theresa and Eugene M. Lang Professor* and head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology, bNAbs don't just neutralize HIV itself. They also prompt the immune system to kill human cells infected with the virus, depriving it of a hideout where it might otherwise linger—something antiretroviral drugs cannot do.

"By virtue of their 200 million years of evolution, antibodies are finely tuned to interact with the immune system, not only directly neutralizing a virus but mobilizing the full immune response against it," he says.

Antibodies owe this superpower to a part of their structure known as the Fc region, which Ravetch has studied extensively in his effort to understand how the immune system functions at large, and how it malfunctions in autoimmune disorders. In fact, he has manipulated the Fc region of Nussenzweig's broadly neutralizing antibodies to boost their efficacy in mice; and the two are now collaborating with researchers at Caltech and the NIH on ways to further engineer bNAbs to make them even more potent.

Nussenzweig's tests, meanwhile, have revealed the surprising synergy that can result when bNAbs begin to interact with other immune cells.

In a recent study, he and his NIH collaborators treated monkeys with simian-human immunodeficiency virus, a variant of HIV engineered to infect primates, with 10-1074 and 3BNC117—the same two antibodies that now are being tested in the clinic—for a limited amount of time. The virus initially disappeared from the monkeys' blood but came surging back several weeks after treatment stopped—similarly to the kind of viral rebound one sees in HIV-positive humans who stop antiretroviral treatment.

Months later, however, something very unexpected happened: Half of the animals spontaneously regained the ability to control their infections. Somehow, they seemed to have overcome their viral rebound-like condition. Further experiments revealed that the antibodies the monkeys received enhanced their immune systems, boosting the response of the same kind of immune cells that prevent some HIV-positive individuals from developing AIDS.

Furthermore, Nussenzweig, Caskey, and Ho are working on strategies to combine bNAbs with a cancer drug called romidepsin, which can wake the virus from its dormant state in a patient's DNA—kicking it out from its reservoir so that it might be purged from a patient's immune system completely.

Only time will tell which of these strategies—bispecific bNAbs, Fc-enhanced bNAbs, or combination therapies—will ultimately progress into useful therapies. But even today, it seems reasonable to imagine a not-too-distant future in which HIV could be prevented, treated, and maybe cured with a syringe full of antibodies.

THE FRUITION OF BROADLY NEUTRALIZING ANTIBODIES into drugs is just one possible scenario. As remarkable as these proteins are, they are not the only game in town.

Just as Nussenzweig and his team are testing long-acting versions of their bNAbs, for example, the researchers at ADARC have been testing injectable antiretroviral drugs that would last longer—and hence be easier for patients to adhere to—than the current daily pills.

Markowitz recently demonstrated that an experimental drug called cabotegravir suppresses the virus in monkeys, and this effect can be obtained with just one injection every other month. He will soon conduct clinical trials at The Rockefeller University Hospital as part of a large international effort to determine whether cabotegravir and another retroviral drug, rilpivirine, can control HIV infection when administered in combination. And he's embarking on a project in China to determine whether cabotegravir alone can provide long-lasting protection against the virus.

Unlike antibodies, which can be injected into the fatty tissue that lies just beneath the skin, cabotegravir must be injected deep into muscle, causing discomfort that can last several days—itself a possible obstacle to adherence. But Markowitz recently concluded an animal study showing that another experimental antiretroviral agent, called MK-8591, is so potent that it could conceivably be administered through an implant that releases the drug over a period of several months, eliminating the need for a painful injection.

MEANWHILE, NUSSENZWEIG'S WORK WITH BNABS has another possible use: as a vaccine. One of the first things he noticed about his broadly neutralizing HIV antibodies was that their genes contained an unusual number of mutations. So many, in fact, that they could not have arisen through the normal process of genetic recombination that B cells ordinarily undergo.

He hypothesized that the process in which the body develops bNAbs must take an especially long time, which would explain why people only begin producing them several years after they get infected. He also supposed it must be an iterative process requiring exposure to many different forms of the virus.

Subsequent studies at Rockefeller and elsewhere confirmed both ideas, and provoked cautious optimism that a workable vaccine—the most distant goal in all of AIDS medicine—is possible.

Just last year, Nussenzweig and his team managed to coax a genetically modified mouse to develop its own bNAbs against HIV, effectively vaccinating the animal. But doing so required injecting no less than nine different bespoke antigens that were prepared with help from colleagues at The Scripps Research Institute. Hence, while their experiment at last offered scientists a blueprint for developing a viable HIV vaccine—a project that draws roughly

"Nussenzweig's work has provoked cautious optimism that a workable vaccine—the most distant goal in all of AIDS medicine—is possible."

$1 billion in funding per year, and has thus far produced nothing but disappointment—it also highlighted the challenges involved. Doing something similar in a human would be even more difficult, and no one, including Nussenzweig, expects it to happen anytime soon. Nor would a vaccine that requires so complex a series of inoculations be anyone's idea of a silver bullet against HIV.

In fact, the path to a vaccine is marred with difficulties—including, somewhat counterintuitively, the introduction of new HIV treatments. Markowitz says the development of long-acting antibodies and antiretroviral drugs could impinge on progress toward a vaccine: For ethical reasons, researchers will never withhold prevention or treatment from potential trial participants, and those who have access to an effective, preventive therapy may be reluctant to give it up in exchange for an experimental one. "The more widespread these treatments become, the more they could complicate the task of enrolling patients in future vaccine trials," Markowitz says.

Even so, the work being carried out in this area could lead to the development of vaccines for other illnesses.

Earlier this year, researchers in Nussenzweig's lab and that of Charles M. Rice, the *Maurice R. and Corinne P. Greenberg Professor*, used Nussenzweig's methods to isolate an especially effective antibody against the Zika virus, which causes a raft of devastating birth defects. In time, their discovery could lead to new ways of fighting the virus—and might even pave the way to a vaccine.

Meanwhile, Paul Bieniasz's investigations into the HIV virus itself might offer a new way to approach vaccine development in general, much as Nussenzweig's work has already provided a new paradigm for antibody-related research.

For decades, Bieniasz has studied how HIV enters T cells, replicates, and bursts forth from

David Ho, the Irene Diamond Professor, and Martin Markowitz, ADARC clinical director.

its diseased and dying hosts. He has identified several mechanisms by which the virus overcomes the antiviral proteins that cells normally use to deal with foreign invaders—mechanisms that could potentially be disrupted by drugs. And together with Theodora Hatziioannou, a research associate professor, Bieniasz has developed a strain of the virus that behaves in a particular species of monkey much the same way as it does in humans—a development that should improve the predictive quality of animal studies.

Recently, however, Bieniasz and his team made a discovery that could have far broader implications.

