ISSUE 04
SPRING 2019

Seek

THE ROCKEFELLER UNIVERSITY

Small brains, big decisions

What flies, worms, and ants can teach us about choice

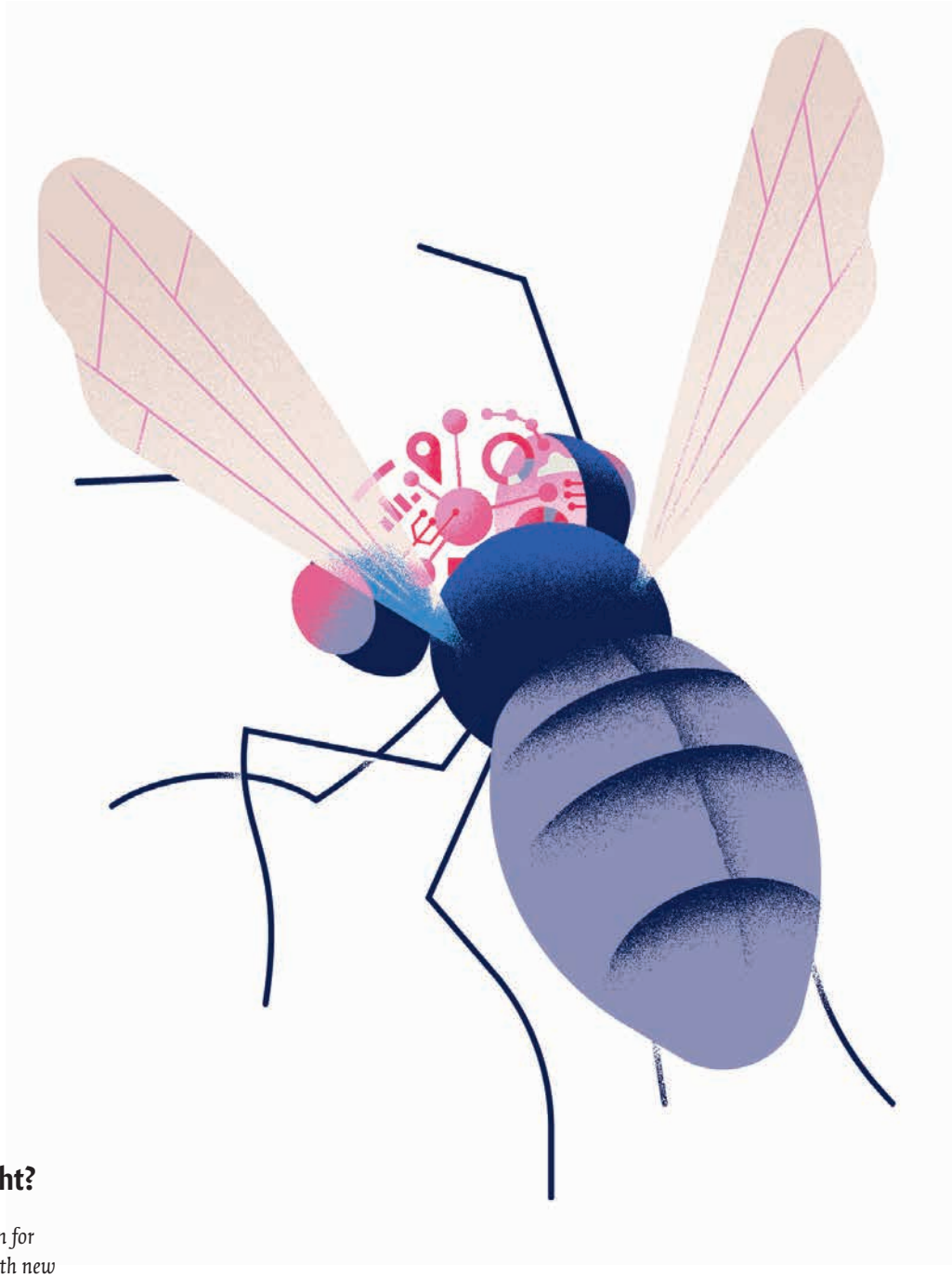
ALSO

Rare diseases, reappreciated

Embryos, ethics, and responsibility

TB's comeback

“Human brains and human motivations are enormously complex. So maybe you reduce the system a little.”



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Stay or go? Left or right?

Life is full of binary choices, even for small animals like fruit flies. With new technologies, scientists can now dissect the mechanisms of decision making in the simplest of brains, at the levels of individual molecules, cells, and networks.

Illustrations by Michele Marconi

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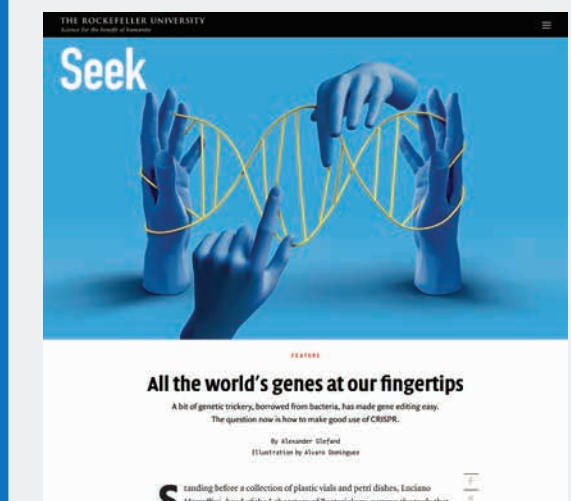

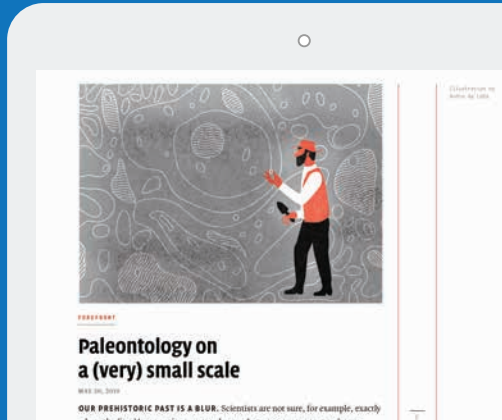

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Why rare diseases are everyone's problem

More than 7,000 medical conditions are considered rare. Many might be low-hanging fruit for scientific discovery, ready to help advance all of medicine.

"You talk with patients about their disease, and your gut tells you that you don't have the full picture. Something's lurking that you don't understand."

Illustration by Carmen Segovia

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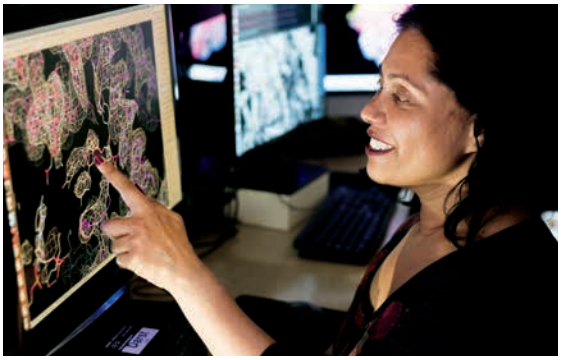
The future of TB is TBD

Deadly and elusive, M. tuberculosis *has ravaged the world for centuries. Armed with new technologies to study the pathogen, scientists may finally be poised to intervene.*



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Interview: Ali H. Brivanlou

With science constantly advancing, ethical boundaries need regular recalibration. It's a task scientists cannot do alone, says Brivanlou; all of society needs to engage.

"Darwin's idea is conventional wisdom for biologists. Mathematicians are still figuring out how to handle it."

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Becoming a scientist

Memories are inherently shifty. A neuroscientist with a new lab of her own, Priya Rajasethupathy likens the brain's memory function to Wikipedia—always evolving, occasionally unreliable.

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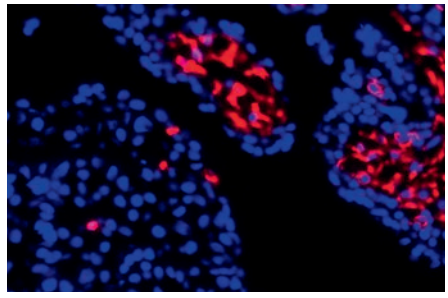
Scientists have drawn **the first map of the human placenta,** found new clues to understanding autism, and studied geckos with an eye toward robotics. Find out what else they've been up to.



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LEFT TO RIGHT: MARIO MORGADO; FRANK VERONSKY; FRANK VERONSKY; LABORATORY OF RNA MOLECULAR BIOLOGY / THE ROCKEFELLER UNIVERSITY

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OPPOSITE PAGE: THE ROCKEFELLER UNIVERSITY / LABORATORY OF MOLECULAR BIOLOGY

Brain botany There are billions of cells in the human brain whose special features scientists are just beginning to understand. In other words, it's a jungle in there. Xiao Xu, Elitsa Stoyanova, and Maria Moya obtained this image of the human cerebellar cortex with antibodies marking two species of brain cell: Purkinje cells (green) and granule cells (red). The three are graduate fellows in the lab of Nathaniel Heintz and are working on a new method to isolate specific classes of neurons, especially those related to neurodegenerative disease.

Reported by Lori Chertoff, Katherine Fenz, Eva Kiesler, Caitlin Shure, and Zachary Veilleux.

FOREFRONT

REWIRING

Learning to see the world differently

PERSONAL GROWTH BEGETS neuron growth. As you learn a language or learn to hang-glide, for instance, brain cells sprout new appendages, known as axons, that send signals to other cells. Researchers have long been aware of the brain's capacity to reconfigure itself, but it is less clear how this quality, known as plasticity, supports various aspects of learning.

In teaching macaque monkeys new visual skills, Charles D. Gilbert and his colleagues were able to study how axons grow during perceptual learning, a process that tunes the brain to more adeptly detect certain sights, smells, or sounds. The researchers showed the monkeys busy patterns within which, with a trained eye, lines could be traced. As the

Illustration by Angie Wang

DATA

Animals have some plasticity; plants have a lot. Being able to change in response to your environment is especially beneficial if you're rooted to the ground, hence unable to escape it.

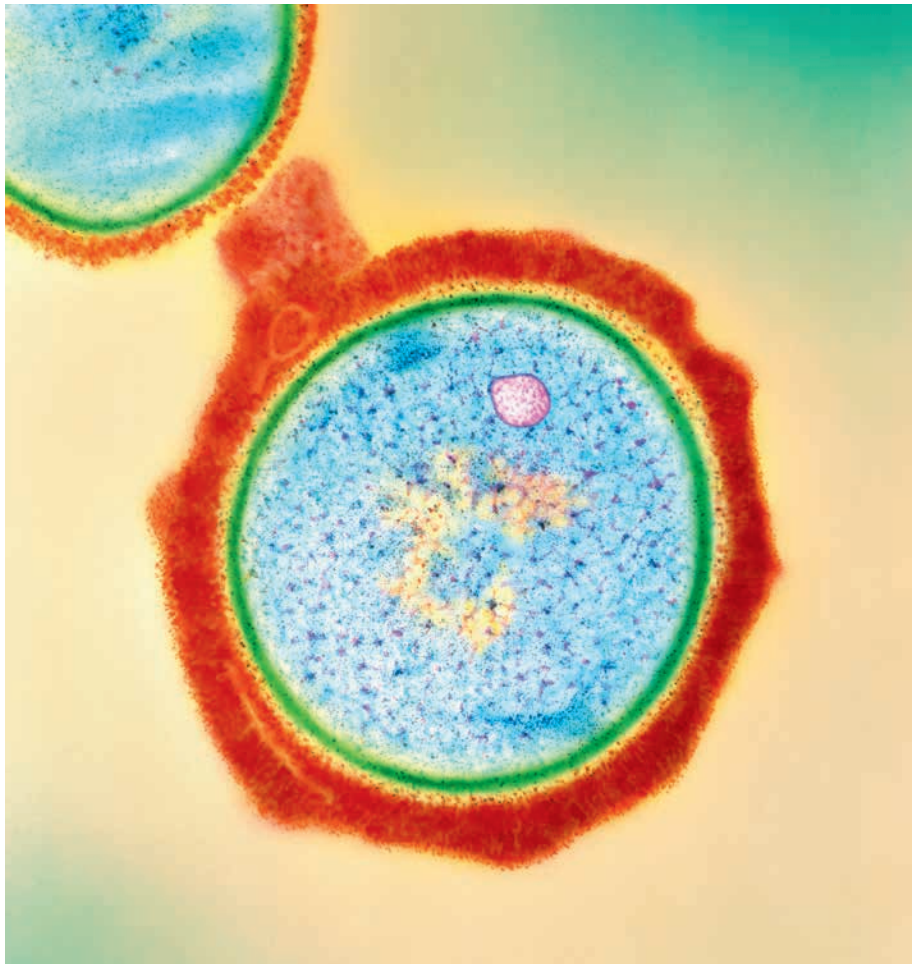
monkeys got better at spotting the lines, the researchers found, their neurons grew fresh axons in the visual cortex, a brain area that processes signals received from the eye. This experiment, described in *Proceedings of the National Academy of Sciences*, offers a fresh look at the precise manner in which experiences change how the brain perceives and responds to the environment.

"We've always known the brain needs some degree of plasticity through adulthood," says Gilbert, the *Arthur and Janet Ross Professor*, "but it turns out that plasticity is more widespread than we initially thought." ◎

DR KARI LOUNATMAA / SCIENCE PHOTO LIBRARY

DRUG INCUBATOR

More than one way to kill a microbe



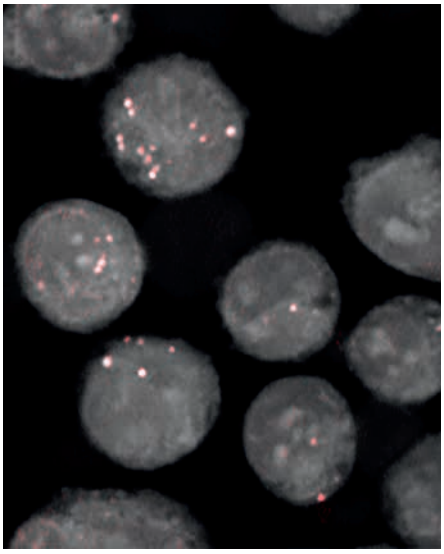
A new drug kills antibiotic-resistant bacteria by destroying their cell walls (green).

It's not just humans that kill bacteria. For bacteriophages, a type of virus, microbe murder is central to survival. In nature, these viruses invade bacteria, replicate inside of them, and then liberate their progeny through the release of lysins, enzymes that dissolve the bacteria's cell walls.

Vincent A. Fischetti has spent the past 20 years studying the bacteria-bursting properties of lysins. His work has long yielded promising results in animal experiments, and now an early clinical trial suggests that this type of treatment could also work in humans.

Sponsored by the biotech company ContraFect, the phase II trial involved patients with methicillin-resistant *Staphylococcus aureus*, or MRSA, a common hospital infection that doesn't respond to conventional antibiotics. The researchers found that, among people whose infection had spread to the blood, the response rate to treatment was 40 percent higher when a lysin-based drug called exebacase was given together with antibiotics, compared to when antibiotics were administered alone.

These findings bring new hope to researchers and clinicians seeking a different way to combat bacterial infections. "Bacteria are growing more and more resistant to antibiotics," says Fischetti, "and we're showing that there are other ways to fight them." ◎



CELLULAR NUTRITION

When cancer cells cut corners, it can be their downfall

CANCER CELLS ARE, by definition, abnormal. But some are odd even by cancer's standards. There are, for instance, those that fail to produce vital nutrients.

Cells that cause a rare form of lymphoma, called ALK-positive ALCL, have forfeited the ability to make their own cholesterol in order to focus on more grandiose tasks, such as wreaking havoc on the body. They compensate for their metabolic deficiency by stealing nutrients from the surrounding environment. For Kivanç Birsoy, the *Chapman Perelman Assistant Professor*, it's a vulnerability that might offer an alternative way to treat the disease, which can grow resistant to chemotherapy.

In research reported in *Nature*, Birsoy's team created a line of ALCL cells lacking receptors for cholesterol uptake to see how they would cope without access to the nutrient. The cells died almost immediately.

"We think therapies that block uptake of cholesterol might be particularly effective against chemotherapy-resistant forms of ALCL," says Birsoy, "and they might be useful for some other cancer types as well." ◎

DATA

5 days

The time it usually takes for a fertilized human egg to become a clump of differentiating cells, called a blastocyst.

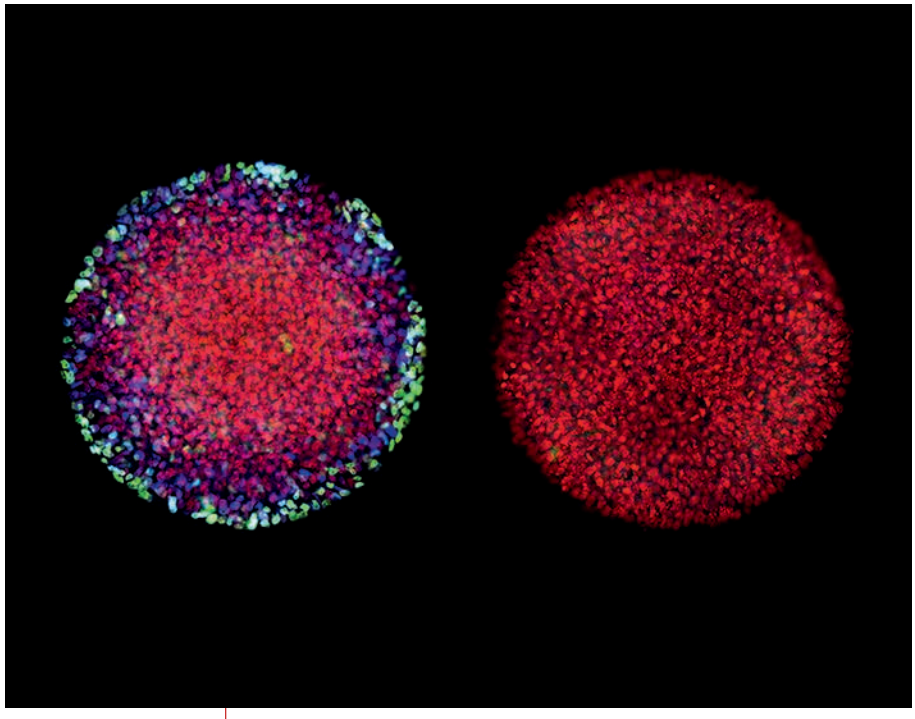
IN DEVELOPMENT

Embryo cells live and learn

NEW RESEARCH SUGGESTS that we are—quite literally—shaped by our earliest life experiences. For the past 25 years, scientists have believed that when cells in the embryo begin to specialize into gut cells, brain cells, or other cell types, they are obeying the instruction of a single signaling protein called activin. Recently, however, graduate fellow Anna Yoney realized things are not quite this simple.