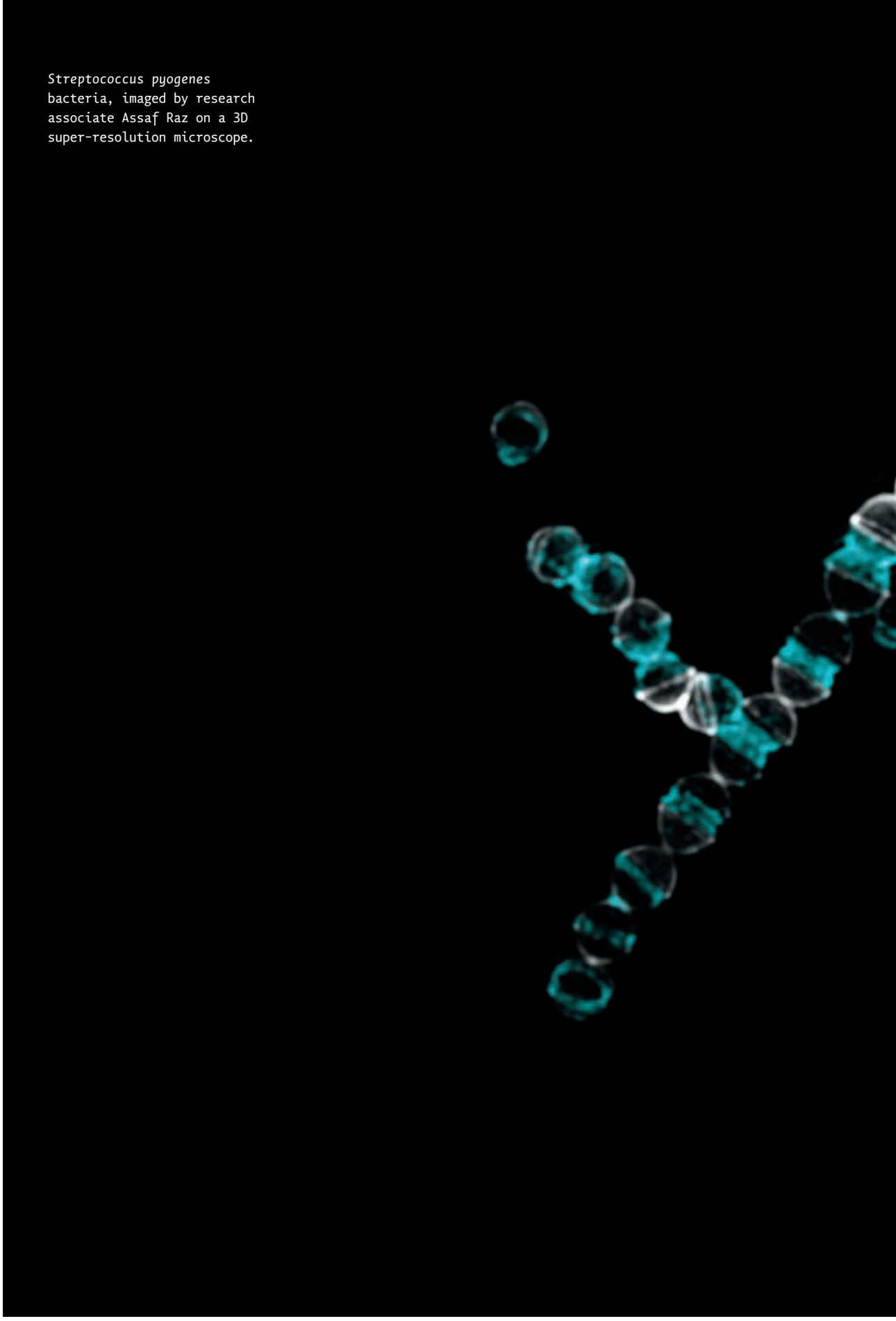
The researchers found that by adjusting the frequency with which a particular genetic sequence appears in the HIV genome, they could persuade a naturally occurring protein, aptly named ZAP, to recognize the virus's RNA as foreign and destroy it. By carefully dialing the amount of that sequence up and down, Bieniasz hopes to synthesize viral RNA that can prompt an immune response without causing illness.

If successful, he would be in a position to create an entirely new kind of attenuated virus, stripped of its ability to infect. And that, in turn, could speed the development of vaccines against a whole range of viral diseases, from Zika to Ebola (though not necessarily HIV, whose ability to hack human DNA makes the use of a live attenuated vaccine too dangerous to consider, at least for now).

New forms of prevention and treatment. Novel tools for combating other global scourges. The ultimate goal of developing a vaccine against HIV may still be a ways off, but as David Ho, who has been in this fight longer than most, emphasizes, the gains made in recent years have been remarkable. And what's to come promises to be even better.

"Science," he says, "is progressing in this field like no other." ◎

LIFE, ILLUMINATED



Streptococcus pyogenes bacteria, imaged by research associate Assaf Raz on a 3D super-resolution microscope.

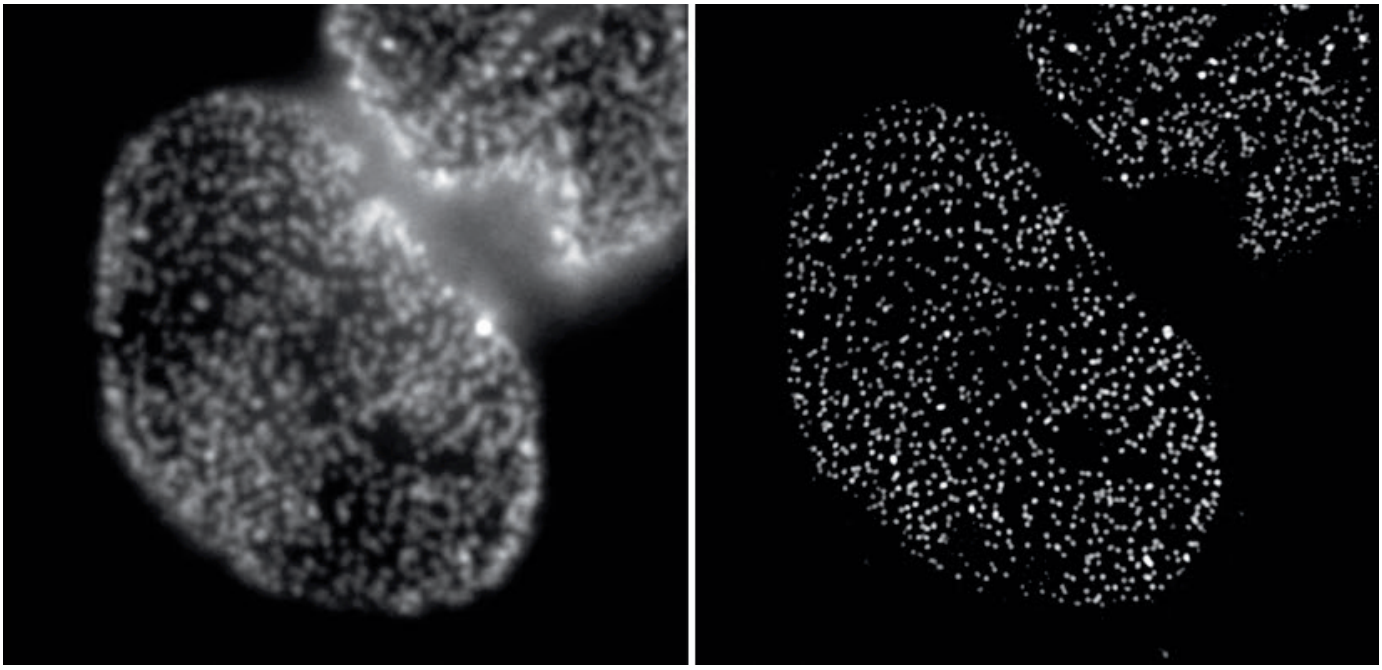
Innovations in imaging are unblurring our world, pixel by pixel.

By Eva Kiesler and Zachary Veilleux

Science, at its core, is observation. More than anything, we want to know what our universe looks like. That's true for the world's greatest experimentalists as well as for kids getting their first peek at a cell though a classroom microscope; we are visual creatures, and seeing is believing.

In the past 500 years, microscopes have evolved from crude pieces of glass capable of magnifying insects into multimillion-dollar instruments—precision-crafted machines that can illuminate, manipulate, record, and quantify the tiniest minutiae of life and disease. Even today, bioimaging continues to improve at breakneck pace, driven by advances in optics, biochemistry, electronics, and computing.

Here's a sampling of images from the front lines of the field.



Human nuclear pore complexes, as seen with a conventional confocal microscope (left) and a super-resolution microscope.

BIO-IMAGING RESOURCE CENTER (THIS PAGE) / LABORATORY OF PATHOGENESIS AND IMMUNOLOGY (PREVIOUS PAGE) / THE ROCKEFELLER UNIVERSITY

Super-resolution superpowers

Alison North

AT ITS MOST BASIC, microscopy is about using lenses to make tiny objects easier to see. For the first few hundred years, advances in the ability to shape and position glass drove most of the improvements in the field; in the 20th century, light microscopes acquired capabilities such as fluorescence imaging and optical sectioning, giving us closer and closer views of subcellular structures and macromolecules. But eventually, we came up against physics; there's only so much detail you can capture before light waves are redirected away from the lens, rendering images hopelessly blurry. It's a principle called the diffraction barrier, and because of it, most light microscopes max out at a resolution of about 200 nanometers (about one-fortieth the length of a red blood cell).

But in Rockefeller's Bio-Imaging Resource Center, research associate professor Alison North demonstrates one of her latest acquisitions: a 3D super-resolution microscope, capable of circumventing the laws of physics. With this instrument, North and her colleagues are producing images that were impossible to obtain only a few years ago. Among them are crisp photos of nuclear pore complexes, protein assemblies that perforate the outer membranes of a cell's nucleus. These structures, which are only about 120 nanometers in diameter, were previously doomed to fuzziness.

Super-resolution technology allows you to hack the diffraction barrier. The microscope superimposes a grid-shaped light pattern on a specimen and shifts the grid while capturing a series of images, which are then fed to a computer. "The patterned light interacts with the fine details to make them coarser," North explains, "bringing the visual information into a range where we can collect it. And once we have the data, we can reconstruct the fine details using mathematical algorithms."

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The result is an oversized cell that is anatomically correct, although its biomolecules are fragmented.