In a new study, published in *eLife*, Yoney, along with Eric D. Siggia and Ali H. Brivanlou, found that activin does set off the specialization process, known as differentiation, but only in embryo cells with particular past experiences. Working with artificial human embryos, the researchers found that cells differentiated only if they were exposed to a different chemical, WNT, before being exposed to activin—a phenomenon the researchers termed "signaling memory."

Until now, scientists failed to notice the role of WNT because, says Yoney, most developmental biologists work with animal cells.



Embryo cells on the right are unable to diversify because they haven't received the right signals.

"Scientists had been watching activin induce differentiation for decades—in mouse cells, frog cells, and in other model organisms," Yoney says. "But the problem with animal cells is that they've already encountered a number of cellular signals. Our artificial embryos hadn't had that kind of exposure." (Read more about embryo research in "Science, society, right and wrong," page 42.) ◎

THE ROCKEFELLER UNIVERSITY / LABORATORY OF METABOLIC REGULATION AND GENETICS (TOP), LABORATORY OF THEORETICAL CONDENSED MATTER PHYSICS (BOTTOM)

To speed across ponds without sinking, geckos rely on buoyancy, movement, and their skin's ability to repel water.

30%

The portion of a cell's outer membrane made of cholesterol. The substance keeps the membrane durable without being rigid, allowing the cell to move and flex without breaking.

PAULINE JENNINGS

ANIMAL KINGDOM

The aquatic superpowers of geckos

Swimming is a great way to get around—unless someone is chasing you. For those situations, some water animals employ special techniques to skedaddle.

GECKOS SHOULDN'T BE able to walk on water. Outside the realm of biblical miracles, water walking is typically reserved for two types of animal: those small enough to balance on water's surface tension, and those large enough to hoist themselves above the water through sheer force. A comfortably midsize animal, the gecko doesn't fall into either of these categories.

And yet Jasmine Nirody found herself watching a video of a gecko that seemed to be easily traipsing across water. A Rockefeller fellow in physics and biology, she immediately began investigating this spectacle.

Working with colleagues at the University of California, Berkeley, Nirody found that, like bigger lizards, geckos use a slapping motion to pull their bodies above water. And, like spiders, they take advantage of water's surface tension. In other words, they combine techniques from opposite ends of the size spectrum to stay afloat. Further, the scientists discovered that geckos have a feature all of their own that contributes to their aquatic agility.

"Geckos have this amazing superhydrophobic skin that repels water and enhances their ability to stay above the surface," says Nirody.

In addition to elevating our respect for reptiles, this research could be used to create tools with real-world applications. "Our work with animal locomotion is geared toward use in robotics," says Nirody. "And an intermediate-sized water-running robot, for example, would be ideal for searching flooded areas after a natural disaster." ◎

EDUCATION

Online recipes for classroom science

AT BARD HIGH SCHOOL EARLY COLLEGE QUEENS science educator Stephanie Kadison (center) is always seeking fresh ways to engage her students. Along with other New York City teachers, Kadison recently collaborated with Rockefeller's Science Outreach program to help develop a new online resource available to learners, educators, and scientists everywhere.

The website, RockEDU Online, features a versatile portfolio of science education materials supporting both teachers looking to enhance their classroom routine and scientists who want to engage with schools in their community.

Find it on **rockedu.rockefeller.edu.**

MARIO MORGADO

BRAIN SCAN

Cellular "trafficker" linked to autism

Mary E. Hatten

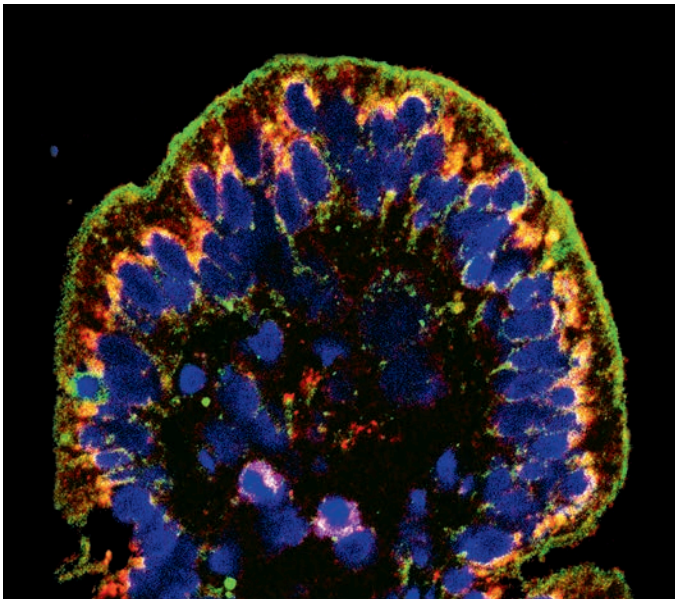
THINGS CAN GET A BIT hectic at synapses, the junctions where neurons connect. To manage an onslaught of incoming chemical signals, nerve cells must perpetually remove old receptors from their surface to make room for new ones, a process facilitated by molecules called protein traffickers.

When these proteins fail to do their job, the ensuing synaptic mess may negatively impact the brain's development. Recently, Rockefeller's Mary E. Hatten, the *Frederick P. Rose Professor*, and collaborators at Johns Hopkins University were able to illuminate the process by which defects in a trafficker known as ASTN2 may lead to autism and other neurodevelopmental conditions.

When studying the cerebellum region of mouse brains, the researchers found reasons to suspect that low levels of the protein might lead to weak neural connectivity and atypical brain function. Supporting this notion, the scientists identified a family in which three children carried ASTN2 mutations and additionally suffered from neurodevelopmental issues including autism and language delays. These findings, published in *Proceedings of the National Academy of Sciences*, are consistent with recent data from population studies linking ASTN2 mutations to a variety of brain disorders. ◎

DIGESTION

How to patch up an ailing intestine (quite literally)



PEOPLE WITH CROHN'S DISEASE and ulcerative colitis have a lot in common. For starters, they share a range of symptoms, such as stomach pain, diarrhea, vomiting, and weight loss. Their treatment tends to involve taking anti-inflammatory drugs. And they have similar reasons to be rather unhappy with those anti-inflammatories: the drugs often don't work very well and come with unpleasant side effects.

Now there is hope for a better treatment, based on yet another common denominator of the two diseases: intestinal leakiness. Both Crohn's disease and ulcerative colitis stem from weakness in a thin cell layer that lines the intestine. When this lining becomes porous, bacteria seep into the surrounding tissues and bowel inflammation ensues.

Research associate W. Vallen Graham thought there might be a way to fix this underlying plumbing issue; and in a search for compounds that block MLCK, a protein believed to undermine intestinal-wall tautness, he recently discovered one that does the trick. Results from experiments with mice, reported in *Nature Medicine*, may point the way for future therapies that boost the effectiveness of anti-inflammatories by sealing intestinal leaks.

"This is exciting, because there's currently no drug that can remedy permeability of the intestine," says Graham, who began the research at Harvard Medical School and is continuing it in the lab of Rockefeller's Thomas P. Sakmar. ◎

MARIO MORGADO (TOP), THE ROCKEFELLER UNIVERSITY / LABORATORY OF CHEMICAL BIOLOGY AND SIGNAL TRANSDUCTION

LEGACY

When breakthroughs break off

"Discoveries are delicate things."

–Jeffrey M. Friedman in Harper's Magazine, November 2018.

THE WORLD HAS NEARLY forgotten Israel Kleiner. A late Rockefeller scientist active in the 1910s, Kleiner conducted pioneering research on diabetes and came close to discovering a lifesaving treatment. Close, but not close enough to bring his work to fruition or make a name for himself. World War I, and Kleiner's bosses, interfered with his hopes of finding a cure for the mysterious disease. At the time, diabetes was claiming thousands of lives, but the university's priorities lay elsewhere—on infectious diseases rampant among soldiers, for example.

It was only a decade later that other scientists, by building on Kleiner's work, were able to show that the hormone insulin could be used to lower patients' blood sugar levels. Kleiner, though, was out of luck, out of funding, and, eventually, out of a job.

Why should we remember the efforts of an obscure, century-old scientist? Because, argues Jeffrey M. Friedman, who chronicles Kleiner's destiny in his article "Discovery, Interrupted" in *Harper's Magazine*, the story of the late scientist's exile holds important lessons for today's society, where the value of open-ended research is being similarly challenged.

"Focusing too much on mainstream notions of what is important or useful carries the risk that the very discoveries that make translational research possible will never be made," writes Friedman, the *Marilyn M. Simpson Professor.* "It also presupposes that we know what will be important in the future," an idea for which little evidence exists. ◎

CHEMICAL KINSHIP

Research on TB returns to earth

HALF A CENTURY AGO, when the antibiotic rifamycin was discovered in soil from a French pine forest, it led to the most potent treatment for tuberculosis ever developed. Unfortunately, victory didn't last.

In recent years, the disease has made a crushing, antibiotic-resistant comeback. Amid scientists' scramble to develop alternative treatments, TB's fast-evolving pathogens are claiming millions of lives.

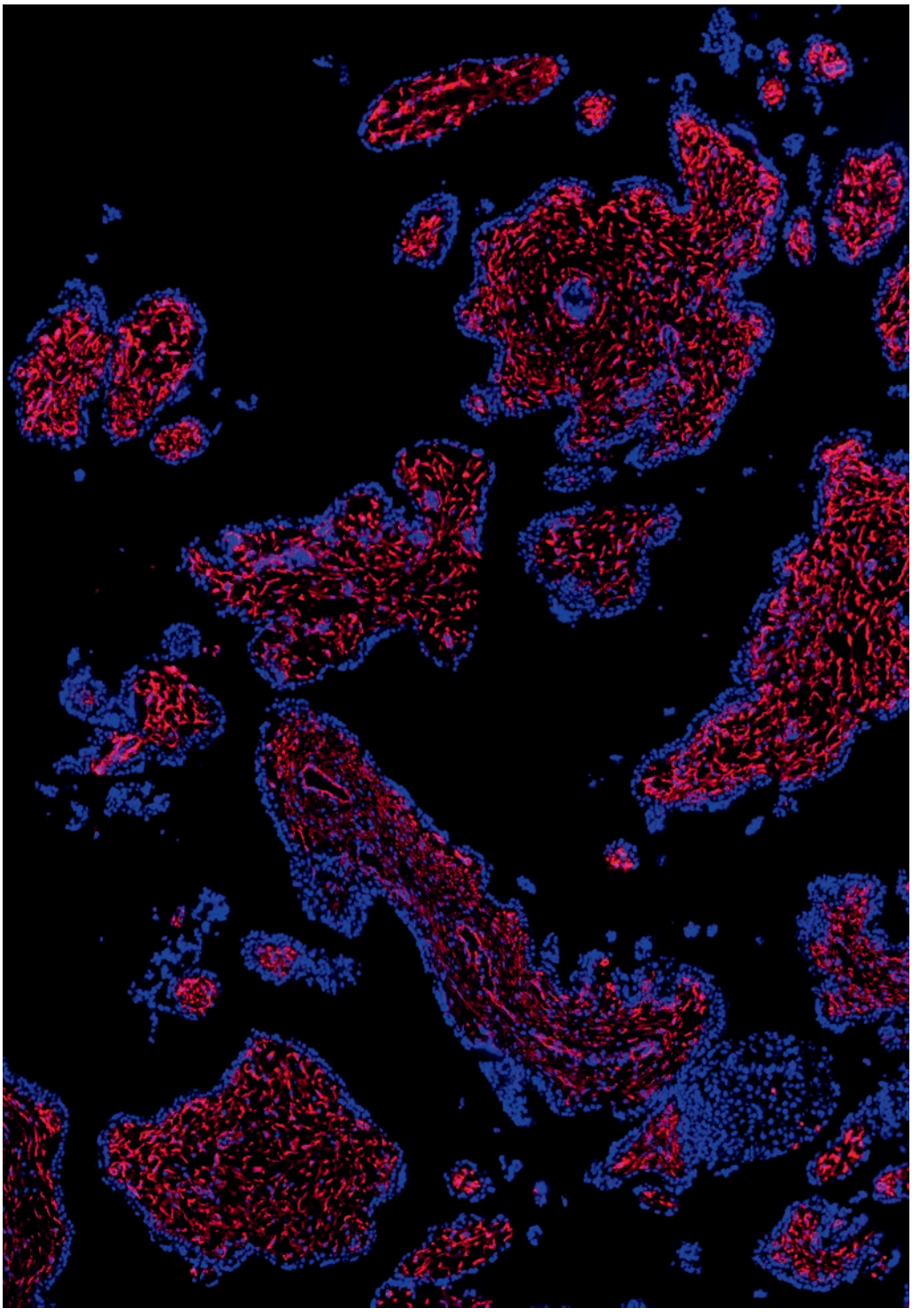
In looking for solutions, a team of Rockefeller scientists have gone back to the source from which rifamycin first emerged: Mother Nature.

"Rifamycin is naturally produced by a soil bacterium," says Sean F. Brady, the *Evnin Professor*, who led the work. "So we wanted to find out whether nature had also made analogs of the compound—molecules that look like rifamycin, but that have slight differences."

Sequencing the genes of microbes found in soil, Brady's lab identified a group of natural antibiotics, known as kanglemycins, or kangs, that are closely related to rifamycin. Further analysis revealed that these antibiotics have structural features that set them apart from their cousin, including an extra sugar and an extra acid.

These tiny differences allow kangs to effectively combat mycobacteria that don't respond to rifamycin. "We'd still like to see increased potency and broader activity against resistant bugs," says research associate professor Elizabeth Campbell, who was also involved in the study, "but our findings tell us that we're on the right track." (Learn more in "TB is changing," page 32.) ◎

JACOB PRITCHARD



LABORATORY OF RNA MOLECULAR BIOLOGY, THE ROCKEFELLER UNIVERSITY

CHILDCARE

A meticulous map of the human placenta

FEW OF THE BODY'S organs are as hard at work as the placenta during its first three months of service: It feeds and protects the fetus while supplying antibodies, hormones, and blood. Yet little is known about this earliest chapter in the mother-child relationship. Now, researchers have developed a new way to analyze the microscopic interactions between fetal and maternal cells.

Stromal and endothelial cells of the plancenta, in red.

DATA

By the end of pregnancy, the placenta filters up to three cups of blood per minute.

Thomas Tuschl and his colleagues recently performed an in-depth survey of human placental and decidual tissues, which contain cells from the fetus and mother, respectively. The researchers identified 20 distinct cell types, and, using a unique RNA-sequencing strategy, made inventories of genes associated with each type.

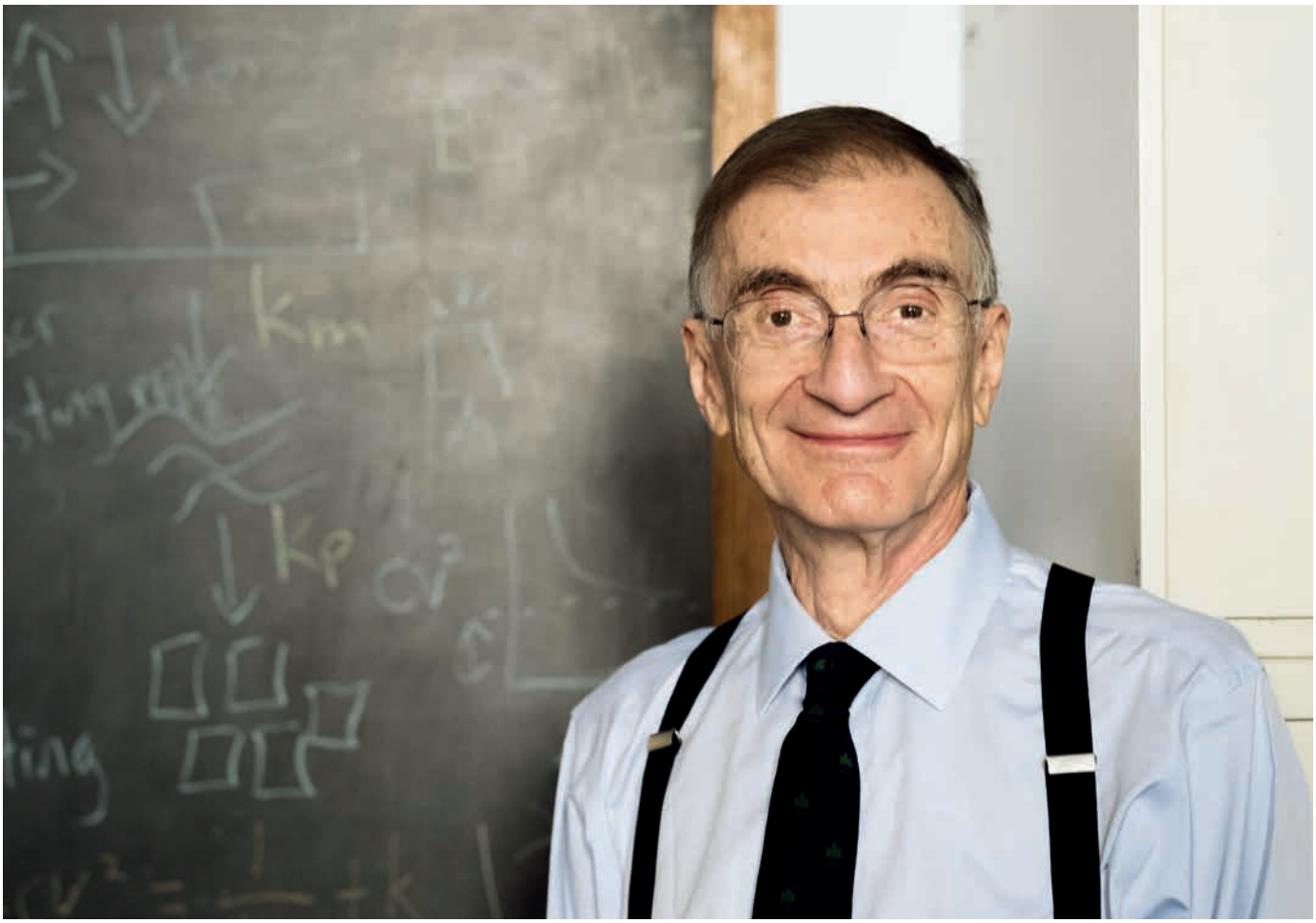
The end result, according to postdoc Hemant Suryawanshi, is the first "cellular atlas" of the early human placenta—a map that, among other things, will help scientists pinpoint causes of pregnancy complications.

"In pregnancy, there are dramatic changes both in cellular composition and at the molecular level," says Suryawanshi, who together with his colleagues reported these findings in *Science Advances*. "Now, for the first time, we have high-resolution pictures of those changes." ◎

Q&A

Math for future millennia

With Joel E. Cohen



MARIO MORGADO

BEFORE CHARLES DARWIN, biology was simple. A horse was a horse, and scientists didn't care much about differences among horses. The concepts of living populations, and the diversity of individuals within them, were not in vogue.

"People just didn't think in those terms," says Joel E. Cohen, a mathematical biologist who has spent more than five decades developing new ways to study populations. "Biological variability was usually regarded as irrelevant noise."

But the alleged noise was highly relevant to Darwin and some of his contemporaries. Variability, they argued, is the raw material of evolution and occurs among all living things. This idea profoundly changed our view of the world and is conventional wisdom for today's biologists. Mathematicians, on the other hand, are still figuring out how to handle it.

Cohen has found beauty at the crossroads of biology and math.

"New biology demands new mathematics," says Cohen, the *Abby Rockefeller Mauzé Professor*. "The tools we use today to deal with population variability are still blunt." Cohen's work focuses on creating better tools, which he hopes will help generate new ways to understand diversity—and potentially take science in directions we cannot yet envision.

We asked Cohen to tell us more.

What is it about diversity that traditional math cannot cope with?

Populations sometimes have strange properties. Imagine, for example, that you measure the heights of 10 people and calculate the average. Then you repeat the experiment with a hundred people, a thousand people, and so on.

Traditionally, we'd expect that as we include more people, our calculated averages will converge to a single number—and for height, this does happen. But for certain other things—like hospital discharge bills, flood insurance claims, and other things people care about—it turns out that the more we increase our sample size, the bigger our chances of including an extremely large value that will yank the average dramatically upward.

Consider extreme weather events, for example. In 2005, the year of Hurricane Katrina, damages from this and other billion-dollar weather events cost a record-high $215 billion. Some people in the insurance industry considered that year a fluke, but they were wrong. In 2017, we had Hurricanes Harvey, Irma, and Maria, and all of a sudden, the record cost jumped to $306 billion.

Traditional statistical approaches sometimes miss the boat by discarding extreme events as outliers. Colleagues at Columbia University and I are pursuing new tools to understand so-called heavy-tailed laws that describe situations when, as was the case with the hurricanes, averages of the past don't predict the future. Part of the challenge is to figure out when and why nature sometimes gives us height-like variations, and other times hurricane-like variations.

So how might biology benefit from this new math?

In the same way biology benefits from any new tool: by seeing things we haven't seen before.

I like to think of the arrival of the microscope. Out of the blue, it revealed the presence of cells, microbes, and other things invisible to the naked eye—things whose existence people hadn't imagined before. Mathematics is biology's next microscope, only better; it can reveal hidden realities both in optics and in other kinds of data. For example, computational tools to compare genetic sequences—which to a large degree are based on algorithms developed by the late Rockefeller mathematician Peter H. Sellers—have transformed our ability to study the genetics of health and disease.

"Most biologists don't give much thought to the fact that many of their most routine scientific tools derive from the brilliance of some dead mathematician."

Most biologists don't give much thought to the fact that many of their most routine scientific tools derive from the brilliance of some dead mathematician. Every time you put data on an x-y plot, you're using an innovation that was revolutionary in the seventeenth century: Descartes added a system of x-y coordinates and numbers onto Euclid's serene plane, creating a virtual microscope for numerical relationships.

I'm betting on the hope that new mathematical models, including heavy-tailed laws, will be similarly fundamental for future life scientists. Today we're mainly using them to study humans, animals, and plants. We're asking, for example, if these tools can change the way we think about epidemics, or what they might teach us about preparing for an Ebola outbreak. In the future, however, they may become just as relevant in the study of cells and molecules.

DATA

Humanity is on the move. An estimated one billion people are presently migrating, and about one-fourth of them are moving to different countries.

So if math is stimulating biology, is biology also stimulating math?

Absolutely, and this is something I experience in my own work. In fact, wanting to solve practical problems—biological or humanitarian ones, or preferably both at the same time—is my main motivation for building mathematical tools in the first place. I'm especially interested in infectious diseases and access to food in poor countries. I also work on human migration and mortality, and how humans affect our environment and vice versa.

For example, my work on heavy-tailed laws arose out of research I'm pursuing with colleagues in Argentina on Chagas disease, a devastating infection that afflicts millions of people, mainly in rural villages of Latin America. We began working on these math tools in the course of studying the insect populations that spread Chagas, and our results have led to affordable, low-tech strategies to limit the spread of the disease by improved bug surveillance and control.

In other work, my colleagues and I have developed algorithms to predict the international migration of peoples, an area of major uncertainty in demographics. Techniques for analyzing the past and projecting the future of migrations, births, and deaths provide crucial foundations for everything from public health policy to climate science.

Maybe the most fun part of our work is when we're trying to solve a problem and realize that it contains a new question that mathematicians haven't yet answered. For me, population biology is the greatest inspiration to explore untapped areas of mathematics—with the hope of maybe proving something new, beautiful, and scientifically useful. ◎

1 The **Bass Dining Commons**, a café with indoor and outdoor seating and sweeping East River views, replaces the university's 1971 lunchroom.

2 Two laboratory floors are each 750 feet long. Horizontally-oriented lab buildings are good for science because they help spur informal collaboration: When people work on the same floor, they are more likely to work together.

3 A huge landscaped roof brings the Rockefeller campus all the way to the water. The outdoor space also features a two-level amphitheater carved out of the western façade.

4

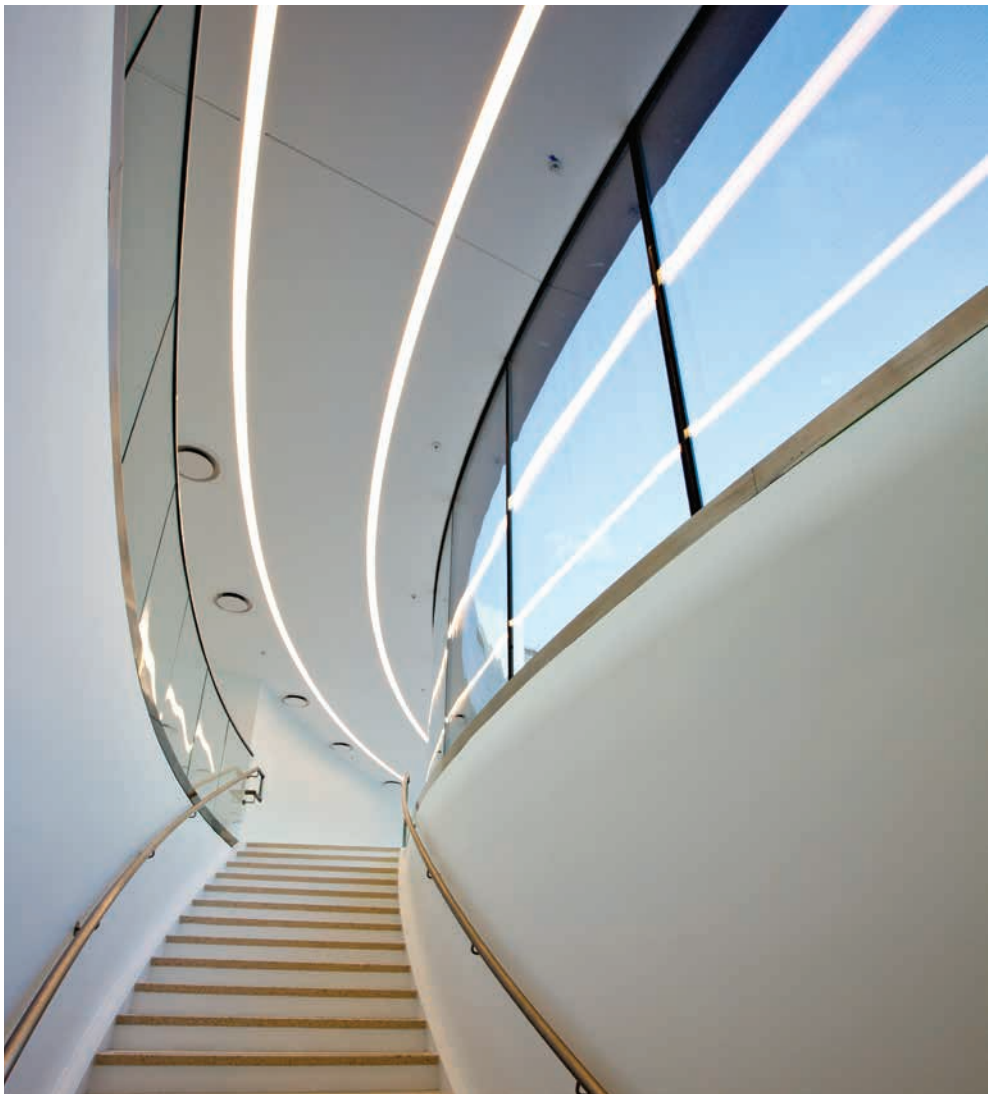
At the water's edge, the public **East River Esplanade** has been repaired and refurbished, with new pavers, benches, lights, and landscaping. Vehicle traffic flows by behind the sound barrier.

5

The **Hess Academic Center** provides spacious new executive offices and two mid-sized conference rooms.

6

A conference facility for up to 100 guests, the **Kellen BioLink**, hosts retreats and small symposia. Sliding glass walls open onto the **Fascitelli Great Lawn**.



8 Graceful curves define common areas and wide stairs encourage walking.

Interior photographs by John Abbott

7 Lab benches receive natural light from floor-to-ceiling windows. Desks and offices are along the east wall, with views of the river.

The new River Campus, unveiled

THE VIEWS UP AND DOWN the East River are inspiring. The breeze, slightly salty, is a pleasure. But standing atop Rockefeller's new campus extension, the most remarkable thing is what you don't see, don't hear, and don't smell: a six-lane urban highway choked with over 100,000 vehicles a day. It's gone without a trace, expertly buried underneath two acres of landscaped green space.

The disappearance of the roadway that has formed Rockefeller's eastern border since the 1940s is just one of the benefits of building over the FDR Drive. More importantly, by siting new construction in the Drive's unused air rights, it is possible to construct a lab building with a unique shape—long and low—that would not otherwise be possible in a dense urban environment.

This is the Stavros Niarchos Foundation–David Rockefeller River Campus, a two-acre parcel of artificial land, and the Marie-Josée and Henry R. Kravis Research Building, a lab building suspended in midair. Nearly four blocks long, the Kravis Building is just two stories high, making it well-suited to the need of modern collaborative science. It's the new home of 18 Rockefeller labs, with space for five more.

The building's landscaped rooftop—accessible both from within the Kravis Building and from the existing campus via two sets of low-slung exterior stairs—is the center of the expanded campus. With ample riverside seating and pleasant landscaping, it's an amenity in and of itself.

"This project is transformational," says Richard P. Lifton, Rockefeller's president. "It is yielding spectacular laboratory space that will house a third of our faculty, a rooftop dining hall, administrative building, and gardens, that all provide beautiful vistas overlooking the East River. The next generation of great scientists will make their key discoveries here."

And underneath it all, the city traffic crawls imperceptibly along. ◎

Photographs by Halkin Mason Photography

Our understanding of memory is being overwritten. Meet the neuroscientist whose new lab is rethinking how our brains handle the past.

Priya Rajasethupathy

By Alexander Gelfand

Ask Priya Rajasethupathy how she came to science, and the memories come flooding back. She recalls a youthful fondness for chemistry and biology. She talks about community service, tutoring elementary school students. She describes how her father emphasized engineering—the best path toward developing quantitative thinking and job security, he believed—and how as a result she took a lot of math and computer science. She speaks of the intellectual thrill she had in her first college lab, and of the influence of her graduate and postdoc mentors.

And then she drops a bomb: you shouldn't necessarily believe her. The next time you ask, her memories could be entirely different.

Rajasethupathy's memories, like all memories, are malleable and subject to constant revision. As a neuroscientist who is dedicating her career to understanding how memories are recorded, stored, and retrieved in the brain, Rajasethupathy knows this better than most. And she knows why memories are so hard to pin down: To remember things, we rely on a series of biological processes that are constantly writing, retrieving, and rewriting our recollections, shifting them between neurons and passing them back and forth from one area of the brain to another.

"There's an old model of memory in which a discrete experience is plucked from a fixed spot in the brain's filing system when it's needed," Rajasethupathy says. "And there's a newer one that suggests a far more dynamic decision-making process. We now see vast numbers of interacting neurons, spread across various brain regions, accumulating evidence and feeding each other bits of information before ultimately arriving at a remembrance—there's a thought process you go through."

Her research has shown that while a specific memory may seem stable, the assemblage of neurons and circuits that conjures it is in fact constantly changing and evolving. According to this model, every time you remember something, you are giving your brain the opportunity to make refinements. In other words, the memory process is less like the Encyclopedia Britannica and more like Wikipedia: constantly evolving and full of facts whose accuracy comes with no guarantees.

Rajasethupathy's journey from aspiring engineer to physician to neuroscientist—as her brain presently portrays it—is in many ways a traditional one. She went to good schools, got good grades, made connections, followed her instincts, and had good luck along the way. From her days as a public school student in upstate New York to her studies at Cornell, Columbia, Stanford, and finally to her current job at Rockefeller, where she runs her own laboratory, Rajasethupathy has succeeded in a notoriously competitive field.

As a teenager, Rajasethupathy spent most of her free time volunteering: she tutored elementary school students in her hometown of Brockport, a village on the Erie Canal; worked at soup kitchens in inner-city Rochester, 20 miles away; and visited patients in hospitals.

"My whole life was really about working with people," she says.

As an undergraduate, however, Rajasethupathy became drawn to biological entities of a much smaller variety. For her thesis, she set about trying to identify aptamers—short stretches of DNA or RNA—that may provide clues toward

Photographs by Frank Veronsky

therapeutic compounds for epilepsy. She was soon consumed by the task, which combined the intellectual thrill of basic science with the prospect of improving the lives of actual patients.

Then, after leaving Cornell, and before pursuing her M.D., Rajasethupathy spent a year working on computational models of memory at the National Center for Biological Science in Bangalore, India, some five hours northeast of the village where her father had grown up. Here, she identified similarities between biochemical and transistor-based switches, suggesting how individual neurons and synapses store information.

The project allowed her to take full advantage of her early training in computer science, and it marked a turning point in her life: Though she still spent her free time doing community service and exploring the clinical side of neuropsychiatric disease, she found her attention turning ever more toward research.

Memory doesn't operate in isolation; rather, it is closely tied to other aspects of cognition such as motivation and attention (try memorizing a phone number without focusing on it). As a result, you can't really understand one without understanding the others. Exploring the basis of memory may also help elucidate the underlying causes of complex neurodegenerative and neuropsychiatric conditions, such as Alzheimer's disease and attention deficit hyperactivity disorder, in which attention, emotion, working memory, and executive function are strongly intertwined.

And this understanding, in turn, could yield novel treatments for them.

Rajasethupathy's work in Bangalore did not address any particular disease, or even answer any questions about how memory works. But it did raise some new ones.

Having just finished a highly theoretical computational project, for her Ph.D. work at Columbia, Rajasethupathy decided to dive into the nitty-gritty of how memory works at the molecular level. To do so, she needed sea slugs.

The discovery that brain regions work together to store and retrieve memories would become the basis for her new lab.

As it turns out, slugs from the genus *Aplysia* are the perfect creatures for this type of work. Each has just 20,000 neurons in its brain, visible to the naked eye and conveniently clustered in 10 well-defined regions. Rajasethupathy embarked on a project to find out how information is stored in individual synapses—asking how, in effect, the fleeting chemical signals that one neuron transmits to another can be inscribed in memory for a lifetime. Working with her Columbia mentor, Nobel laureate Eric Kandel, as well as with Rockefeller's Thomas Tuschl, she discovered that a special kind of RNA molecule can migrate from a synapse to the nucleus of a neuron, permanently altering its DNA. The finding hinted at more permanent mechanisms for memory inscription.

At Stanford, Rajasethupathy traded slugs for mice in order to conduct behavioral experiments. How, she asked, does memory emerge from the interactions between different parts of a complex mammalian brain? By training mice to navigate virtual reality environments in which different rooms contained either rewards (a bit of sugar water) or threats (a sudden blast of air), and imaging their brains during their behavior, Rajasethupathy was able to trace the activity of clusters of cells in different brain regions as the animals created, stored, and retrieved memories.

In so doing, she discovered a previously unknown connection between the hippocampus and the prefrontal cortex, a part of the brain responsible for higher cognitive functions such as decision making and analytical thinking. She further demonstrated that this newfound neural circuit plays an important role in memory retrieval. This discovery—that brain regions work together to store and retrieve memories—would become the basis for her new Rockefeller lab.