Seeing by swelling

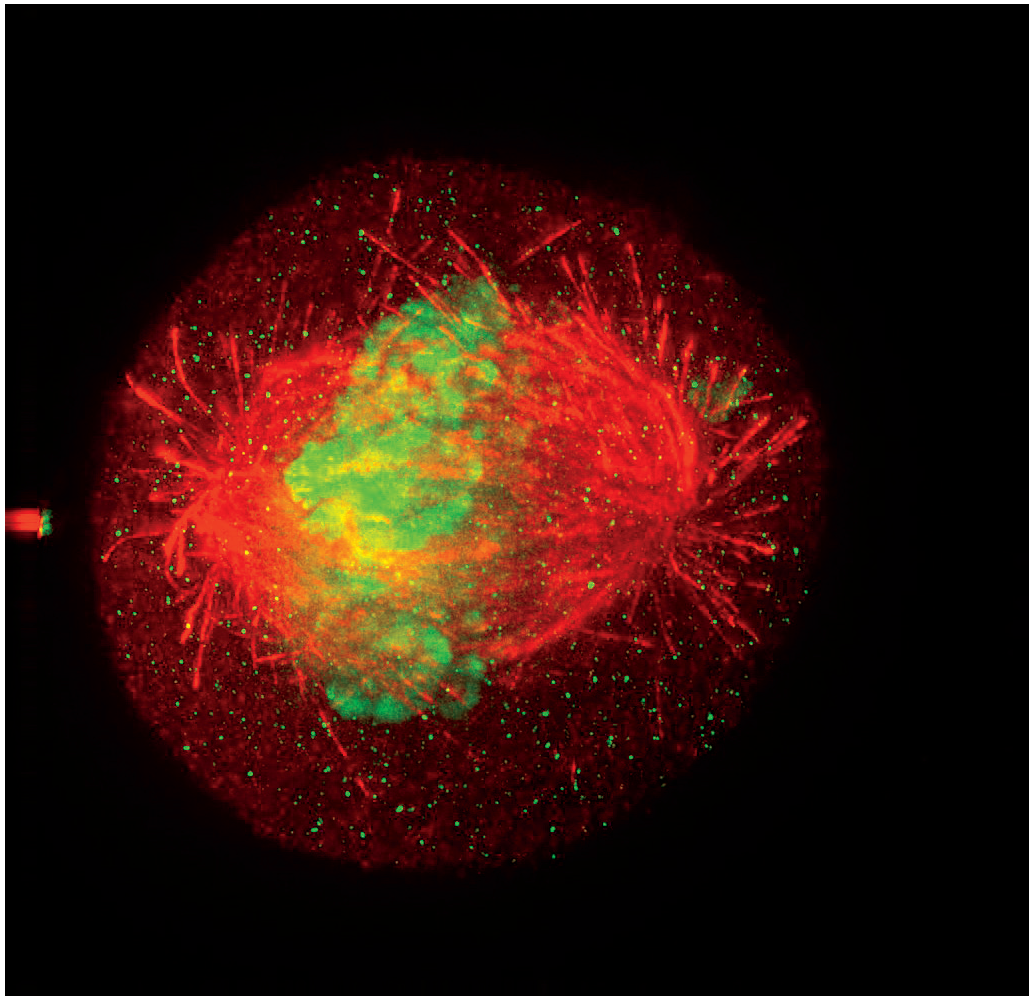
WHEN EVEN SUPER-RESOLUTION doesn't work, it's time for plan B. Hironori Funabiki, who studies how cells segregate chromosomes during cell division, employs a surprisingly simple solution: he makes his sample bigger.

Pavlan Choppakatla, a graduate student in Funabiki's lab, uses a technique known as expansion microscopy to visualize the distribution of proteins that are thought to fold DNA into chromosomes. The method relies on a superabsorbent polymer, the stuff that retains liquid in diapers. When exposed to water, the material expands and can eventually reach up to one thousand times its original volume. Initially developed at MIT, expansion microscopy requires scientists to build the polymer within a cell, and anchor it to various attachment points before initiating a chemical reaction to trigger expansion.

The result is an oversized cell that is anatomically correct, although its biomolecules are fragmented. These fragments sustain the configurations the molecules had before expansion, but with everything spaced further apart. In effect, Choppakatla can quadruple the power of a microscope with this technique.

"Because it gives us an overall view of numerous molecules across an entire cell, this technique is ideal for studying how very long stretches of chromosomal DNA are individually organized into rod-like structures that can be moved apart during cell division," Funabiki says. By labeling the proteins of interest, his lab gets the same images they might otherwise obtain but with four times the level of detail.

Hironori Funabiki



A dividing human cell, inflated to four times its normal size.

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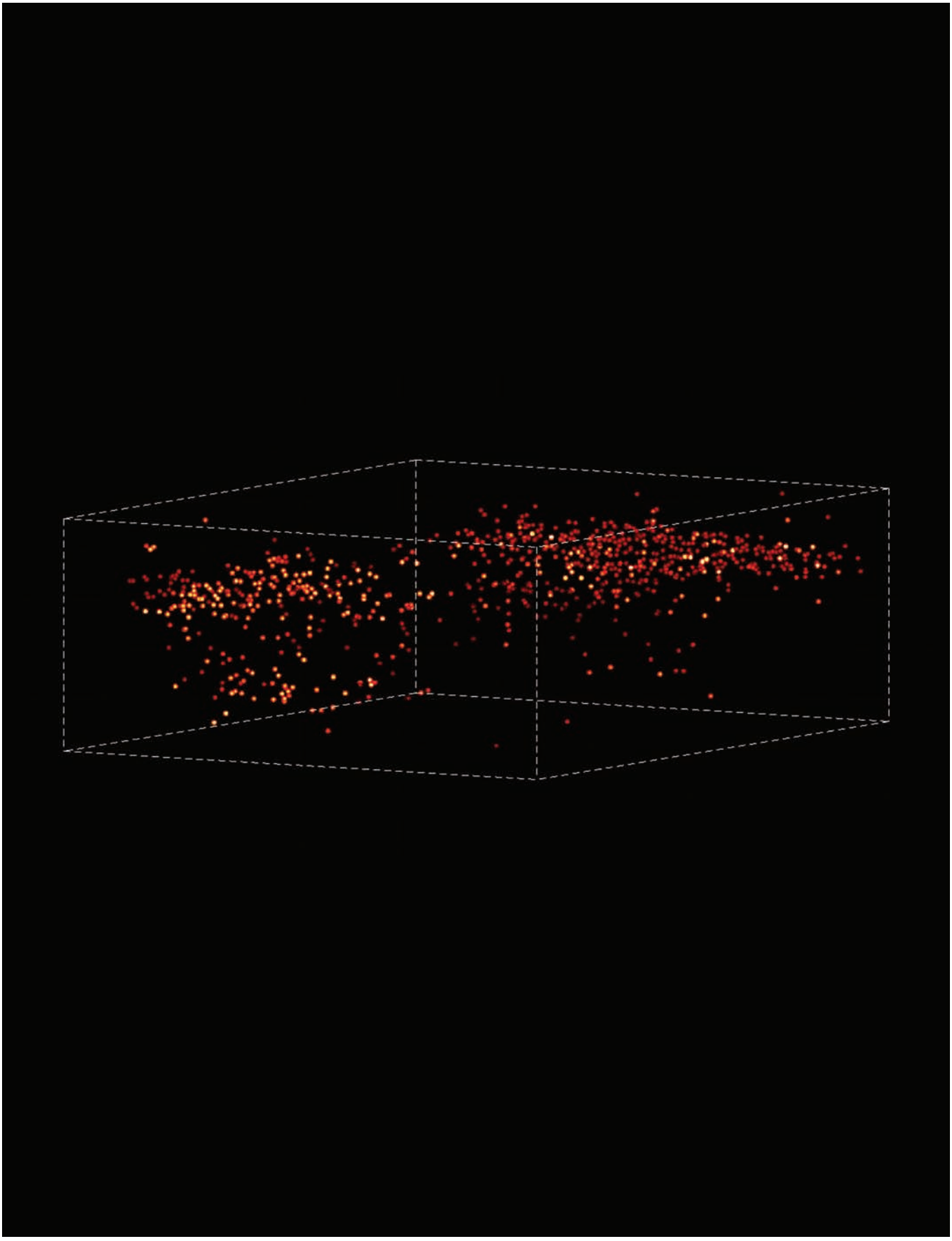


LABORATORY OF NEUROTECHNOLOGY AND BIOPHYSICS / THE ROCKEFELLER UNIVERSITY

Cells in action

HERE'S WHAT YOU MIGHT TRY in order to find out if a neuron is doing something: Attach a specific fluorescent marker to it and illuminate it with a laser. When the neuron is active, it will brighten.