In the fall of 2015, Rajasethupathy was ready to strike out on her own—to build her own lab after more than a decade of working in others'. It's an enormously competitive undertaking: At Rockefeller she was one of 452 applicants.

Unlike many institutions, which conduct searches one at a time (a neuroscientist working on memory has just retired, so it's time to find a new one), Rockefeller conducts an annual open search in which applicants from any bioscientific specialty are invited to apply. The university-wide search committee chooses the most promising scientists regardless of field. Some years, no one makes the cut, and in other years, there may be as many as four or five. Dozens of faculty members participate in the process, representing all major areas of study.

In Rajasethupathy's case, there was little dissent.

"Her work was consistently innovative, even from the time she was a graduate student," says Charles D. Gilbert, the *Arthur and Janet Ross Professor*. "Beginning in her postdoctoral work, to the present day, she has applied cutting-edge techniques to study important problems in neural systems research."

Despite offers from other institutions, it was also an easy choice for Rajasethupathy, who was impressed by both the scientific excellence and the collegial and collaborative spirit on campus.

"You're seen as a real person here," she says. "At every level, you feel like people care about the decisions you make and what you're trying to do."

Letters were signed, boxes were packed. And on March 1, 2017, Rajasethupathy showed up in an empty Flexner Hall laboratory for her first day of work as an assistant professor.

Rajasethupathy with graduate student Nakul Yadav. Since starting her own lab, she has made mentorship a top priority.

THE THING THAT nobody tells you about starting a new laboratory is that it's nothing like starting a new job. It's more like building a new company. There are people to hire, students to recruit, budgets to manage, equipment to buy, supplies to order, and a million decisions to make. You're expected to be a manager, mentor, editor, technician, engineer, accountant—and also a scientist.

"You're completely ill-equipped to do this job when you start," Rajasethupathy says with a laugh. "You come to really appreciate the luxury that students and postdocs have to focus on their own projects and devote all their time to science." At Rockefeller, administrators offer much support, and there are helpful colleagues to provide advice, but the responsibility to convert a winning research proposal into a functioning laboratory still rests on the new recruit.

It didn't take long for Rajasethupathy to find her groove. Within a year, she had realized that the best part of the job is the very thing that got her started down this road in the first place: service to others.

"Number one on my list now is to mentor my students and get them to love and appreciate science," she says.

She has also recommitted herself to community service through the university's outreach programs: engaging with undergraduates, high school students, and even the kids in the university's Child and Family Center, where her children attend day care.

Her scientific priorities have evolved as well. In the past, Rajasethupathy focused largely on fundamental research. But increasing encounters with patients, donors, and those who have witnessed the impact of mental illness and brain disease—combined with the acknowledgment that taxpayers fund much of her research—have prompted her to think more about projects with significant medical applications.

Traditionally, neuroscience has relied on inbred or genetically engineered animals that lack the genetic variability of human populations. Rajasethupathy and her team are therefore using wild-derived strains of outbred mice to capture that variability. This allows them to observe the natural development of cognitive deficits associated with specific human disorders, including Alzheimer's and ADHD.

By analyzing the animals' genomes, Rajasethupathy and her collaborators at Cornell hope to identify novel genes and gene pathways, as well as the resulting neural-circuit features, that drive these cognitive traits. That, in turn, will lead to a better understanding of the molecular pathways and neural circuits involved in complex human diseases: pathways and circuits that could provide new avenues for treatment, whether through novel drugs that latch on to particular molecular targets or nonpharmacological therapies such as deep-brain stimulation that directly target the neural circuits.

DESCRIBING HER WORK to a standing-room-only crowd of Rockefeller scientists last December, Rajasethupathy discussed her finding that brain cells known as hub neurons recruit other neurons from different areas of the brain to help form and retrieve memories. This discovery hints at why memories are so stable and can be recalled so rapidly; but it also suggests that the high metabolic activity of these hub neurons, which serve adaptive and integrative functions for memory, may make them particularly vulnerable to destruction during neurodegenerative disease.

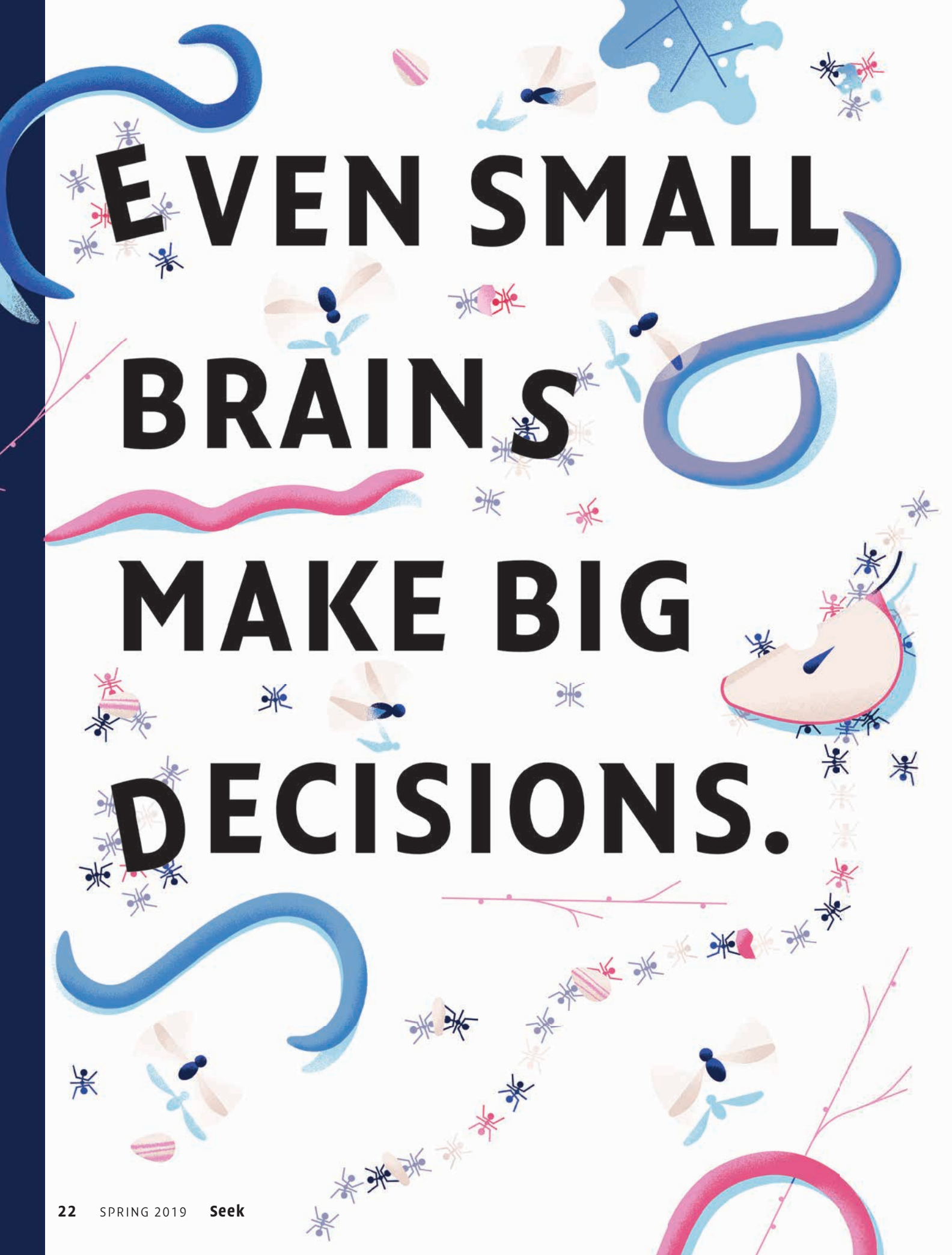
She also outlined her ongoing efforts to understand the give-and-take that occurs between the hippocampus and other brain regions, work that could in time provide insights into the physiological processes of forming and retaining long-term memories, and help explain how these processes sometimes go awry.

If she was nervous delivering her first, formal research update, it didn't show. On vivid display was not only her lab's recent data, laid out in striking multicolored slides, but also Rajasethupathy's unmistakable love of her work and infectious sense of humor. Her audience reciprocated, asking probing questions and volunteering helpful advice.

"Their support reminded me of how thankful and fortunate I am to be here," she says. "Joining Rockefeller is the best decision I ever made."

Or at least, that's how she'll remember it. ◎

EVEN SMALL BRAINS MAKE BIG DECISIONS.



Understanding choice is the next frontier in neuroscience.

By Caitlin Shure

A TINY FRUIT FLY AMBLES through a barren landscape. As the minutes go by and the temperature rises, she grows anxious to find food and shade. Then, along the horizon, she spots the sun—or something like it. The fly makes a decision: She will walk away from the glaring light and hope for the best.

Although she is not aware of it, the fly's every step is being observed and recorded by a coterie of curious humans and a bank of sophisticated tracking equipment. The "sun," it turns out, is a vertical bar illuminated on an LED display, part of a virtual environment. The ground is a pea-sized foam ball, floating on a cushion of compressed air, that spins as the fly traverses its surface. And this entire scene—the heat, the hunger, the bright light—has been carefully orchestrated by neuroscientists in the lab of Gaby Maimon to shed light on one of the trickiest questions in biology: how behavioral decisions are made.

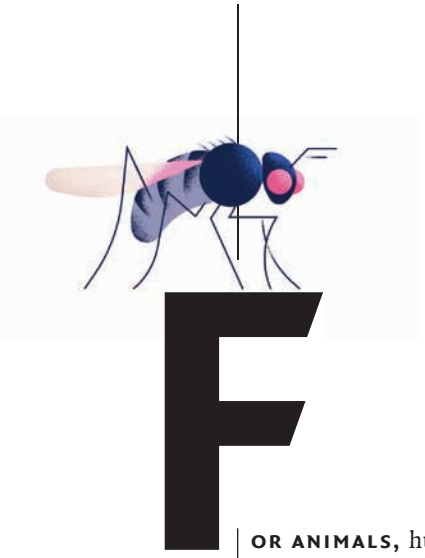
To be sure, scientists are still far from understanding how a nervous system makes choices—or, really, how it does anything at all—even on the relatively small scale of a fly brain. But increasingly, innovations in technology are making it possible to dissect brain computations at the level of molecules, cells, and neural networks, especially when applied to microcosmic systems such as fruit flies, worms, or ants.

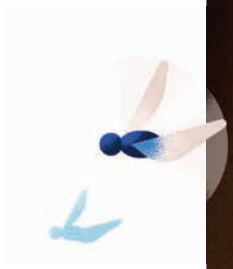
"By working in a smaller brain with fewer neurons, you can more readily understand how cells guide behavior," Maimon says.

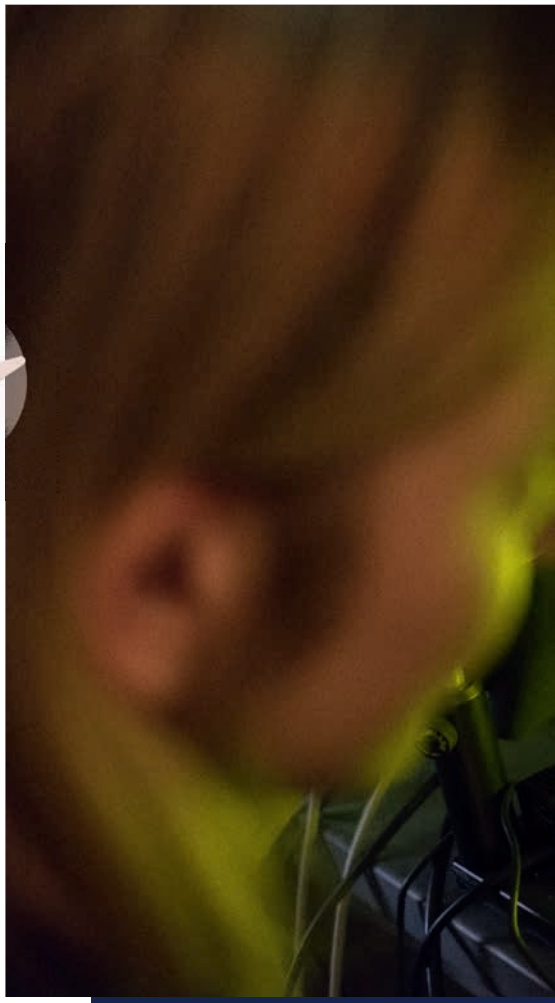
In this respect, a parade of tiny critters is showing the way as neuroscience moves toward its next frontier. The simplicity of microscopic organisms allows scientists to make headway in understanding otherwise intractable aspects of cognition, knowledge that will one day be applicable to the study of all brains, including humongous ones like our own.

In that sense, our smallest peers in the animal kingdom might have grand things to teach us—including, perhaps, some of the basic rules that govern our thoughts and actions.

Illustrations by Michele Marconi







FOR ANIMALS, human and otherwise, life consists of a series of decisions—junctures that call for an individual to either fight or flee, hunt or hide, flirt or forget about it. Resolving such dilemmas requires the ability to detect what's going on in the environment, process that information, compare the situation to past experiences, and behave in a way that is appropriate to the circumstances.

Which is to say, it requires a brain.

Brains can consist of millions of cells—or billions, at the high end of the spectrum. To navigate decisions, each cell must engage in its own kind of deliberation. Neurons repeatedly grapple with the same binary choice: either produce a burst of electrical activity, or don't. In neuro lingo: fire or don't fire.

In theory, much of what you say or do can be boiled down to a network of firing brain cells. In practice, however, we don't have a good picture of what such networks look like or how information flows through them. In other words, it is quite difficult to establish reliable relationships between what neurons do and what organisms do.

Further complicating matters, a given behavior can have more than one underlying cause, each involving the activation of a unique brain network.

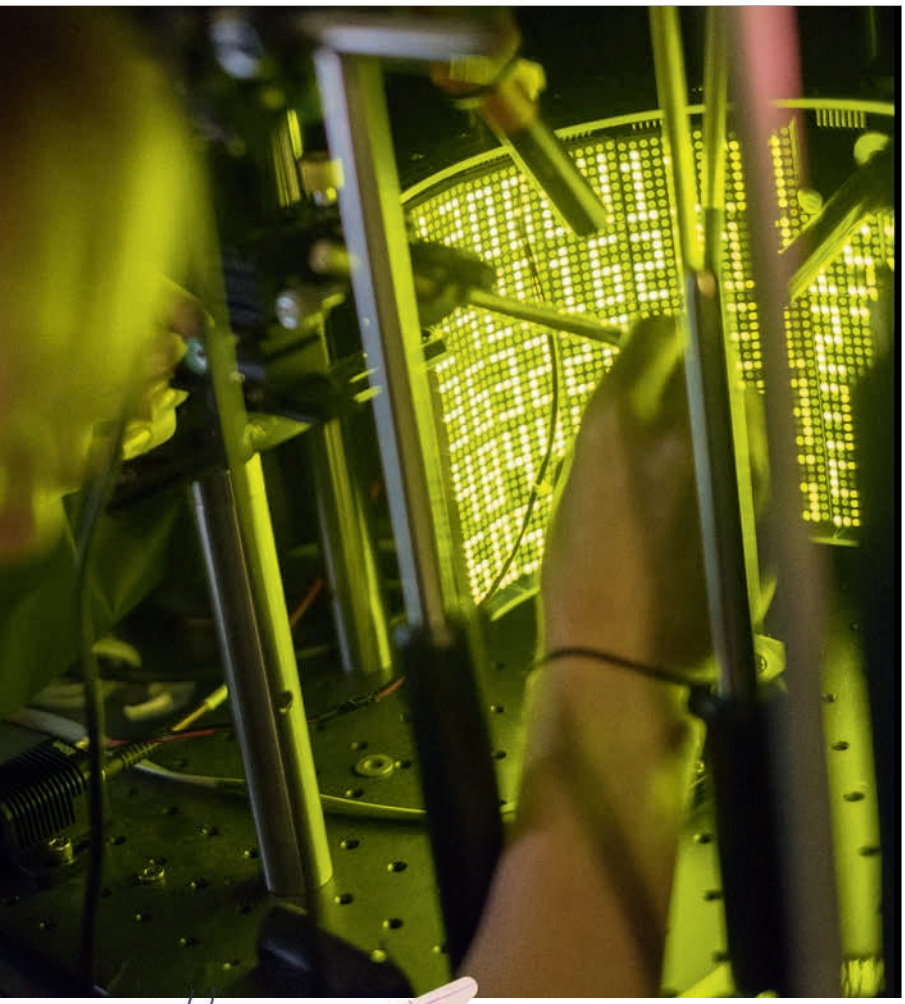
"If I decide to walk out the door, it may be because it's hot in here. Or because I see my grad student outside the door. Or because I want to go get lunch," says Maimon, who is head of the Laboratory of Integrative Brain Function. "Human brains and human motivations are complex. It's an enormous task to tease apart that sort of complexity. So maybe you reduce the system a little."

This is the idea behind the virtual environments Maimon's lab has engineered. While striding on her spherical treadmill, the fruit fly is made to respond to a few carefully controlled cues—like temperature or light—that influence her navigational decisions. All the while, her brain is under a microscope that measures bursts of firing neurons.

The fruit fly is prepared to walk for meters if it means finding respite from the heat, and she has a plan: As long as she keeps the sun at a constant angle, she knows she's walking in a straight line—a line that, she hopes, will eventually lead her to a more hospitable climate.

But when the LED "sun" confoundingly moves, the fly comes to believe that she has strayed from her intended path. She corrects, turning her body so that the sun is, once again, where she prefers it. Like other fruit flies before her, the animal has just consulted

In theory, much of what you say or do can be boiled down to a network of firing brain cells. In practice, however, we don't know what such networks look like.