It works well when the neuron is sprawling on a glass slide. But what if you want to watch it in its natural milieu, deep inside the brain of a living organism? What if you want to study not just one neuron, but thousands? And what if you need to deduce precisely which of them are communicating, millisecond by millisecond?

Alipasha Vaziri, a physicist and neuroscientist, is building instruments and computational algorithms that can accomplish all these things, and more. Stationed in an all-black, windowless lab in the basement of Smith Hall, his group's microscopes cut through enormous amounts of data in order to capture wide-ranging brain functions at single-cell resolution.

"With most traditional microscopes, much of the data we collect from a sample is redundant," Vaziri says. "In neuroscience applications, for example, the size of the cells and their locations remain virtually constant over the duration of imaging—we don't really need to acquire that information over and over again if what we are actually interested in is the activity of the neurons." By putting the known information into a computational model, Vaziri is able to extract only the data that pertains to changes in the activity of nearby neurons from one moment to the next. The result is that less visible activities occurring within a mouse brain, for instance, become easier to see.

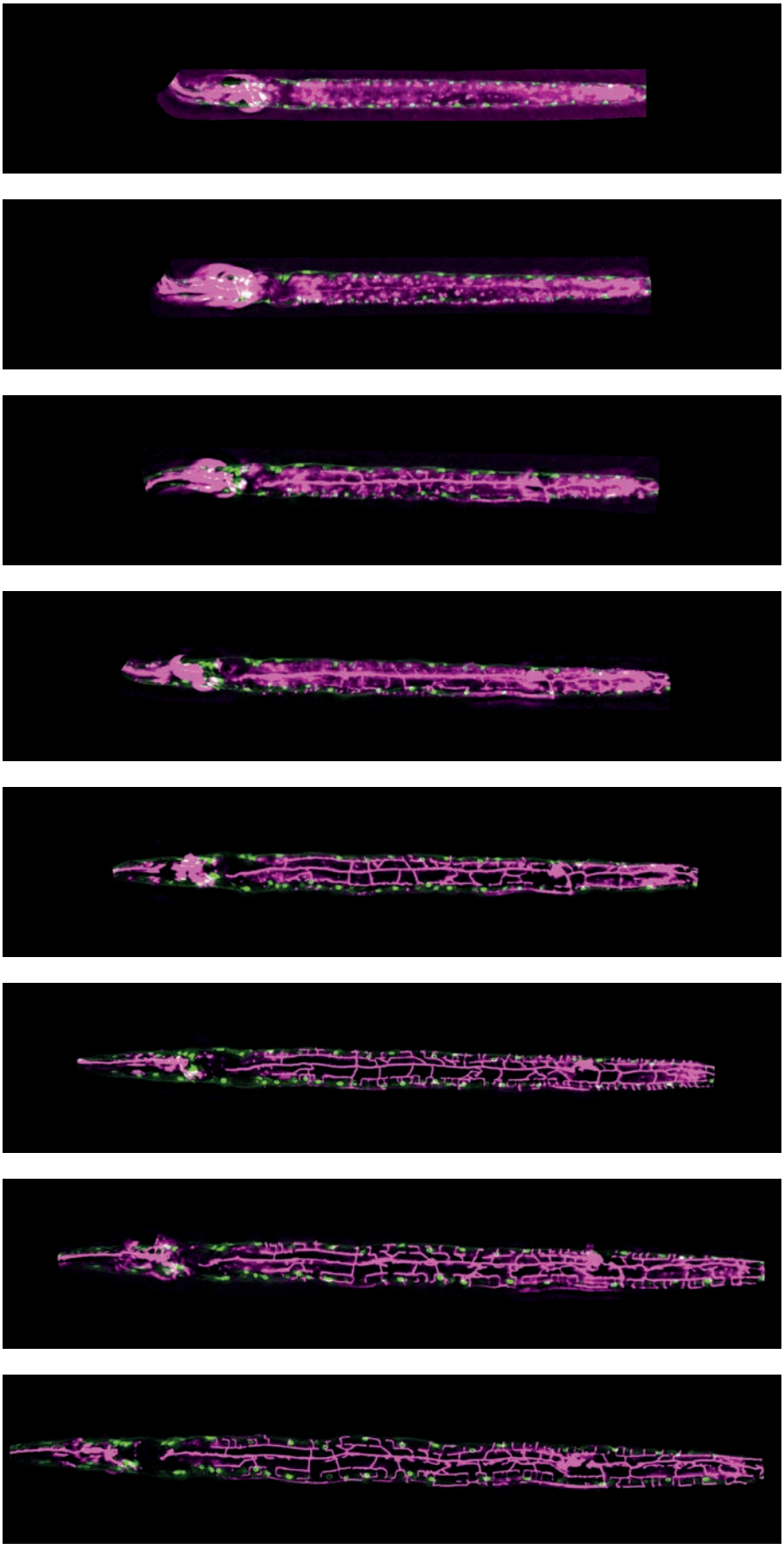
Essentially, Vaziri is using computation both to boost the sensitivity of the optics and to utilize that sensitivity to maximum effect. "We're asking our algorithm: Given the patterns we are observing, and what we know about our sample and our equipment, what is the most likely position of neurons and their activity in time?"

The method can be used to compensate for the tendency of light to scatter as it travels through semi-opaque tissue, yielding striking moment-to-moment snapshots of neural activity. It can do it at high speed and over large areas of the brain, making it possible to capture an overall picture of activity patterns in even relatively large brains, like a mouse brain.

Alipasha Vaziri

"Much of the data we collect from a sample is redundant. We don't need it if what we are actually interested in is the activity of neurons."

Neurons within a mouse brain flicker with activity, enhanced by an algorithm that eliminates extraneous data.



Developing neurons (magenta) imaged over 24 hours in a growing worm.

LABORATORY OF DEVELOPMENTAL GENETICS / THE ROCKEFELLER UNIVERSITY

Worms on the move

THERE'S ANOTHER CHALLENGE WITH imaging living things: They tend to be delicate. Even the most powerful imaging system will be of little use if it squashes or distorts the very thing you're trying to look at. It's a problem that Wolfgang Keil, a postdoc working in the labs of Shai Shaham and Eric D. Siggia, is acutely aware of.

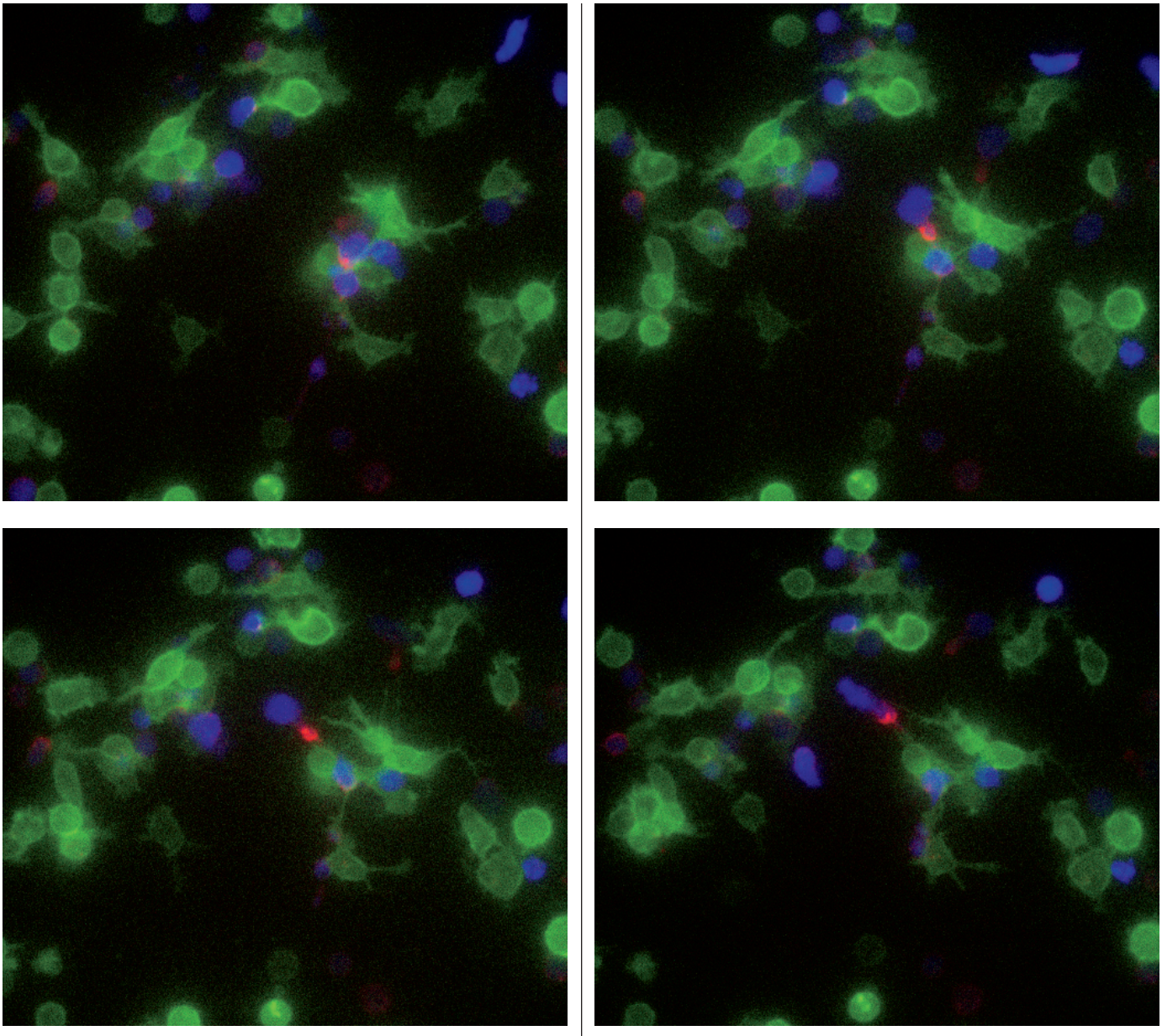
Keil, who studies how organs and neural circuits develop in *C. elegans*, has developed a new way to get his squirmy subjects camera-ready. Traditionally, the flea-size worms are glued to a microscope slide when imaged, to keep them under the lens. It's an unnatural setup that causes numerous problems: A trapped worm will soon get stressed, hungry, or hurt, so the microscopist must hurry.