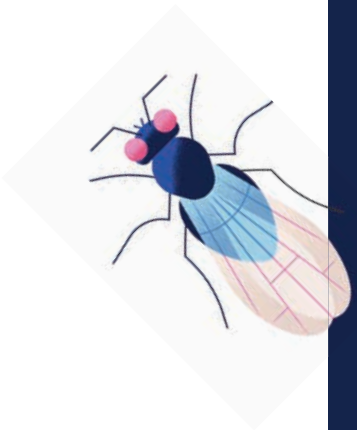


In Maimon's lab, scientists use panels of LEDs to create a virtual reality environment for fruit flies.

an internal signpost to make a navigational decision. And Maimon, along with Jonathan Green and Vikram Vijayan, two scientists in his group, has come one step closer to figuring out how the fly brain accomplishes as much.

Previous studies have shown that this fly species, *Drosophila melanogaster,* has a doughnut-shaped brain structure containing a set of neurons called E-PGs; as a fly turns its body, different E-PGs around the doughnut become active, indicating the fly's orientation. The activity of E-PGs functions as a sort of compass needle for the fly.

Like the activity of most neurons, E-PGs depend on input from other cells. Just as a person might solicit advice from close confidants when facing a decision, deliberating neurons weigh input from their fellow neurons, communicating with one another through the release of chemicals known as neurotransmitters. Some of these chemicals are excitatory, meaning they nudge a neuron toward activation. Others are inhibitory, tilting the scale toward inaction. When receiving this oft-contradictory counsel, a neuron sums up the totality of its input to "decide" what to do next. If excitation exceeds inhibition, for example, it fires.



In 2017, Maimon's lab discovered that a group of neurons, called P-ENs, monitor how fast a fly's body is rotating and feed this information to E-PGs, influencing their decision to fire. In one experiment, the researchers stimulated brain cells that rotate the E-PG compass as a fly attempts to walk in a straight line. The insect, believing that she has deviated from her path, turns to realign herself.

These and other of Maimon's experiments illustrate how groups of neurons, like E-PGs and P-ENs, interact to generate an internal sense of orientation—a sense that influences which direction a fly turns, how hard it turns, and how quickly it walks forward. Maimon has also found that flies participating in this kind of experiment always reorient themselves in the most efficient way possible. "If you rotate the compass 30 degrees clockwise, then the fly rotates its body 30 degrees counterclockwise—it rarely takes the long route," he says.

For a fly, the ability to walk in a straight line can mean the difference between starvation and a lovely lunch, between life and death. For Maimon and his colleagues, working with this organism provides a rare opportunity to pinpoint the precise neuronal processes that keep track of the animal's goals and guide its behavioral decisions. Using the framework of navigation, his lab hopes to elucidate how chemical and electrical processes interact to give rise to basic aspects of memory and cognition—a big question that, he says, is most readily answerable in small brains.

A FEW STORIES DOWN, another fly navigates an arguably more difficult scene—the dating scene. Typically, male fruit flies have strict courtship criteria. They mate only within their own species, and they strongly prefer a female that hasn't mated before.

MARIO MORGADO

More than a matter of taste, this pickiness is a vital trait: A male's choice of mate will affect the fitness of his offspring and, ultimately, the future of the species.

Under normal circumstances, a *D. melanogaster* would never be interested in, say, a *D. simulans,* even though females of the two species look indistinguishable and run in similar circles. Today, however, one particular fly finds himself attempting to mate with a ladybug. Objectively, this makes no sense. Among other problems, the ladybug is many times the fly's size. It doesn't go well.

The fly, a resident of the Laboratory of Neurophysiology and Behavior, is under the spell of a high-tech love potion of sorts. Vanessa Ruta, head of the lab, has genetically engineered one of its neurons, known as P1, to fire when exposed to light, a technique called optogenetics. Using this approach, Ruta shows that every time the light gets turned on, so does the fly. P1 neurons control a fly's decision to court, and they are capable of overriding the fly's best judgment.

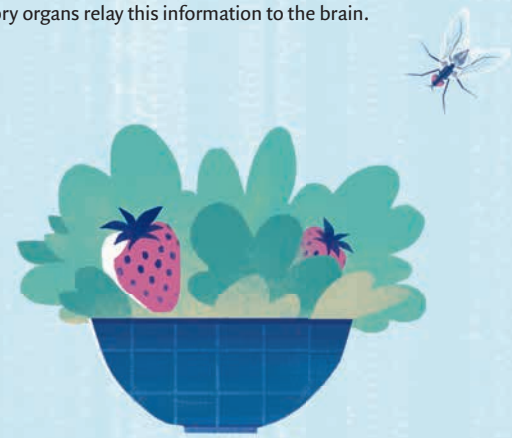
In nature, of course, P1 does not receive optical stimulation and *D. melanogaster* flies don't mate with ladybugs. In fact, Ruta has found that P1 neurons become active only when a fly is in the presence of a female of the same species, suggesting that the neurons discriminate between appropriate and inappropriate objects of affection. Which, to Ruta, raises the crucial question of how P1 neurons carry out the discernment. How, she wondered, do approximately 20 male-specific cells evaluate the suitability of a potential paramour? And how do these processes differ across species?

To find out, her team used the gene-editing technology CRISPR-Cas9, along with advanced imaging techniques, to compare the nervous systems of *D. melanogaster* and *D. simulans.* Specifically, they evaluated how the two species respond to the pheromones of *melanogaster* females. Here, the relative compactness of the fly's brain was a crucial asset.

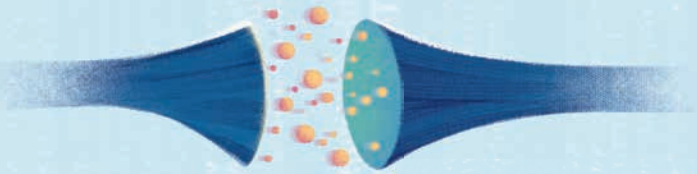
"Because the circuitry is concise and simple, we were able to trace activity cell by cell, and study neural architecture and function at every level," says Ruta, the *Gabrielle H. Reem and Herbert J. Kayden Associate Professor*. "That allowed us to make explicit comparisons between the two species and pinpoint any variation."

Decision making: How it works

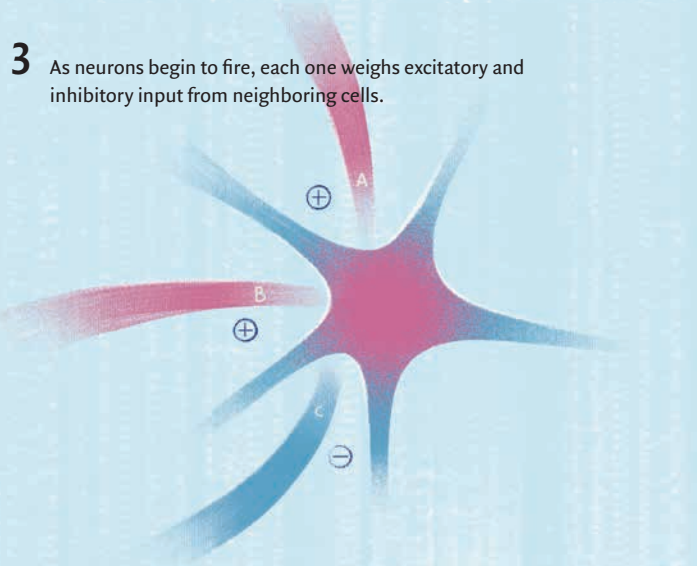
1 An animal encounters something interesting in its environment. Sensory organs relay this information to the brain.



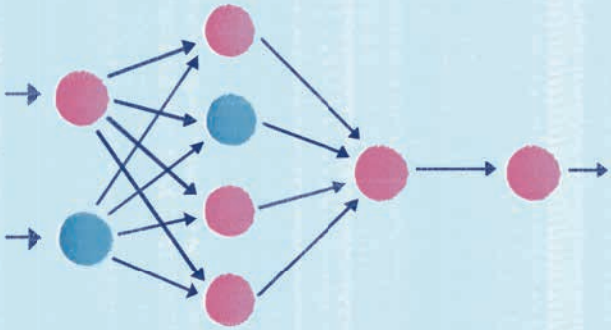
2 The information causes sensory neurons in the brain to fire, initiating a cascade of brain activity.



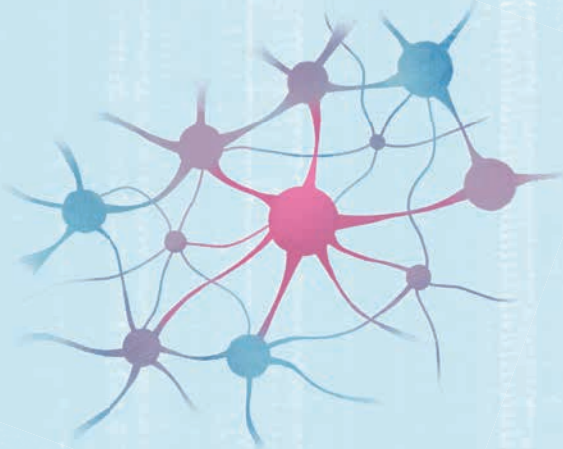
3 As neurons begin to fire, each one weighs excitatory and inhibitory input from neighboring cells.



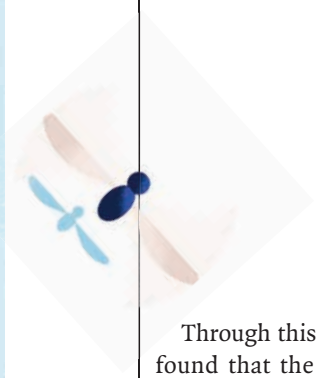
4 Input from these various cells influences the activity of a key deciding neuron. Its decision generates a new signal.



5 The firing of the deciding neuron causes other neurons to execute a specific behavior.



6 The animal reacts.



Through this exhaustive exploration, the scientists found that the sensory organs of the species were identical, as were their P1 neurons. However, the cells sending excitatory and inhibitory inputs to P1 neurons behaved differently. When researchers presented a *D. melanogaster* male with the pheromones of a *D. melanogaster* female, P1 neurons received predominantly excitatory input—urging the fly to make his move. But when they presented a *D. simulans* male with *D. melanogaster* pheromones, P1 neurons were strongly inhibited, splashing cold water on the entire interaction.

This outcome, says Ruta, makes good evolutionary sense, because if a *D. simulans* were to mate with a *D. melanogaster,* the couple would yield infertile offspring. The research contributes to her lab's broader mission of examining the interaction between behaviors that are selected over the course of evolution, and those that are learned through individual experience—a "nature versus nurture" interplay that characterizes species of all sizes.

"You would think that it's under your control to make the right decision," she says. "But it turns out some decisions are so essential for the perpetuation of the species that they're hardwired into the nervous system."

WHEN ENCOUNTERING an eligible female, a male fruit fly does not agonize over whether the insect in front of him is his soul mate, or even whether she shares his taste in overripe bananas. Rather, any deliberation about romantic compatibility occurs on a cellular scale: Upon detection of the female's pheromones, the male's P1 neurons receive excitatory input, they fire, and he pursues her. End of story.

That doesn't mean, however, that small organisms amount to automatons. Nor does it mean that their decisions can always be explained by the presence of some specific stimulus in the environment. In addition to external cues, decisions can be driven by internal motivations.

"When we talk about decision making, we often talk about it as though the whole problem is the sensory information that's in front of you," says Cori Bargmann, the *Torsten N. Wiesel Professor* and head of the Lulu and Anthony Wang Laboratory of Neural Circuits and Behavior. "But a lot of the decisions that an animal, or a person, makes are driven by internal needs."

Illustration by Jasu Hu

Consider Maimon's meandering fly. Sure, its directional decisions were influenced by a fake sun and some brain stimulation. But the fly was also hungry—which is why it was so motivated to scurry along in the first place.

Hunger is a powerful behavioral motivator for all animals, including the microscopic roundworms that Bargmann studies. Her lab houses a collection of petri dishes filled with these organisms, known as *Caenorhabditis elegans*, whose nervous system consists of a mere 302 neurons, all of which have been thoroughly mapped. Exploiting the simplicity of this system, Bargmann and her colleagues have been able to investigate highly specific relationships between genes, brain activity, and behavior.

C. elegans spend most of their time investigating where to find something to eat. They perpetually scan their surroundings for edible bacteria; and if they fail to find any, they go to new lengths—quite literally—to satisfy their cravings. At the first hint of hunger, a typical worm surveys the region where it last found sustenance, a strategy called local search. This can go on for up to 20 minutes, as the worm checks and rechecks its proverbial cupboard. Eventually, however, the animal abandons this tactic and goes hunting in foreign terrain—raising the question of what changed in its brain to incite this new behavior.

Because the worms continue to search locally long after food is removed from their surroundings, Bargmann suspected that they're dwelling upon some kind of memory—nostalgia for meals past that compels them to search in a spot previously brimming with bacteria. The decision to switch hunting strategies, then, could be explained by the eventual waning of that memory.

Hoping to determine how the worm brain might store this kind of information, Alejandro López-Cruz, a member of Bargmann's lab, identified a receptor, known as MGL-1, that is involved in detecting food. Activation of MGL-1, the researchers found, leads to a circuit change that modifies the behavior of neurons for minutes at a time—sustaining food-related memories, and keeping worms close to home. When this chemical memory eventually fades, the animals move on from their comfort zone and forage elsewhere.

Though it is perhaps intuitive that memories should affect an animal's decisions, how this process works on a molecular scale is hardly straightforward. But with increasingly sophisticated tools to exploit the *C. elegans* nervous system, Bargmann's lab has a unique opportunity to identify the biological machinery through which past experiences guide present decisions. Building on this work, the researchers hope to better understand how memories form and degrade, and how those memories affect behavior.

To make an informed decision, a brain must be attuned to the goings-on of the environment, its own needs, and its memories. And in case that isn't enough to deal with, there's also the matter of other individuals.

JACOB PRITCHARD

Ruta in the environmentally controlled fly room where she conducts behavioral experiments.

For ants, who are often literally walking all over each other, it is especially important that everyone stays in step. Luckily, ants are pretty sensitive to the needs—or at least the pheromones—of their peers.

The clonal raider ant *Ooceraea biroi* is a particularly social species: Members of a colony collectively find and retrieve food and take care of their offspring. Daniel Kronauer, head of the Laboratory of Social Evolution and Behavior, has developed elaborate techniques for studying these miniature collaborations. Using an automated tracking apparatus and a vibrant color-coding system, he can monitor more than 100 different colonies at a time. Employing this approach, his lab has demonstrated, among other things, the importance of social cues in *O. biroi* behavior.

Kronauer has observed, for example, that when larvae are around, ants stop laying eggs and instead tend to the kids that they already have. Further investigating this behavior, his team learned that the presence of larvae reduces expression of a gene coding for insulin—a signaling substance that, in ants, promotes reproduction. In other words, a social cue, the presence of ant larvae, alters levels of a neurochemical, insulin, which controls a decision, to halt reproduction. In establishing this kind of link between sociality and biology, says Kronauer, the advantages of a small nervous system are myriad.

"Because ant brains are relatively simple, it is easier to see how a molecule like insulin is affecting the animal, and what aspects of behavior, exactly, are being modulated," he says. "In ants you are also able to observe effects that might be too subtle to detect in bigger organisms."

Of course, being a responsible member of the *O. biroi* community requires a lot more than occasional babysitting. Ants must coordinate the activity of not just a nuclear family, but an entire colony, which can consist of hundreds of individuals. Often, every ant in a colony makes the same decision simultaneously—requiring remarkably efficient signaling both among the cells within an individual brain, and between brains.

Asaf Gal, a postdoc in Kronauer's lab, is studying the dynamics of this kind of groupwide behavior. Specifically, he is investigating how *O. biroi* respond to increases in temperature, and how this behavior changes as group size increases. He has found that when

"You would think decisions are under your control. But some are so essential for the perpetuation of the species that they're hardwired into the brain."

Notable decision makers

CAENORHABDITIS ELEGANS

Nickname: worm, nematode
Number of neurons: 302
Contributing to science since: 1963
Why scientists like them: Their entire nervous system has been extensively mapped.
Common decision: Is the food on the left or the right?

DROSOPHILA MELANOGASTER

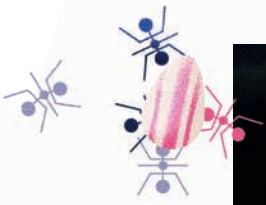
Nickname: fruit fly
Number of neurons: about 135,000
Contributing to science since: 1910
Why scientists like them: Their genes are well known and easy to manipulate.
Common decision: Is this other fly a good mate or not?

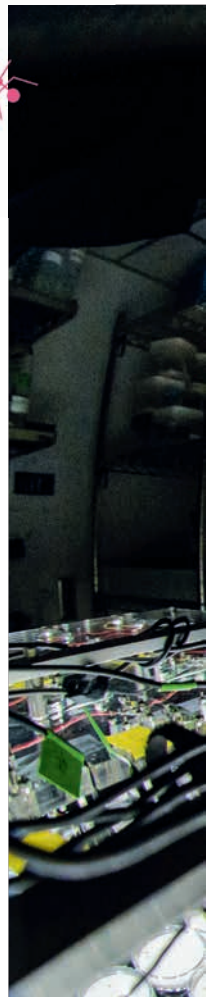
OOCERAEA BIROI

Nickname: ant
Number of neurons: 100,000–200,000
Contributing to science since: 2010
Why scientists like them: Every ant in a colony is genetically identical.
Common decision: Should we move our nest or stay here?

HOMO SAPIENS

Nickname: Human, person, Doug, Amanda, etc.
Number of neurons: 80 billion or more
Contributing to science since: around 2 million years ago
Why scientists like them: Highly relevant.
Common decision: Should I watch CNN or *The Bachelor*?





a solo ant is exposed to rising heat, it scurries away almost immediately. When in a group, however, that same ant will take longer to make a move—and it does so in synchrony with the rest of its colony. Gal has also found that as group size increases, so does the amount of time it takes for a colony to start relocating—but only as long as the temperature change is moderate. When faced with a more dramatic heat wave, he notes, large colonies disperse as quickly as small ones.

"You only see this social phenomenon in borderline cases—when the temperature change is not too extreme," says Gal. "The group's decision is slower in these circumstances because there are opposing forces: Some ants feel it's time to go, but others disagree. This suggests that the ants are communicating with each other, probably through pheromones, to figure out what to do."

When enduring a still-tolerable hot spell, an ant might release a pheromone suggesting that it's starting to get a bit too warm for comfort. As the temperature continues to increase, more and more ants emit this pheromone, and their peers pick up on the signal. Eventually, accumulation of these signals reaches a threshold that prompts the entire colony to march to a cooler climate. It's not unlike the process by which individual brain cells detect chemicals released by their neighbors before making a determination to fire (see "Decision making: How it works," page 26).

In this context, an ant is at once an individual and a node in a larger processing system—the colony. And within an ant itself is a smaller processing system, the brain, with neurons that perform calculations of their own. In this way, ant behavior illuminates multiple scales of biological deliberation—scales that confuse our assumptions about when, where, and by whom decisions are made.

IN CASUAL PARLANCE, a decision connotes a conscious choice, sometimes accompanied by a fraught period of deliberation: Should I buy this house? Should I marry this person? Should I cut my hair?

These big questions, however, represent only a slim portion of the decisions that the brain faces. Because underlying everything that you do or think is a flurry of

Illustration by Jasu Hu

Kronauer during an experiment in which cameras track ant movements.

ALEX WILD

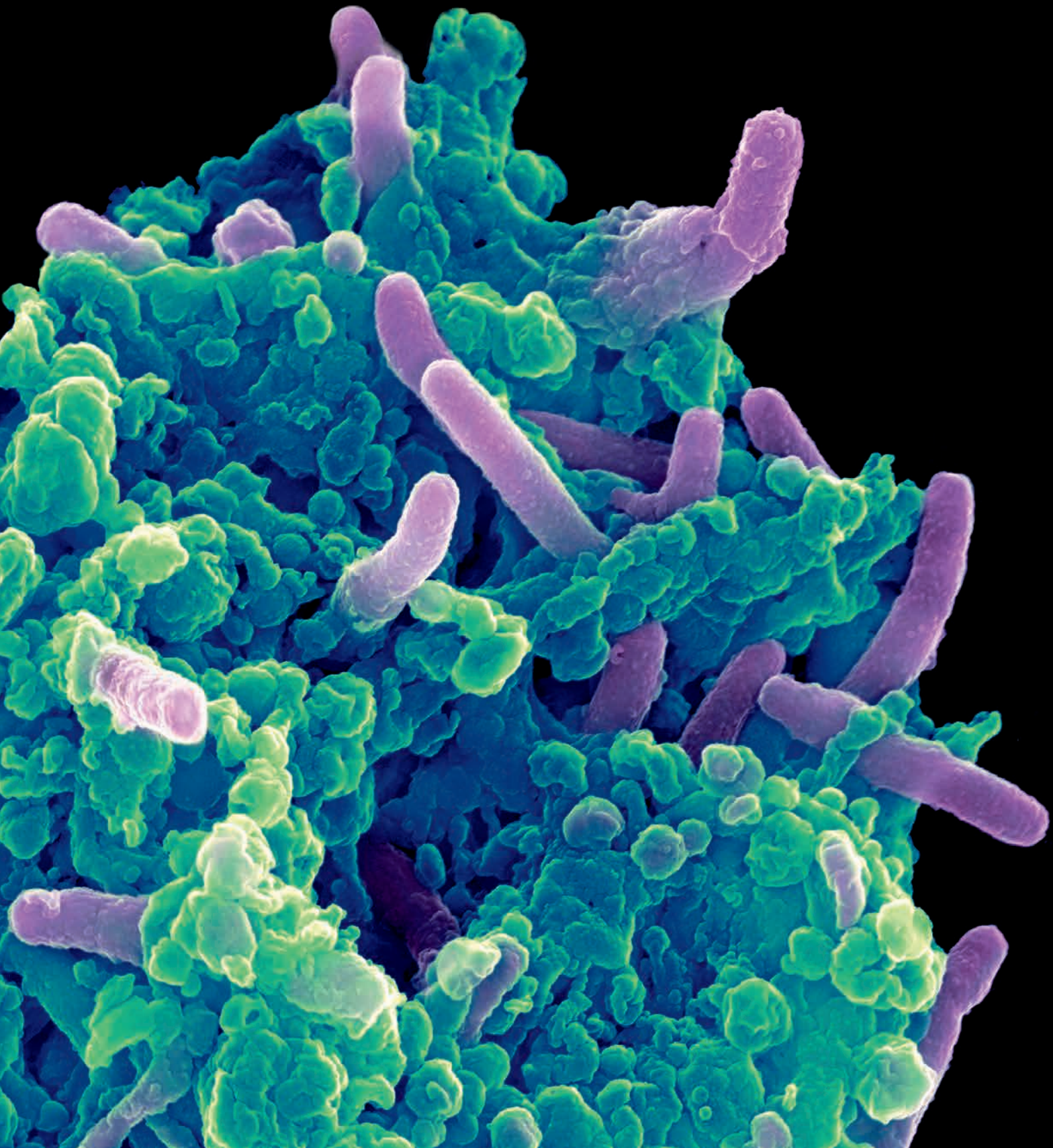
microdecisions—neuronal computations made in the absence of conscious consideration.

By analyzing the decisions of individual cells, small-organism researchers can define direct links between genes and neurotransmitters, neurotransmitters and firing patterns, firing patterns and behavior. As such, little animals are laying the groundwork necessary for neuroscientists to understand how all brains, big and small, function at the most rudimentary level.

In the immediate, research on tiny critters will not resolve how we arrived at our choice of haircut, house, or spouse. But it provocatively calls into question whether *we* choose anything at all. Research on humans is complicated not just because our brains are so inconveniently big but because when we consider our own behavior, we often get distracted by abstract concepts like consciousness, love, and freedom. In the context of small organisms, it is easier—conceptually and experimentally—to see decisions for what they really are: the upshot of cells firing or not firing due to the influence of chemical input.

"People tend to think of ants as these programmed robots," says Kronauer. "At the same time, we think about ourselves as these free-willed, free-spirited organisms. And that dichotomy is probably not correct."

In a sense, the attribution of decisions to chemical-induced moods or hardwired circuitry may seem at odds with the kind of autonomous actors that we fashion ourselves to be. On the other hand, we may rest assured knowing that even our most regrettable choices adhere to some neuronal logic—complex cellular calculations that we are only just beginning to understand.



TB is changing. So is science.

BY ALISON MCCOOK AND EVA KIESLER

Tuberculosis keeps reinventing itself. As drug-resistant strains spread across the globe, it's becoming increasingly harder to wipe out. But researchers, too, are adjusting—and they're better positioned than ever to attack one of humanity's most ancient health problems.

Mycobacterium tuberculosis bacteria, in purple, infecting a human white blood cell.

Outmaneuvering TB will involve designing drugs that act faster. The sheer duration of existing therapy has likely contributed to the drug-resistance problem.

FOR A TIME WHEN ELIZABETH CAMPBELL was in her early 20s, any sweat that trickled down her brow or armpits was an eye-catching bright orange.

"I felt quite self-conscious in the gym," she recalls.

Orange perspiration is a known side effect of a drug used to treat and prevent tuberculosis, one of the world's most deadly diseases. When Campbell started graduate school, a decade after she and her family had immigrated to the United States from their native Guyana, she was required to take the drug for six months because telltale antibodies had been detected in a blood test. (The antibodies were most likely due to her childhood vaccinations, not to an active infection, but with TB it's best not to take chances.) Six months is a long time to be on a strong medication you almost surely don't need, but Campbell swallowed her neon pills every day, without complaint.

"I come from a place where, if you don't take your antibiotics, you die," she says.

Across the developing world, Guyana included, TB remains a scourge, and yet those of us with access to good health care, hygiene, and nutrition pay little attention to it. TB kills more people than any other infectious agent, even malaria and HIV. In 2017, 10 million people became sick with TB, and 1.6 million died.

Antibiotic resistance is one of the reasons the disease is out of control. Campbell's orange drug, rifampicin, along with a few others, are currently the best treatment available for TB, but several *M. tuberculosis* strains have evolved techniques to survive them. It's an escalating problem that public health experts warn might soon bring on a full-blown disaster—a world in which antibiotics offer no protection whatsoever and people everywhere become infected—and it has sent researchers like Campbell, a research associate professor, and Jeremy Rock, a new assistant professor, scrambling to come up with better drugs.

It's often a struggle. For decades, scientists' hands have been tied by a lack of adequate tools. For a variety of reasons, *M. tuberculosis* is difficult to study; the techniques that have worked for scientists focusing on other infectious diseases have failed with TB. But this is starting to change.

Although the pandemic remains fierce, Campbell, Rock, and their colleagues believe the TB field is poised to turn a corner.

THE FIRST TIME Rock held a flask filled with enough bacteria to infect almost the entire world with TB, he felt a little nervous. He was a postdoc at Harvard University, working in the labs of Sarah Fortune and Eric Rubin, and brand new to the study of deadly infections; his former research subjects had been harmless, easygoing yeasts.

Rock's plan as a newcomer to the field was to search the *M. tuberculosis* genome for genes the microbe cannot live without. He hoped those genes would lead him to new targets for future drugs. But many people were doing similar searches. "The work was very difficult and slow," Rock says. "If you wanted to manipulate genes to figure out their function, you had to knock out each gene one by one." If you were unlucky, targeting even a single gene could involve years of trial and error.

Rock was sure there had to be a more efficient, more systematic way to comb through *M. tuberculosis* DNA. If only he could get the right tools, he felt optimistic that the search would turn up something useful.

The first few roadblocks he encountered were anticipated. One was the incredibly slow growth rate of *M. tuberculosis*, which makes experiments very time-consuming. (It may also be a reason the pathogen is so effective at spreading—it is able to lurk in the body for years before symptoms develop, so many infected people don't even know they have it. Public health experts estimate that up to one-quarter of the global population is currently infected with this latent form).

Another well-known hurdle is the infectious prowess of *M. tuberculosis,* among the deadliest microbes known to prey on humans. In the real world, a cough, sentence, or song from an infected person can put you at risk; to handle it in the lab you need specialized, expensive containment gear.

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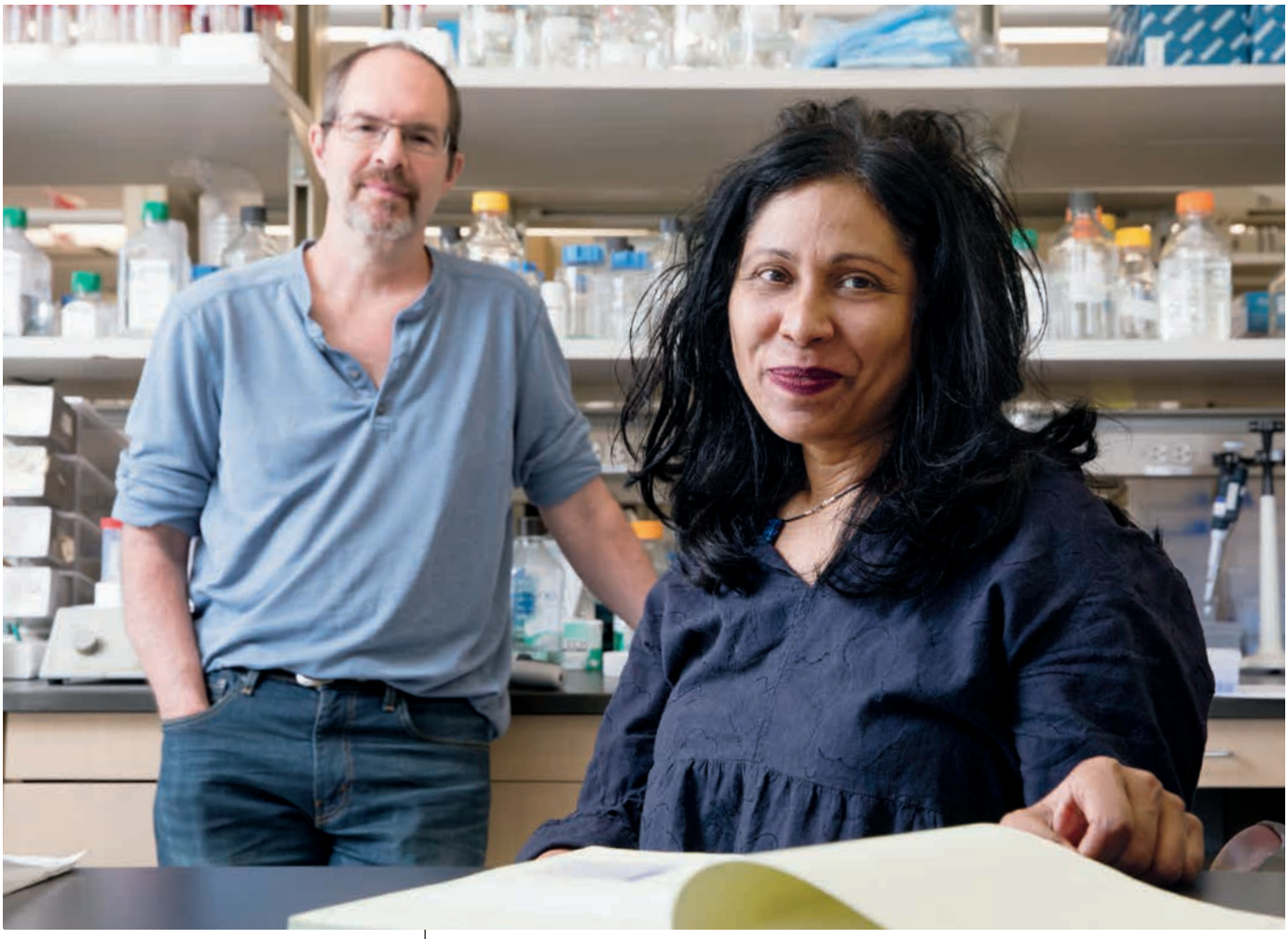


Darst and Campbell are looking to old drugs for new ideas.

ALEXANDRA ROWLEY

But there were novel obstacles as well. Rock believed that if anything could energize research on TB, it was CRISPR interference, a technology that makes it possible to easily turn off genes and study the consequences. The method can be scaled up to allow for very broad searches, with lots of genes being explored side by side.

CRISPR interference had already begun to revolutionize biology; scientists working on everything from maize to mice were getting in on it. But when Rock tried it on his finicky but deadly bacteria, it didn't work. Either CRISPR didn't knock genes down properly, or it killed the cells before any data could be collected. He tweaked his strategy in every conceivable way before he finally gave up. "It took us two years to accept that a tool that works great for everyone else didn't work well for us," Rock says.

And so, he began the laborious work of building his own tool.

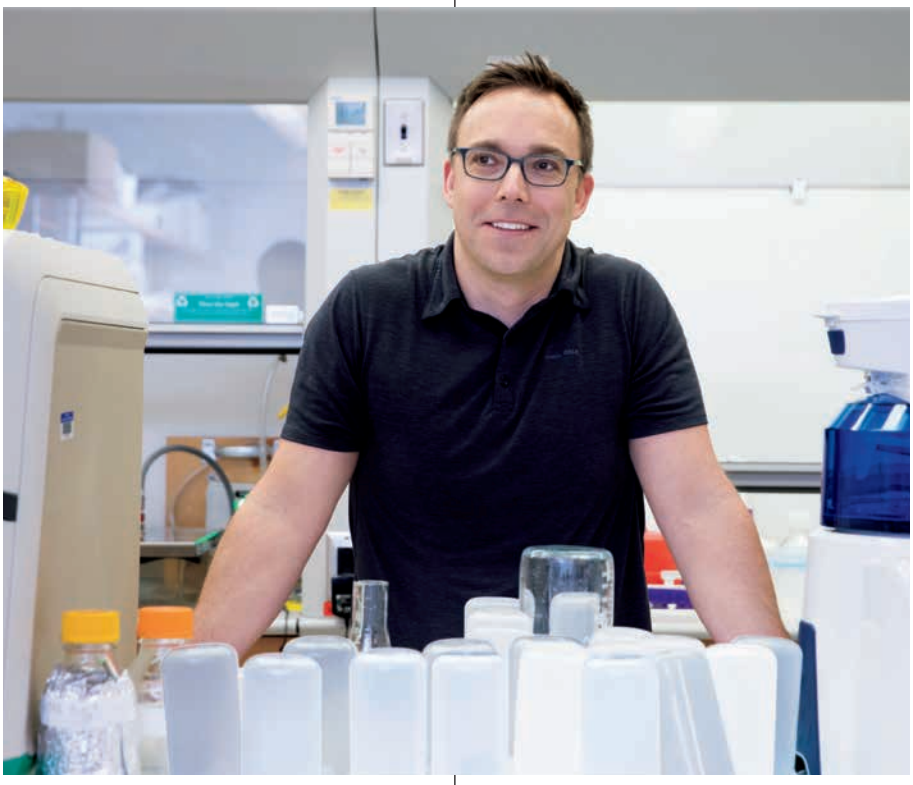
One common method to edit an organism's genome takes advantage of two collaborating bacterial proteins: CRISPR (hence the name "CRISPR interference") and Cas9. In nature, CRISPR-Cas9 serves as a kind of immune system for bacteria known as *Streptococcus pyogenes*, but Rock knew there are other microorganisms with different versions of Cas9. What if one of these Cas9 cousins just happened to be more suitable for *M. tuberculosis*?

Rock tried 11 different systems before stumbling upon *Streptococcus thermophilus*, a bacterium commonly used to ferment dairy products. "I'll never forget watching the results come out in real time," recalls Rock. "I almost didn't believe it, given how many failures we'd had up to that point."

Last year, after completing his postdoc at Harvard, Rock launched his own lab at Rockefeller where he is now "carpet bombing the TB genome" with his custom-built CRISPR interference technology. The wide-scale approach will not only help the lab identify the pathogen's weakest spots more quickly, Rock says, but will also allow them to study the relationships between genes—information that is highly relevant for developing combination or "cocktail" therapies.

"TB is always going to have to be treated with a combination of drugs," Rock says. "Even now, you need to take a four-drug combination cocktail to curb the infection. So we're very interested in learning how to build stronger drug combinations. For example, can we exploit synergistic interactions between genes by pairing drugs that enhance each other's effects?"