To be able to image worms over long periods, Keil built a microfluidics chamber in which his *C. elegans* roam around and eat freely, except during short photo ops. When it's time to take a picture, Keil gently draws a worm to the edge of the chamber, then lowers a ceiling to hold it still. Seconds later, the worm is free to go about its business—until the next snapshot.

"The chamber has enabled us to do something that's never been done before: to study a developing animal that's feeding, growing, and interacting with its environment," Keil says. Post-processing software can line up the worm snapshots in precisely the same orientation no matter which way the worm is facing, so the resulting time-lapse movies give a clear view of changes over time.

Because Keil's system can image 10 worms at once, the method improves greatly on the statistical power and efficacy of previous ones. "The field has been completely lacking this capability," says Shaham, the *Richard E. Salomon Family Professor*, "so people missed a lot of phenomenology."

In a test drive, his team used the chamber to track four events in the development of *C. elegans* larvae. "In every single stage, we discovered new biology that hadn't been described before," Shaham says.



LABORATORY OF LYMPHOCYTE DYNAMICS / THE ROCKEFELLER UNIVERSITY

Cellular smoochers

Gabriel D. Victora

As the immune system's T cells (blue) interact with B cells (green), they smear each other with a marker (red).

IF SOME BIOLOGISTS SEEK to prolong their imaging sessions, others are more concerned with speed. Gabriel D. Victora, the *Laurie and Peter Grauer Assistant Professor*, studies fleeting interactions between immune cells—encounters so brief that he refers to them as "kiss-and-run."

In a crowd of cells that look more or less the same, an occasional one will suddenly run up to a peer and make contact, then bashfully move away. "Virtually all of immunology is based on these exchanges," says Victora, "in which two cells exchange signals to kick-start a response against a pathogen."

Scientists previously examined these events only inside Petri dishes, but Victora has devised a way to capture them in living mice. It involves injecting the animals with immune cells engineered to produce a fluorescent marker—the biological equivalent of lipstick—then tracking the marker as it travels. Every time an immune cell kisses another, it smears it.

The spectacle is fascinating to watch under the microscope, and it's also well-suited to detection via flow cytometry, which allows Victora to quickly count interactions within a big cell population. "This is how we figure out precisely which immune cells interact in a given scenario," he says, "and how their communication changes over time." ◎

The human brain is capable of understanding gravitational waves. It can produce equations, arguments, music. But will it ever make sense of its own inner workings? We posed the question to neuroscientist Cori Bargmann.

Deep secrets

By Eva Kiesler

When a *Caenorhabditis elegans* worm smells diacetyl, it has no time to twirl. Instead, it sets off toward the smell like a bullet, its microscopic mind aflame. Ahead are probably soil microbes, the worm's idea of a delicious meal.

The behavior should be somewhat relatable because diacetyl attracts humans, too. Used industrially as butter flavoring, it really does smell of the good life (think croissants, popcorn, Chardonnay). Yet there is reason to suspect that the worm's appreciation of the scent is more refined than ours. Although *C. elegans* may be primitive in almost every other sense, it is king of olfaction in the animal kingdom.

It was Cori Bargmann who discovered, in the early 1990s, that the humble creature will detect puffs of almost any chemical present in its natural environment, a skill it owes to possessing close to 1,000 smell receptors (dogs have roughly 800, while we humans get by with 400).

Illustration by André da Loba

Moreover, she found that different smells produce specific behavioral outcomes: A worm inside a Petri dish will chase after odors it perceives as good, flee bad ones, and calmly ignore neutrals.

To Bargmann, whose work centers on understanding how sensory experiences lead to behaviors, the worm's superb sniffing skills provide fertile scientific ground. For close to three decades, her lab has developed increasingly advanced tools to manipulate olfactory neurons and receptors in *C. elegans,* and has studied how the animals' reactions vary in response to particular smells. With such experiments, she has shed light onto the basic processes by which the brain assembles cues from genes, experiences, and the environment to make us think, feel, and act—processes that rule all animals' minds, big or small.

Bargmann, who is the *Torsten N. Wiesel Professor* at Rockefeller, runs her lab while also serving as head of science at the Chan Zuckerberg Initiative, an organization with a $3 billion investment in biomedical research. We spoke with her in her Rockefeller office, seven stories above New York City's East River.

Behavior seems inherently different from many other aspects of our biology—less tangible than, say, metabolism or immunity. To study its essence, where do you even begin?

My approach has been to explore how genes influence the brain's activity. Many behaviors are in fact evolutionarily hardwired and genetically available at birth, which is fascinating. Newly hatched ducklings, for instance, will instinctively bond with the first moving object they lay eyes on, usually their mother.

By asking what makes such a system work, we might learn a lot about the molecular and cellular aspects of behavior. Are parts of a newborn's brain prewired to solve particular problems? And what might this wiring actually look like?

What made you decide to pursue these questions in a tiny worm rather than in humans, or another animal more similar to us?

People are such complex organisms. So many factors determine how we behave—our DNA as well as our environment, experiences, thoughts, feelings. And if you want to understand how genes produce behavior at the most rudimentary level, *C. elegans* provides a very practical model. The worm's nervous system has been fully mapped, and can be systematically manipulated using powerful genetic tools. In a sense, it's a microcosm that allows us to see the inner workings of a brain more clearly.

There are, of course, many other ways to approach these questions, and part of what makes neuroscience so much fun is that it's always been inclusive of people working in different systems—squid, rat, fruit fly, songbird. Some scientists will argue that to truly understand how our brains work, we need to study humans since no other organism is able to generate the same complexity of cognition and communication. But ultimately, I think all of these pieces will come together to create a deeper understanding.

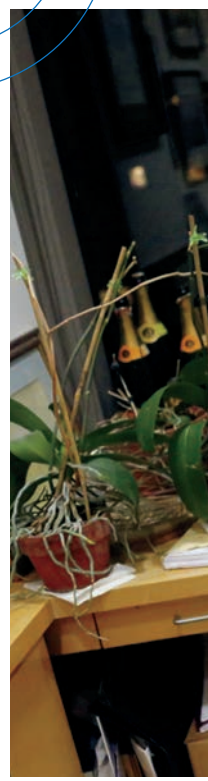
Can you give us an idea of what that deeper understanding might look like?

Historically, big breakthroughs tend to happen when insights from different systems combine to illuminate an underlying principle. For example, not long ago we thought of brain cells as individual cogs in a machine, each performing a dedicated function. But we're learning that the brain is far more dynamic and holistic than that. Its activity tends to manifest in large sweeps, called dynamic states, moving back and forth through many cells and brain regions in parallel, like water flowing through a set of sluices.

When these holistic activity states were first seen in human brain scans about ten years ago, most people didn't think they meant much. It was only after their existence was discovered in other animals, including

"The brain is incredibly robust and forgiving. It is quite happy to receive noisy and chaotic information and collapse it to produce a perfectly coordinated course of action."