"Can we exploit interactions between genes by pairing drugs that enhance each other's effects?"



Rock is building a powerful system for TB drug discovery. Gone are the days of looking for needles in haystacks.

Seven years into his research with TB, and one year after starting his own lab, handling a deadly pathogen doesn't scare Rock anymore, and he's become quite comfortable with the Tyvek suits, HEPA masks, and double gloves required to work with it, even if it gets hot in the summer.

Although he is currently conducting his work in a highly secure facility in the lab of Carl F. Nathan, chair of microbiology at Weill Cornell Medicine, Rock is also helping design a new high-biosafety facility on Rockefeller's campus, set to open this year. It's an investment in the future of tuberculosis research, setting him and other scientists up for a vast range of experiments.

Already, Rock's lab has identified genes that may have the markings of a drug target, and he hopes to soon initiate functional studies of those genes in TB-infected human cells or mice. Although it's promising work, and enough to keep Rock and his lab members busy for years to come, he's quick to point out that his approach is but one piece in a much larger puzzle. Having thwarted humanity for many centuries, *M. tuberculosis* won't give up without a fight.

Campbell and her colleagues are attacking the disease from a different angle. Experts in structural biology—a school of science that solves problems by drawing precise three-dimensional maps of interacting molecules, atom by atom—she and her team are looking to old drugs for new ideas. In particular, they are conducting extraordinarily detailed investigations of how rifampicin interacts with its target, gaining information that might prove useful in multiple ways. By elucidating how *M. tuberculosis* interacts with the drugs currently in use, Campbell hopes to create opportunities for medicinal chemists to either troubleshoot and improve these drugs, or design new ones that could be used in combination with existing therapies.

Campbell and her collaborator Seth A. Darst, the *Jack Fishman Professor*, share an interest in TB but came to it from somewhat different perspectives.

A biochemist, Darst has devoted most of his career to understanding an enzyme called RNA polymerase, or RNAP (pronounced "ar-nap"). The enzyme is in charge of one of life's most basic operations: It reads DNA to make RNA, the blueprint for proteins, in a feat known as gene transcription. Every cell on the planet depends on it.

In other words, RNAP ranks high on the list of evolution's biggest innovations, and Darst has never had a shortage of reasons to be interested in it. But RNAP also happens to be the target of several antibiotics, including rifampicin.

Campbell, on the other hand, is trained in microbial pathogenesis and witnessed people dying from infectious diseases as a child. When she joined Darst's lab in the early 2000s, her main goal was to understand the therapeutic potential of RNAP. But when the two started to ask questions about RNAP in relation to TB, they soon realized that answers would be very hard to obtain.

At the time, the only way to visualize how rifampicin acts on RNAP was to coax the embracing molecules into a crystal, then bombard that crystal with a beam of x-rays. However, as you might expect from a pathogen with a proud legacy of frustrating scientists, *M. tuberculosis*'s version of RNAP turned out to be notoriously difficult to crystallize.

For years, the pair tried work-arounds. They were able to glean several details from

ALEXANDRA ROWLEY

RNAP present in a similar bacteria, *Thermus aquaticus*, which also responds to rifampicin. They learned that rifampicin disables RNAP by latching on to a structure deep inside one of the enzyme's elaborate pockets and throws a wrench into the machinery that transcribes DNA into RNA. As the enzyme glides along a DNA strand, it produces an ever-lengthening tail of fresh RNA—and sooner or later, this tail bumps into the antibiotic and falls off, preventing further transcription.

They also discovered that a handful of *M. tuberculosis* mutations that were known to cause rifampicin resistance all appeared to make tiny structural changes to the very site of RNAP where the rifampicin normally inserts itself, presumably preventing the drug molecule from docking. "This was a big step toward understanding both antibiotic resistance and how RNAP works in general," says Darst. "When we understand where the antibiotics bind, and how they work, that tells us a lot about the enzyme's basic function."

A few years ago, Darst and Campbell got their first good look at the *M. tuberculosis* RNAP, thanks to new technology that circumvents the crystallization process. With cryo-electron microscopy, or cryo-EM, which uses electrons rather than x-rays, and allows scientists to study protein structures without crystallization in their native states, Darst and Campbell can now visualize RNAP from *M. tuberculosis* itself, in more exquisite detail than ever before.

But even this breakthrough didn't come easily. Cryo-EM requires a purified sample of *M. tuberculosis* RNAP. And that's when the arguments started.

Campbell recounts how she, working with a research assistant in the lab, purified batch after batch of the RNAP, all showing zero activity—the enzyme was virtually dead. "When we showed our results to Seth, he told us we simply didn't know how to purify RNA polymerase," Campbell laughs. "And so we went back to the bench. We couldn't get it to work."

For months, the two debated what was going wrong. Darst, with his deep understanding of RNAP, claimed Campbell needed go back to basic biochemistry textbooks to figure out the glitch, while Campbell insisted that the *M. tuberculosis* RNAP wasn't working the way it does in other organisms. Gradually, he began to realize she may be right.

A breakthrough came when collaborators Michael Glickman and Christina Stallings at the Memorial Sloan Kettering Cancer Center sent the lab a sample of a protein called CarD, which they had discovered was essential for *M. tuberculosis* survival. On a whim, the Rockefeller scientists poured some CarD on their biochemically impotent RNAP, and—lo and behold—it came alive.

Since that moment, new insights have been flooding in, and show no signs of slowing down. Campbell and Darst have discovered that, unlike other bacteria, RNAP from *M. tuberculosis* requires two helper proteins—CarD and another cofactor called RbpA—to function properly.

If the discovery of four-letter cofactors sounds esoteric, it also happens to be news we could use. For example, drugs already exist that bind to RbpA when it is bound to RNAP, potentiating the drug's activity. One of them might boost the effectiveness of rifampicin against TB, the scientists speculate, or perhaps new drugs could be developed that thwart CarD. An exciting aspect of this idea, says Campbell, is that drugs targeting such cofactors would specifically kill *M. tuberculosis* without disrupting the body's "good" microbes—like those of the gut—and may therefore be less likely to cause side effects.

As their TB work is making Campbell and Darst busier than ever, their teenage daughters—did we mention they are married?—have had to lay some ground rules, like taking breaks from talking science at their family dinners. (One of the girls, who once captured her parents quarreling about purification protocols on Snapchat, complains that "other couples fight about money, but all you guys ever fight about is RNA polymerase.")

In January, the pair published cryo-EM results in *Nature* showing snapshots of the *M. tuberculosis* RNAP in action, just as it's separating the two strands of DNA to make RNA. Their findings revealed just how slowly the enzyme works—explaining, perhaps, why this pathogen grows at such a leisurely pace compared with other bacteria. They're hoping this insight might help explain other aspects of the infection, including why the bacteria lies dormant in so many patients.

THERE'S STILL A LONG WAY to go, but every day more of the picture comes into focus. Campbell and Darst are starting to team up with Rock, as well as with Sean F. Brady, Rockefeller's *Evnin Professor*, who is looking for natural products that could be useful in treating TB and other infections (read more about Brady's research in the Fall 2017 issue of *Seek*). They are hoping their work will yield new strategies to outsmart the bacterium's tendency to acquire drug resistance, including, possibly, new faster-acting drugs.

This is important, Campbell explains, because the sheer duration of existing therapies—six months in her own case, often years for people with antibiotic-resistant strains—has likely contributed to the emergence of drug-resistant strains.

"I won't make a claim that our work is going to cure TB," Campbell says, "since that will require a combination of efforts and approaches. But here at Rockefeller, a number of scientists are taking different approaches to the same problem. And working together, we can really make some headway." ◎

THE 7,000 FIELDS THAT SCIENCE FORGOT

Research on rare diseases has more to offer than meets the eye—including the promise of discoveries that could help advance all of medicine.

By Eva Kiesler

Illustrations by Carmen Segovia

FAME EQUALS FORTUNE, EVEN in the world of disease. A small number of well-known disorders get the lion's share of the attention while more than 7,000 diseases classified as rare or "orphaned" go largely unstudied.

"It's a real problem," says Sanford M. Simon, whose lab investigates a group of rare childhood cancers that thus far have received next to no federal research support.

This isn't to say we should be focusing less on things like breast cancer or Alzheimer's—clearly, conditions that affect millions are crucial to investigate. Rather, the problem is our failure to simultaneously pay attention to other, more-obscure maladies, many of which have long been overlooked by research funding agencies, pharmaceutical companies, and other systems that medicine relies on to move forward. Lacking the muscular advocacy groups that lobby Congress and organize fun runs, the majority of rare diseases remain understudied, mysterious, and untreatable.

The lack of progress is obviously a problem for the patients Simon works with—or, for that matter, anyone who has been diagnosed with a condition that doctors don't know how to treat. What may be less obvious is the opportunity at stake for society at large. Patients, it turns out, are not the only ones who stand to benefit from more research into unexplored afflictions.

In fact, experience shows that the information gained by looking under the hood of a rare disease often has implications for science at large. Increasingly, those pursuing this work are finding unique windows through which to observe the maneuverings of genes, cells, and biological systems, empowering them to crack open new fields of investigation. Such off-the-beaten-track discoveries can be surprisingly potent, sometimes advancing medicine in unforeseen ways.

"Rare diseases often represent well-defined biological questions," says Simon, "and studying them can reveal insights into basic biology, physiology, and pathology, with far-reaching impact. It may be counterintuitive, but I've come to believe that furthering our understanding of these conditions would be a great long-term investment for our country."

Here are three examples that are already paying off.

FANCONI ANEMIA

An up-close look at how DNA stays safe

Agata Smogorzewska

IT IS SOMETIMES SAID that diseases are the experiments of nature. Notwithstanding the grim twist of that metaphor (if nature is conducting experiments, we're all lab rats waiting to be plucked by our tails), it is apt in the sense that some disease-altered cells and tissues provide a useful setup in which to ask certain kinds of biological questions—almost as if they had been designed for that purpose.

Agata Smogorzewska had this realization as a postdoc, working in the lab of Harvard geneticist Stephen Elledge to study the repair mechanisms cells rely on to fix breaks or typos in their DNA. She became captivated by the mysteries of a rare disease almost by accident, after she discovered a previously unknown component of the cell's DNA-repair tool kit.

When Smogorzewska depleted cells of this component, a protein called FANCI, and then exposed the cells to a DNA-destroying chemical, they were unable to recover from the insult they way a normal cell would. Under the microscope, their chromosomes looked weird: Some were broken while others sported eccentric shapes.

A pathologist, Smogorzewska happened to know these shapes: They looked like positive results from a clinical test for Fanconi anemia, a heritable disease that often causes bone-marrow failure, developmental defects, and cancer. Of course, the resemblance wasn't a coincidence. As Smogorzewska soon found, some patients with previously unexplained forms of the disease turned out to have mutations in FANCI—in other words, their disease likely stemmed from the very type of defect she had engineered into her lab cells.

The discovery was a turning point in her career. "The more I looked at the cells," she says, "the more questions I had—about the disease, about DNA repair, and how the two fit together."

Over the past 10 years, Smogorzewska, now an associate professor and head of the Laboratory of Genome Maintenance, has established a range of methods to explore DNA repair by using Fanconi anemia as a backdrop. Her lab has now identified several other mutations that can lead to the disease—there are at least 22 of them—and the team is tracing these findings back to the molecular processes that cells employ to keep their DNA intact.

"Understanding the basic biology is really essential," Smogorzewska says, "and could be helpful in research on several diseases." For example, she and her colleagues are exploring the role of BRCA2, a protein that is altered in some patients with Fanconi anemia as well as in subsets of women with breast or ovarian cancer. Cells normally rely on this protein to patch up so-called double-strand breaks in a process that involves mending parallel cracks in DNA's double helix. Deciphering this mechanism is a first step toward understanding why BRCA2 mutations may cause these widespread forms of cancer.

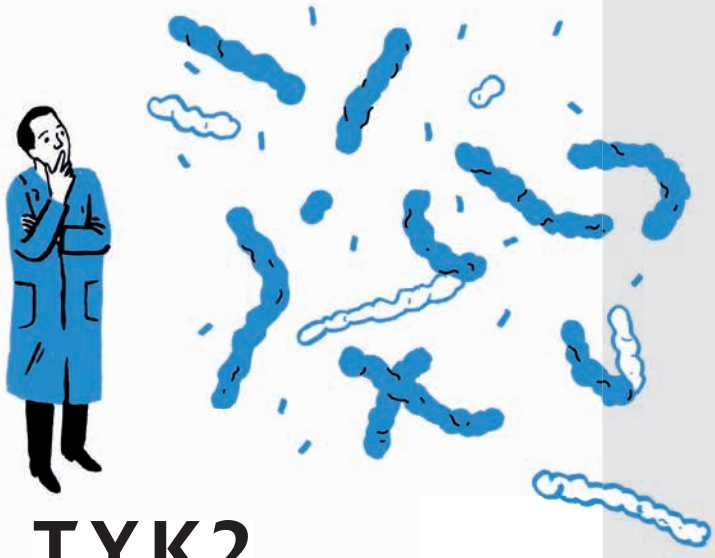
At the same time, the work remains highly relevant to Fanconi anemia itself. Patients with this disease tend to die young, and while stem cell transplants are often effective for bone marrow dysfunction, the disease causes many other problems, including head and neck squamous cell carcinoma, a relatively common type of cancer. The lab maintains a registry with clinical information and samples from over 1,000 patients and their family members; Smogorzewska is using that data to begin to parse out why individual patients are prone to developing particular tumors, hoping to eventually discover ways to prevent or treat these cancers.

The work requires the lab to constantly go back and forth between lab experiments and the real thing: patients and the disease they live with.

"Based on lab experiments alone, you think you understand how DNA is repaired," Smogorzewska says. "You've identified the molecular players in a process, you think you've figured out what they do. But then you talk with patients about their experience, and your gut tells you that you don't have the full picture. Something's lurking that you don't understand, which raises new questions—and you're back in the lab for more experiments."

1 in 10

Americans suffer from a rare disease. About half of them are kids.



TYK2 TUBERCULOSIS

A rare disease that's actually quite common

AS MANY SCIENTISTS WILL tell you, there's something dubious about calling a disease "rare" or "common." Some will go even further. "Diseases don't exist," says Jean-Laurent Casanova, a geneticist who studies how certain mutations affect people's vulnerability to infections.

That is to say, diseases don't exist in the way other biological entities—genes, cells, people, and so on—exist. They make useful headlines but will invariably crumble under scrutiny, dissolving into subtypes and any number of sub-subtypes. "When we use a word like diabetes," Casanova says, "we are really talking about a vast group of biological derailments. In reality, each patient has a unique form of the disease."

This is true even for diseases in which an external pathogen, such as a bacteria or virus, is the culprit. Casanova, now head of the St. Giles Laboratory of Human Genetics of Infectious Diseases at Rockefeller, discovered this himself in the mid-1990s, while finishing his pediatrics training in a Paris hospital. At one point, he learned about odd cases of children becoming inexplicably ill after receiving a standard tuberculosis vaccine previously proven safe and effective. Doctors couldn't explain why the vaccine, which contained disseminated BCG bacteria believed to be harmless, would suddenly induce life-threatening symptoms in these exceptional kids.

80%
of rare diseases have been traced to DNA mutations.

8 years
is the average time it takes for a person with a rare disease to obtain a correct diagnosis.

Jean-Laurent Casanova

Determined to get to the bottom of this mystery, Casanova embarked on an exhaustive study into the pathology of one patient whose reaction to the vaccine had been particularly dramatic. It took him six years, but he solved it: A rare mutation had left a blind spot in this child's immune system, making it unable to cope with the normally benign BCG.

It was the first of many similar discoveries that Casanova has made since. Over the past two decades, his lab has developed increasingly advanced genomic approaches to explore the relationship between our genes and our immune system, and has used these methods to uncover hidden genetic vulnerabilities to numerous infections, from herpes simplex to influenza, pneumonia, and brain encephalitis. While many of these alterations would previously go unnoticed until the pathogen attacked—at which point the patient's health might deteriorate quickly—they can now be detected ahead of time, making the conditions more manageable.

For instance, Casanova's team recently reported that many people carry mutations in the gene TYK2 that severely heighten their risk of developing tuberculosis. The alteration is particularly common in Europe, where about one in 600 people have it—although, as Casanova points out, most people will never know they are carriers since the risk of infection is low in most European countries. Nevertheless, TYK2-associated TB may be a ticking bomb among globe-trotters. Imagine, for example, that you're a British health care worker inspired to volunteer in a refugee camp in Myanmar, where TB is rampant. Before entering that environment, you may want to make sure you don't have the TYK2 mutation, which would render such an expedition very dangerous. "Now that we've discovered the mutation," says Casanova, "people will be able to take a genetic test before traveling to assess their risk."

Moreover, in exploring the mechanism by which the gene normally helps the immune system function, he and his colleagues were able to identify an existing medicine that, theoretically, might be useful in treating the disease in those already infected. (Read more about tuberculosis in "TB is changing," page 32.)

While it's easy to appreciate the broad impact of Casanova's current work, it is also easy to forget how it began—with an in-depth exploration of a single, unusual case. All of which highlights a crucial fact about medical outliers: Their significance in relation to other people's health will often go unnoticed—unless, of course, someone decides to take a closer look.

Sanford M. Simon

FIBROLAMELLAR CARCINOMA

Building knowledge and community

AS WOULD BE THE case for any parent in his situation, Sanford M. Simon's world fell apart in 2008 when he learned that his 12-year-old daughter Elana had fibrolamellar hepatocellular carcinoma (FLC), a rare and usually lethal form of liver cancer. But unlike most parents with this experience, Simon was able to channel his fear and frustration into his work. A Rockefeller biophysicist, he taught himself cancer biology and launched a crusade against his daughter's disease and other rare childhood cancers.

Despite a bleak prognosis, Elana's treatment was successful. She grew up, went to college, and remains cancer-free. But most patients with FLC do not survive, and Simon's work in this area feels as urgent as ever. If federal research funding is insufficient for rare cancers in general, it is virtually nonexistent for a subset of rare cancers affecting children and young adults. "These are the hardest cancers to raise money for," says Simon, "yet they are really worth going after. It's easier to learn new things about cancer if you study it in young people."