Depression is a towering global health threat affecting 300 million people.



C. elegans, that we realized we needed to pay attention to them, and that they might in fact tell us something very fundamental about the way nervous systems work.

How else is our understanding of the brain changing?

Modern technologies are gradually revealing how much there is we don't know. About a decade ago, for example, scientists studying artificial intelligence set out to build computer systems based on neuroscience principles—systems that were supposed to solve problems in the same way the brain does. But it turned out that those systems didn't operate like the brain at all, presumably because we hadn't been thinking about neural networks in the right way to begin with. In the last couple of years, however, AI systems based on different principles have emerged, and to everyone's surprise they're starting to look more and more like the brain. This has resulted in a very interesting dialogue taking place between the two fields.

Another transformative technology is optogenetics, which makes it possible to activate or silence an animal's neurons by shining light on the tissue. In one experiment, a group of scientists used it to shut off motor neurons in the right half of a mouse's brain, keeping the left-side motor neurons active. With a broad intervention like that, you would think havoc could ensue; the mouse might fall over, get confused, or have a seizure. But instead, the mouse simply began walking around in circles.

This tells us that the brain is in fact incredibly robust and forgiving. It is quite happy to receive noisy and chaotic information and collapse it to produce a perfectly coordinated and seemingly deliberate course of action.

So what's missing from our picture of the brain and how it operates?

That's tricky to answer since we don't know what we don't know. What's certain is that, at this point, we are not even close to understanding how any nervous system works, including the most primitive ones. We know how information moves through a synapse, and we know that specific brain regions are involved in particular tasks, like movement or face recognition. But there's a huge disconnect between looking at individual cells and a system made up of 86 billion cells, and to bridge that gap we need to learn how information from these billions of synapses gets organized, how it flows through the brain, and how it becomes rewired under different circumstances.

In particular, I'm very interested in how the brain is affected by emotional or motivational states. Say, for example, that you smell meat cooking on a grill. If you're hungry, it may cause you to salivate, but if you have the flu, the exact same stimulus may make you nauseous. What changed, and at what level?

Understanding this will be very important for brain science, and I'm convinced it will have profound clinical relevance. Drug addiction, for example, seems to involve a shift in motivational state—you begin to crave a substance you were previously neutral to or merely attracted by. Likewise, depression shifts the brain's emotional state so that we perceive things differently.

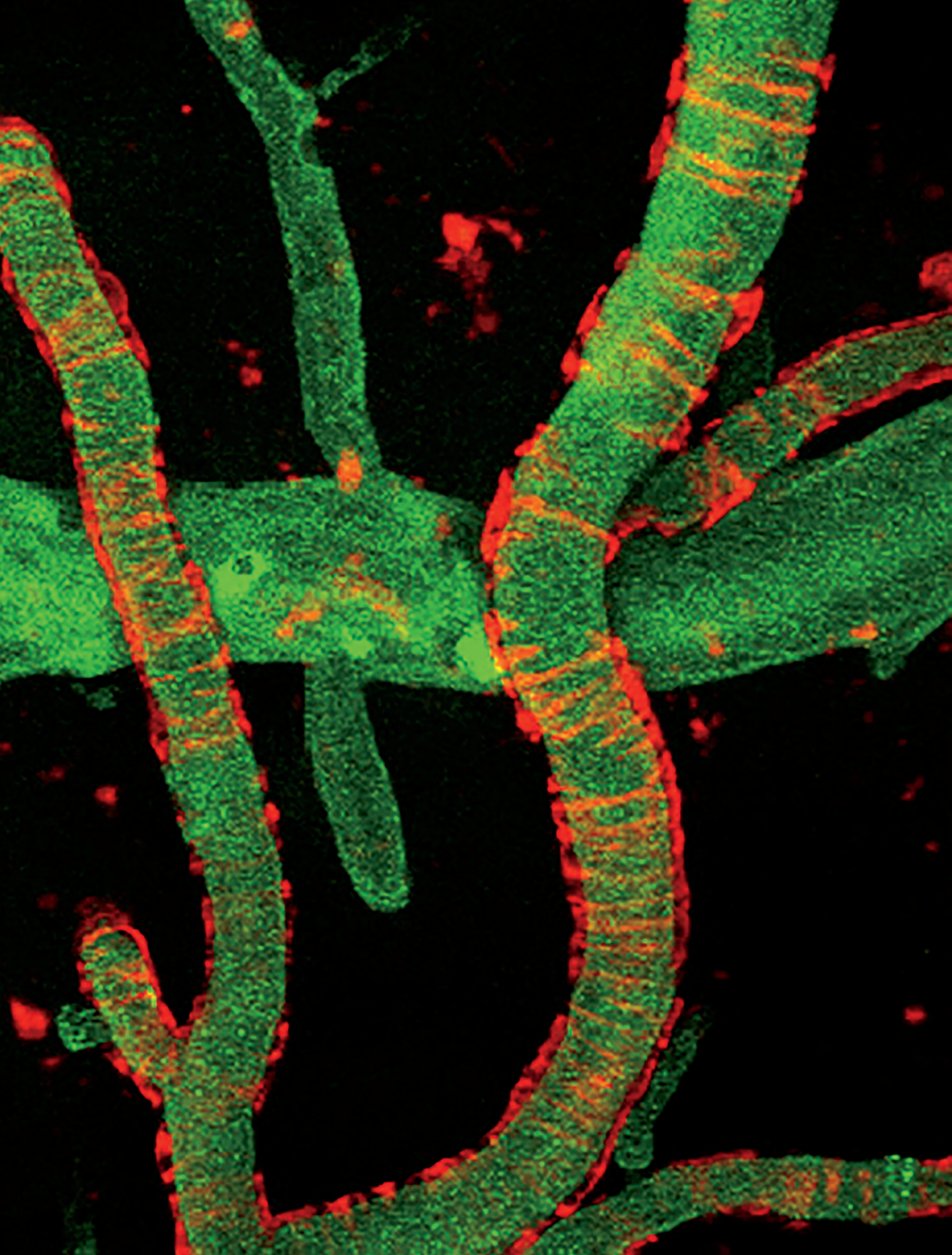
Do worms get depressed?

I don't think so, but they do have serotonin and dopamine, neurotransmitters that have been linked to mood disorders in people. They also have oxytocin, but I don't think they use it to fall in love. Clearly, their psychological processes don't align with ours in any simple way.

Even so, I think *C. elegans* will help us answer basic questions about motivational states in general, and maybe even develop strategies to manipulate these states with drugs—something that could ultimately lay the foundation for new ways to manage brain-related human disease. We obviously have a long way to go in that regard, and I'm sure the work will continue to turn up new surprises. ◎

YANA PASKOVA

Bargmann in her Rockefeller office.



AGAINST THE GRAIN

For years, people thought Sidney Strickland was barking up the wrong tree.

He wasn't.

By David Noonan

Healthy blood vessels are crucial to healthy neurons, but we know little about how they interact.

Strickland became concerned that a single disease pathway had come to dominate an entire field. “I think Alzheimer’s has suffered from oversimplification,” he says.

GOOD NEWS IS RARE IN THE FIELD OF ALZHEIMER’S.

Sidney Strickland knew what he was up against when he began working on the disease more than two decades ago, and little has changed: Alzheimer’s remains a deadly health threat and among the most feared diseases on the planet, unchecked in its power to destroy brain cells and erase minds.

In the last 15 years, more than 400 new Alzheimer’s drugs have failed clinical testing in humans. That’s 400 times that the hopes of scientists and doctors, along with those of patients and their families, have been squashed.

But if the harsh reality of Alzheimer’s hasn’t changed, something else has. Scientists are finding new ways of thinking about the disease and studying its biology, thanks in part to a question that Strickland began asking in the 1990s.

What role, Strickland wanted to know, do impairments in the brain’s blood supply play in Alzheimer’s? At the time, Strickland, now a Rockefeller scientist and head of the *Patricia and John Rosenwald Laboratory of Neurobiology and Genetics*, was working on problems related to the circulatory system at the State University of New York at Stony Brook.

It was a new idea, a question that had not been asked before. But over the past two decades, Strickland’s ongoing efforts to answer it have opened up whole new avenues of research into the nature and causes of Alzheimer’s, which currently affects 5.7 million Americans, and is expected to reach nearly 14 million by 2050.

Unlike most people in the field, Strickland has no formal training in brain disease or neuroscience. He is a developmental biologist who has climbed a steep learning curve, motivated in part by his concern that a single disease pathway had come to dominate an entire field.

“I think Alzheimer’s has suffered from oversimplification,” he says.

To this day, most Alzheimer’s research focuses on a sticky protein called amyloid-beta, the accumulation of which leads to the formation of gummy plaques in the brain. To be sure, amyloid-beta deserves the attention: It has been shown to drive the development and progression of Alzheimer’s and scientists have found that the plaques can interfere with neurons’ ability to send signals, as well as sentence them to an early death. The question is whether other types of brain changes help fuel the disease as well, and Strickland thinks there is much to be gained from thinking more broadly. Like cancer, he says, Alzheimer’s is fundamentally complex and may arise from multiple pathogenic pathways. And one mechanism that has been largely overlooked involves irregularities in the brain’s vascular system.

In particular, Strickland has zeroed in on the brain-damaging effects of fibrinogen, a protein that gives rise to blood clots. Under normal circumstances, fibrinogen, which circulates in the bloodstream at high concentrations, is beneficial: Whenever a blood vessel gets damaged, a cascade of molecular

Sidney Strickland has found that fibrinogen can "leak" into the brain, causing mesh-like structures to form.

events is triggered to convert it into fibrin, a mesh-like substance that stops bleeding and initiates repair of the vessel wall.

However, as Strickland has discovered, fibrinogen can sometimes leak into the brain, where it does not belong, and cause fibrin to accumulate. In an analysis of postmortem brain tissue, Strickland found fibrin buildups in multiple areas of the brains of people with Alzheimer's—much more fibrin than would be expected in healthy brains. In the hippocampus, a part of the brain essential for memory, Strickland and his colleagues discovered more than 20 times as much fibrin, and in the superior frontal cortex, which is involved in many higher cortical functions, 100 times as much.

Exactly how fibrinogen seeps into the brain is something of a mystery. To get there, the protein needs to cross the blood-brain barrier, the brain's primary defense system. "The blood-brain barrier is made up of several different types of cells," says Erin Norris, research assistant professor in the lab. "Presumably, something goes wrong in some aging brains, and these cellular components of the blood vessel wall start to break apart." The rupture allows fibrinogen to gain access to the interior of the brain.

It's unclear at this point exactly when in the course of Alzheimer's fibrin deposits become a factor and whether they are a primary cause of the disease or a consequence of other, earlier pathogenic mechanisms. What they are not, says Strickland, is a mere comorbidity, a separate condition that happens to accompany aging. Leaking fibrinogen and fibrin clot formation contribute to Alzheimer's, he says, by increasing neurovascular damage, neuroinflammation, and neuronal degeneration, as well as contributing to the deposit of amyloid-beta in and around blood vessels. That assertion is supported by a set of observations his lab made in mouse models of the disease—mice genetically engineered to develop Alzheimer's. In those experiments, they found that fibrin deposits in the brain

Photograph by Sari Goodfriend

increased over time and correlated with the level of amyloid-beta plaques. Conversely, decreasing fibrinogen levels in the Alzheimer's mice reduced neuronal death in the hippocampus.

The mechanisms by which fibrin accelerates neuronal degeneration remain unknown, but the scientists have a few promising leads. Inflammation, commonly found in the brains of Alzheimer's patients, is a likely contributor, and Strickland points to the interaction between fibrin and amyloid-beta in the brain as a major source of that inflammation. That interaction, which Strickland has analyzed in detail, is what slows the breakdown of blood clots, a process the body normally undertakes after a wound has healed, when the integrity of the blood vessel has been restored and the clot is no longer necessary. But amyloid-beta disrupts this natural system and prevents fibrin aggregates from dissolving normally.

The result is an ever-increasing load of fibrin that may lead to chronic inflammation. While the protein's pro-inflammatory function is normally beneficial—it is part of the body's wound-healing process—the chronic inflammation that ensues when fibrin lingers in the brain can lead to cellular damage.

Another way renegade fibrin clots could kill neurons, says Strickland, is by collecting in and around blood vessels, reducing or even blocking the flow of blood to brain cells, a problem known as ischemia. "If the ischemia is happening in micro-vessels, capillaries, rather than in veins or arteries, then you're not going to collapse from a stroke," Strickland says. "You're going to lose one neuron at a time. And over the course of decades, enough neurons die."

Though it left him well outside the mainstream of Alzheimer's research, Strickland's decision in the 1990s to investigate the role of cerebrovascular dysfunction in the disease was based on more than mere intuition. As he points out, other types of dementia have long been associated with abnormal blood flow in the brain, often caused by stroke, that deprives neurons of oxygen and nutrients. In addition, half of all Alzheimer's patients were known to have some kind of impaired cerebral circulation. And multiple studies have shown that physical exercise, which improves cerebrovascular health, can decrease the risk of developing dementia and delay the progression of age-related cognitive decline.

Nevertheless, it took many years for Strickland's lab to be recognized as an important front in the war on Alzheimer's. Katerina Akassoglou, now a professor of neurology at the University of California, San Francisco's Gladstone Institute of Neurological Disease, trained with Strickland as a postdoc and was involved in the lab's earliest work on fibrinogen. "When I would tell other neuroscientists I was working on fibrinogen," she recalls, "they would say, 'Oh, we're so sorry you're leaving the neuro field.'"

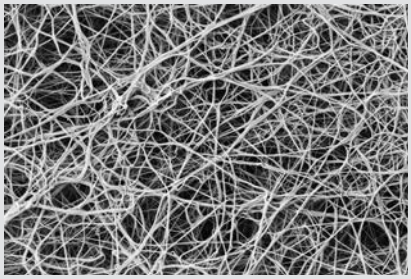
Howard Fillit, a neuroscientist at the Icahn School of Medicine at Mt. Sinai and executive director of the Alzheimer's Drug Discovery Foundation, has tracked developments in Alzheimer's for decades. "When research started back in the eighties," he says, "it was totally focused on amyloid and similar proteins because those were the only clues we had." So today, the majority of drugs being developed are focused on those proteins. "There was no research on vascular pathology. But Sid was persistent and he did really good work."

So it's something of a new era for Strickland, who recently published what amounts to a summation of his Alzheimer's work to date in the *Journal of Clinical Investigation*. "I think the pendulum is swinging," he says. "About 10 years ago I was describing our ideas to the head of an Alzheimer's foundation. He said I was barking up the wrong tree. Now he supports our work."

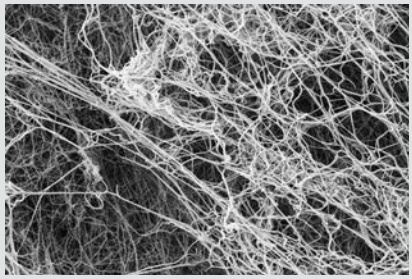
In Fillit's view, one of the most important aspects of Strickland's research is the way it establishes cerebrovascular abnormalities—including common aging disorders such as hypertension and atherosclerosis—as part of the pathology of Alzheimer's. This way of understanding the disease

Lingering lattices

Amyloid-beta, the protein responsible for plaques in the brains of people with Alzheimer's, also affects blood circulation. It binds to fibrin, the substance that forms blood clots, making the the clots harder to eliminate.



In clots that lack amyloid-beta, the fibrin mesh looks tidy and is readily degradable.



When amyloid-beta is added, the fibrin structures are tangled and don't easily break down.

STEVEN CAJAMARCA / LABORATORY OF NEUROBIOLOGY AND GENETICS / THE ROCKEFELLER UNIVERSITY

Erin Norris (left) and graduate student Anna Amelianchik.

MARIO MORGADO

"Just as treating multiple disease mechanisms in cancer has improved outcomes, a similar evolution of therapy can be envisaged for Alzheimer's."

expands the number of possible therapeutic targets and invigorates the search for new drugs. "Just as treating multiple disease mechanisms in cancer has improved outcomes, a similar evolution of therapy can be envisaged for Alzheimer's," Strickland says. He and his team are currently looking at antibodies that could inhibit the interaction of fibrinogen and amyloid-beta in the brain.

Strickland's research could also contribute to new methods for diagnosing Alzheimer's sooner—such as testing patients experiencing cognitive impairment for vascular abnormalities and inflammation—and new ways to track its progression. Multiple studies already have shown that high levels of fibrinogen in plasma increase the risk of dementia, and the protein was recently established as a biomarker for Alzheimer's.

The disease has so far managed to resist all efforts to disrupt its lethal course, and Strickland may or may not find success where so many others have failed. Whatever happens, he has already succeeded at broadening the scope of Alzheimer's research and changing the way we think about this maddeningly complex disease. That's a breakthrough by any measure. ◎

SCIENCE GADGET

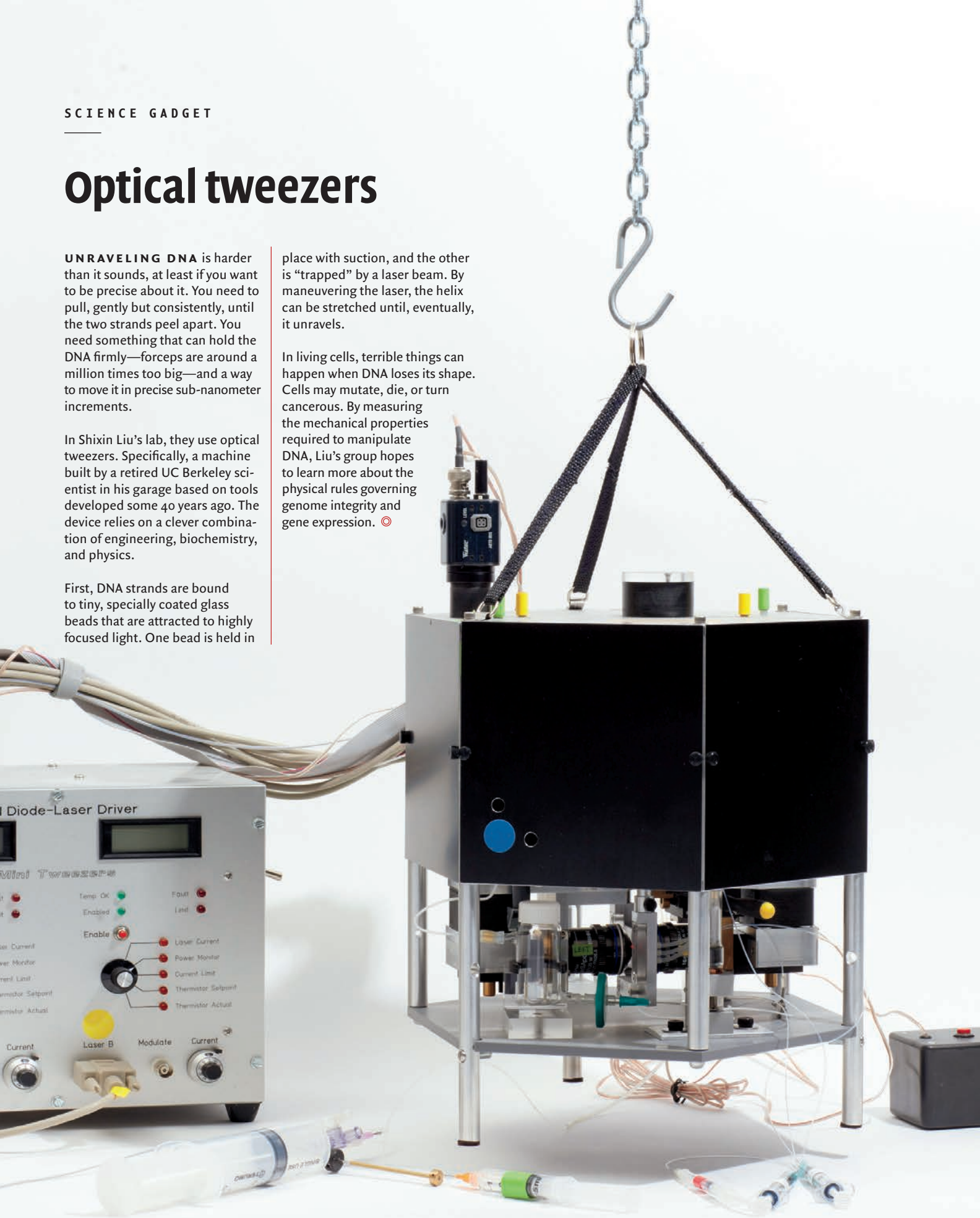
Optical tweezers

UNRAVELING DNA is harder than it sounds, at least if you want to be precise about it. You need to pull, gently but consistently, until the two strands peel apart. You need something that can hold the DNA firmly—forceps are around a million times too big—and a way to move it in precise sub-nanometer increments.

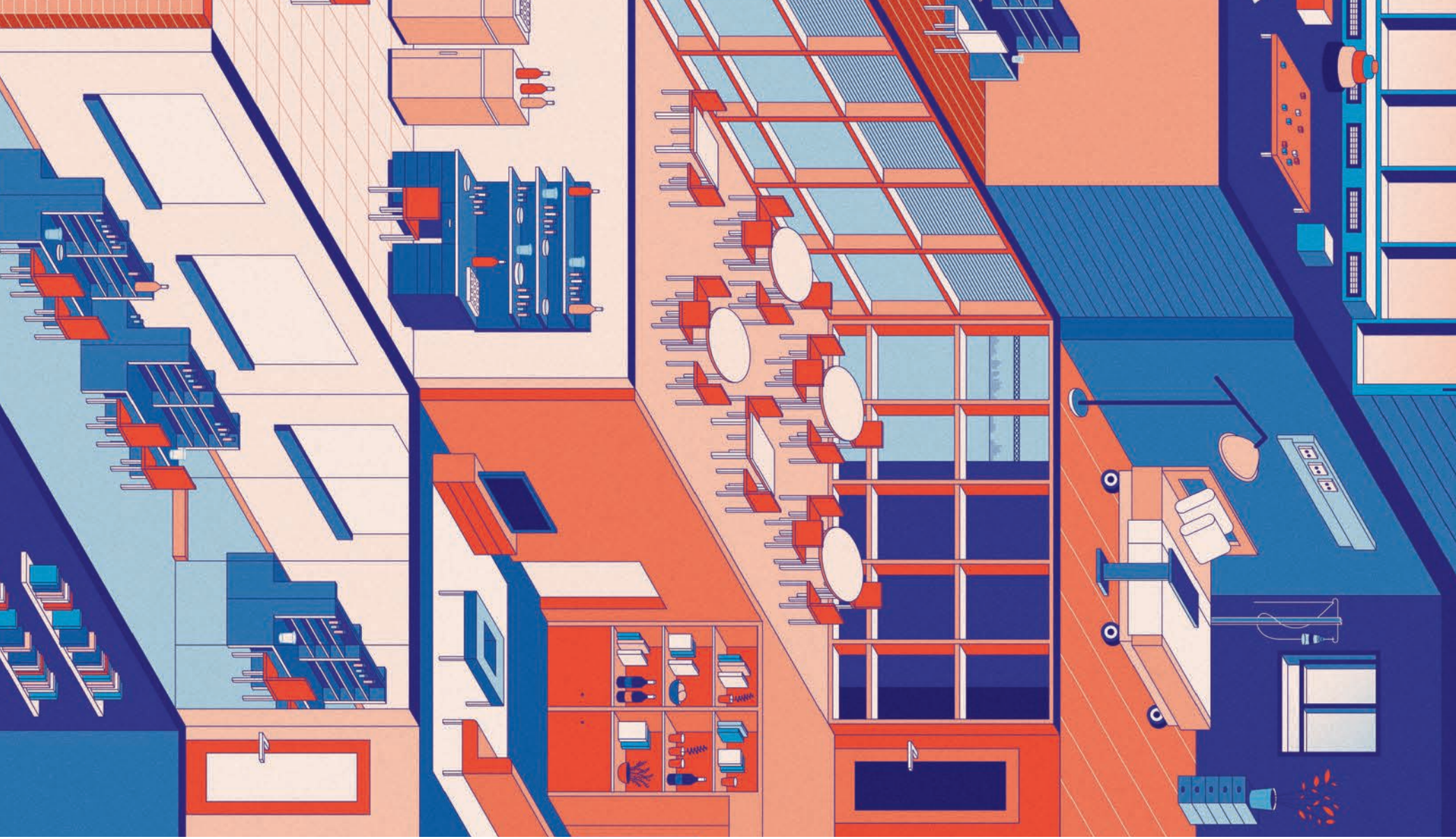
In Shixin Liu's lab, they use optical tweezers. Specifically, a machine built by a retired UC Berkeley scientist in his garage based on tools developed some 40 years ago. The device relies on a clever combination of engineering, biochemistry, and physics.

First, DNA strands are bound to tiny, specially coated glass beads that are attracted to highly focused light. One bead is held in place with suction, and the other is "trapped" by a laser beam. By maneuvering the laser, the helix can be stretched until, eventually, it unravels.

In living cells, terrible things can happen when DNA loses its shape. Cells may mutate, die, or turn cancerous. By measuring the mechanical properties required to manipulate DNA, Liu's group hopes to learn more about the physical rules governing genome integrity and gene expression.



Photograph by Matthew Septimus



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