This is because, from a genetic point of view, adult tumors are full of noise. They contain lots of mutations, most of which are not responsible for fueling the cancer but have arisen either as a side effect of the cancer or independently of it. Young people's tumors have not had as much time to acquire mutations, making it easier for scientists to identify the "drivers"—the important mutations that can provide clues about how cancer cells dodge therapy, hide from the immune system, or metastasize in the body, for example. In that sense, rare childhood tumors are low-hanging fruit for biologists seeking to develop better tools for treating any type of cancer.

Recently, Simon and his colleagues—including his daughter, who worked in his lab during high school—identified a single mutation present in each of hundreds of FLC tumors the lab has analyzed. They were able to confirm that this mutation is a bona fide disease driver ("when we engineer it onto mice, it mimics the disease," Simon says), and they've even figured out how it arises: Essentially, a stretch of a chromosome is deleted, causing two genes to fuse together. The result is a faulty gene that produces a cancer-promoting enzyme.

"Here's a cancer where, only a few years ago, we didn't even know if it was one disease or many diseases lumped together," says Simon, who is head of the Laboratory of Cellular Biophysics. "And now we know exactly what the driver is and how it works, and we're beginning to design therapeutics."

To that end, the researchers are exploring a novel therapeutic strategy that teaches cells how to recognize and destroy the faulty enzyme. If successful, the same tactic could be applied against several other childhood tumors known to arise from gene fusions—including Ewing's sarcoma and rhabdomyosarcoma, among others—that together affect tens of thousands of kids.

In addition to the hardship of funding, researchers who study rare diseases are grappling with the challenge of amassing enough clinical material to be able to obtain reliable data. After Elana was diagnosed, her mother, Rachael Migler, established a nonprofit medical registry connecting FLC patients and researchers working on the disease—a network that now includes detailed medical records from more than 150 people all over the world. Thus far, patients have provided Simon and his colleagues with more than 115 tumor specimens, an unusually robust collection for a cancer affecting less than one in five million people. (A few patients who donated tissues have even joined the lab to train as scientists and help advance knowledge about their own disease.)

In turn, members of the lab contribute to the registry by sharing information about rare pediatric cancers, writing easy-to-comprehend updates on the latest research, and answering patients' questions. "It's a way to give back to the patient community without which our work would not be possible," Simon says.

95%
of rare diseases lack an FDA-approved treatment.

1 in 2
rare diseases do not have a foundation or advocacy group to promote research and help patients.

How far should scientists go to obtain new knowledge? We asked Ali Brivanlou, an explorer of human development for whom the question is always top of mind.

Science, society, right and wrong

By Eva Kiesler

He knows a thing or two about boundaries. Ali H. Brivanlou's life has taken him across cultural and continental frontiers—he grew up in Iran, moved to France at age 17, and has spent the past 35 years in the United States. Moreover, his work has made him keenly aware of different sets of boundaries: scientific ones, which are always expanding, and ethical boundaries, which shouldn't be crossed.

In 2002, shortly after joining Rockefeller, Brivanlou made a pivotal decision: He abandoned the frog, his long-favored model system, to study development in human embryos and embryonic stem cells.

Developmental biologists tend to be quite fond of frogs. A female frog lays thousands of eggs each day that are big, are easy to see, and develop very quickly, providing an enormously convenient model to study early embryonic development. But for Brivanlou, the frog had taken him as far as it could go. He wanted to understand not just life, but humanity.

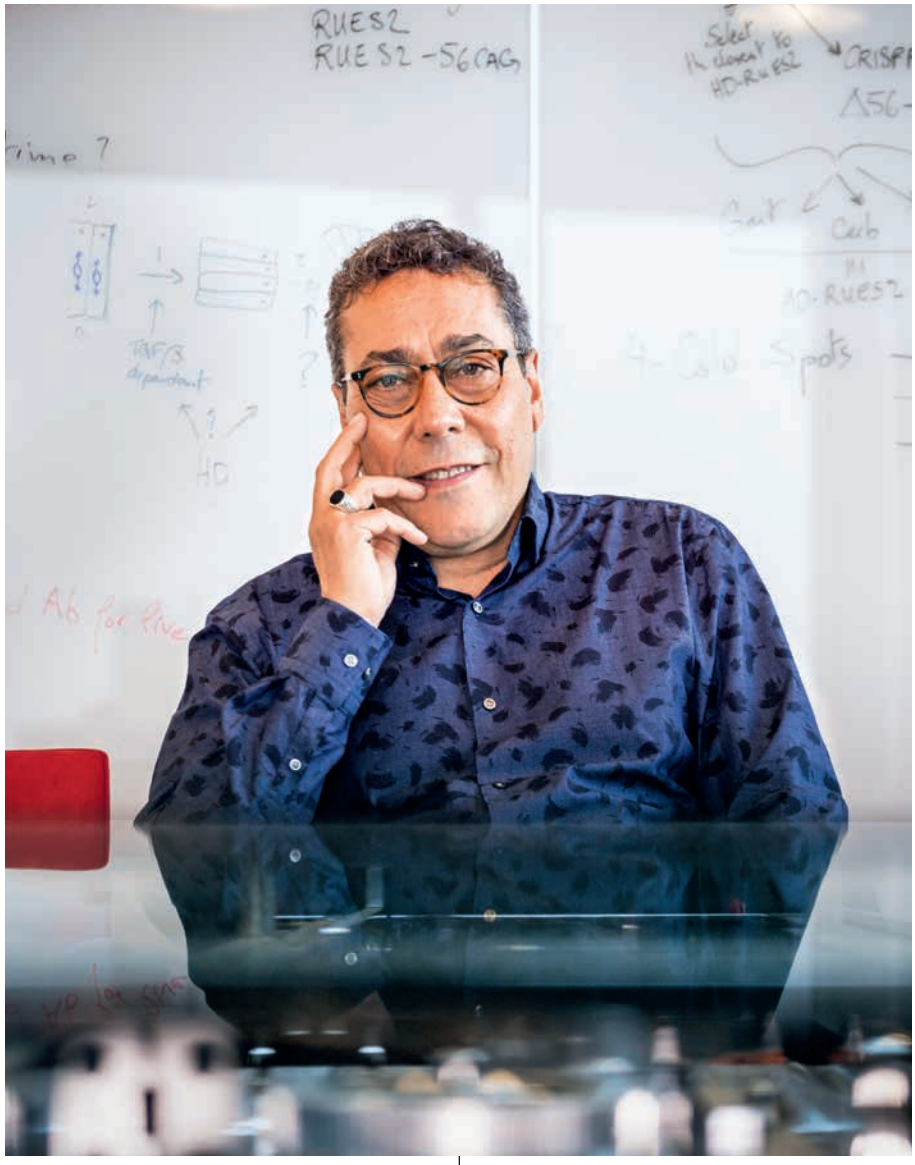
Illustration by Shout

Research on human embryos and embryonic cells raises questions across society—from religious concerns about trampling on the sanctity of life itself, to fears that new scientific tools could open the door to "designer babies" or other dystopias. Yet as Brivanlou and others have shown, the field abounds with opportunity to demystify incurable diseases, develop lifesaving therapies, and help people give birth to healthy babies—all of which creates a strong ethical incentive to move it forward.

In recent years, for example, Brivanlou's lab has developed groundbreaking technology to explore the biology of human embryo implantation. With this technique, scientists now have a way to study one of the earliest stages of development, when a nascent embryo first attaches itself to the uterus. His work has also shed light on the biology of specific developmental diseases such as Huntington's and has driven new investigations into the causes of pregnancy loss.

Every step of the way, Brivanlou, who is Rockefeller's *Robert and Harriet Heilbrunn Professor*, has been inviting dialogue about the possible impacts and risks of his work, integrating scientists' perspectives with those of people from all walks of life.

We spoke with him about the delicate balance between scientific progress and bioethics.



When you first began studying human development, did you realize how difficult it would be?

I was well aware of the technical and scientific challenges involved, as well as the bioethical ones. In fact, the government policy back then, during the George W. Bush administration, was extremely hostile to research on embryo-derived cells—to the extent that many of my colleagues either left the field or left the country to conduct their work elsewhere. Only a few embryo-derived cell lines had been established, and a ban was put on any further efforts to develop new ones. The injunction was catastrophic for human development research.

Why then, did you persist? It sounds like sticking with frogs would have been easier.

It would have been easier, and I did consider it. The frog is a beautiful model organism, and incredibly useful. Still, when you work in any model system, there comes a time when you pause and ask yourself, "model for what?" And ultimately, the answer is *us*. For me, it became very important to understand how much of what my colleagues and I had learned in model organisms could actually be extrapolated to humans.

Certainly, some aspects of development are shared by all animals. For example, the early human embryo is shaped more or less like a frog embryo, and similar molecules dictate its overall symmetry, deciding which part will become the head or where the left arm will stick out. But there is also a high degree of species specificity. In fact, once my lab began working in human cells, we were surprised to find that many of the pathways that drive human development are unique to us—confirming that it's necessary to complement animal studies with research in human cells.

Not everyone agrees on that necessity, however. Pope Francis, for example, has said that nothing—not even research on fatal diseases—justifies the use of human embryos for science. Can you understand this point of view?

I respect this perspective very much. For those who believe, like the Catholics, that life starts at the time of conception, it may follow logically that a fertilized egg can be considered a human being, and hence using

FRANK VERONSKY

For Brivanlou, bioethics is inherently multicultural.

it for scientific purposes becomes highly problematic. What all of us have to remember, though, is that we live in a multicultural society where different people will have different perspectives on this issue.

Many Muslims and Jews, for example, believe life begins with the first heartbeat, approximately 40 days after conception. Some Buddhists will say you are essentially an organ until the umbilical cord is cut.

The scientific point of view is that conception marks the beginning of a *potential* human being, not a human being as such. No new individual will come into being unless an egg is fertilized, but this doesn't mean a fertilized egg will necessarily produce a baby. In fact, it most likely won't produce anything at all—a long list of biological events will have to occur, all in the right sequence, for a fertilized egg to become a new person. From a biologist's standpoint, a fertilized egg has no purpose or finality—it isn't *trying* to *become* anything—so interrupting it at early developmental stages is not the same as taking a life.

All of these viewpoints merit the same degree of consideration, and none should be allowed to dominate at the expense of others.

Given the different perspectives people have, is it even possible to reach common ground?

I think it is, although it often takes time. It's certainly doable if we understand that the goal is to find ethical common ground, not moral common ground. Ethics and morality are often mistaken to mean the same thing, which causes a lot of confusion.

Morality refers to a person's individual assessment of what is right and what is wrong, based on his or her upbringing and culture. Ethics, on the other hand, is the integration of moralities held by all the individuals within a society. And in a multicultural society like ours, the pursuit of ethics has to incorporate a broad spectrum of moralities held by people with different backgrounds and educational heritages.

Say, for example, that we want to understand the conditions under which researchers should be allowed to perform a certain experiment, and how we can make sure those conditions are met. These questions should not be answered by scientists alone, just as war is too important to be left to the generals. It is our responsibility as scientists to call on different groups to weigh in and put everyone's thoughts on the table.

How does this type of bioethics dialogue play out in practical terms?

I've served on a number of international panels that seek to shape ethics guidelines for new science. To give you an idea, in one of the recent meetings I attended, more than 100 people came together to discuss ethical issues related to embryology and stem cell research. Only a fraction of us were scientists—which is the way it should be—and the rest were philosophers, social scientists, religious thought leaders, physicians, blue-collar workers, and legal experts, among others.

When everyone's opinion is adequately represented and respected, we can begin to understand and address individual concerns—using logic, rationalization, brainstorming, and dialogue. Not uncommonly, people's reservations about new science are rooted in fear.

Humans are naturally afraid of the unknown. Like all other animals, we react with fear to anything we haven't seen before. And although it's easy to see how this instinctive fear may once have helped organisms survive and propagate their genes, it can often be a dangerous force in modern human life. Fear of the unknown is the essence of racism and many other social problems.

The good news is that this fear will often dissolve by itself as we gain more knowledge and engage in conversation. It's natural to be afraid, but it's also quite possible to overcome it.

Nevertheless, from a philosophical standpoint, some aspects of biology will remain challenging in and of themselves—notably, anything that involves the origin of life or the end of life. We seem to have a hard time dealing with beginnings and endings. Many times, groups of people can reconcile their conceptual differences and move forward, but sometimes they cannot—in which case we must respectfully agree to disagree.

What happens when scientists or other members of society fail to engage in constructive discussion about science ethics?

Unfortunately, we've been able to watch this in recent months after He Jiankui, a Chinese scientist, announced to the world that he had used CRISPR technology to create gene-edited babies—experiments that he claims have resulted in the birth of twin girls.

Personally, I will not be convinced until I see the data. I remain very skeptical that such experiments could have been carried out successfully, in China or anywhere else.

More importantly, the recklessness of this supposed pursuit—conducted in a total vacuum of discussion and transparency—is the worst thing that can happen. It has set off a public outrage that could hurt the work of serious scientists for years to come.

You mentioned that fear often undermines people's trust in science. Is there anything about science that scares you?

Not really. I have seen many awful things, none of which were related to science. I was living in Iran both during the Islamic Revolution and during the Iran-Iraq War. I've seen tremendous violence—bombs exploding, people dying right in front of me, destruction everywhere. I know the atrocities human beings are capable of even without genetic engineering or other such innovations, and this scares me more than anything.

Science, I believe, is the opposite of destruction: It can reveal the truth about our existence rather than demolish it. Science is in fact an extension of philosophy, and it's all about answering the main questions: Where do we come from, what are we doing here, and where are we going? ◎

The Sharpie

WITHOUT THE SHARPIE, science would grind to a halt. Samples would get mixed up, data would go unrecorded, glassware would disappear into neighboring labs. A staple of the laboratory since the 1960s, the Sharpie is prized for its ability to reliably write on just about anything. Its utility makes it ubiquitous: Rockefeller scientists alone go through some 6,500 Sharpies a year.

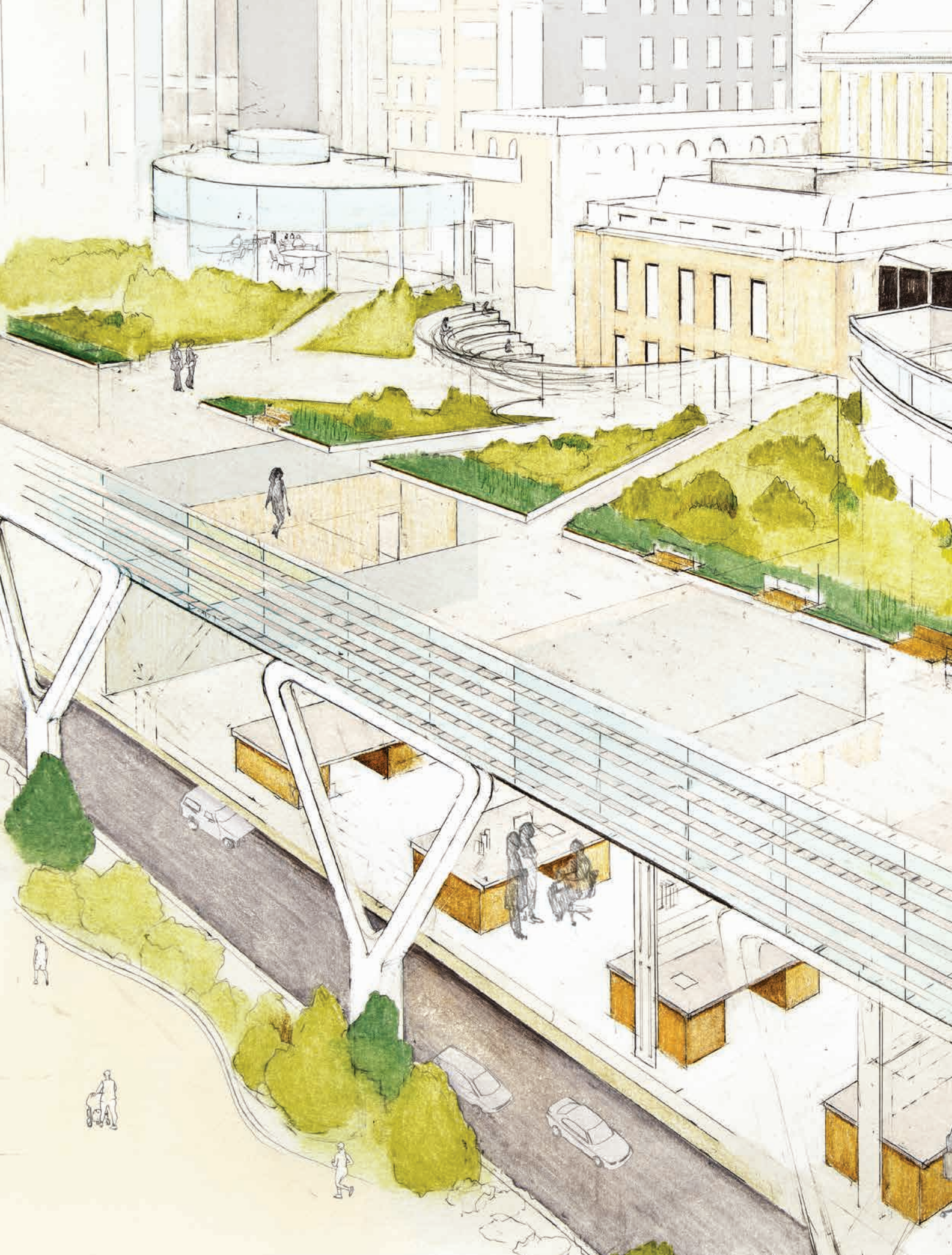
In neuroscientist Daniel Kronauer's lab, they have even become experimental equipment. It turns out that *Ooceraea biroi* ants, the species used in much of Kronauer's work, shun fresh Sharpie ink. That makes Sharpies a great tool for confining ants to small areas, or for testing their olfactory function. (For more on Kronauer's research, see "Even small brains make big decisions," page 22.)

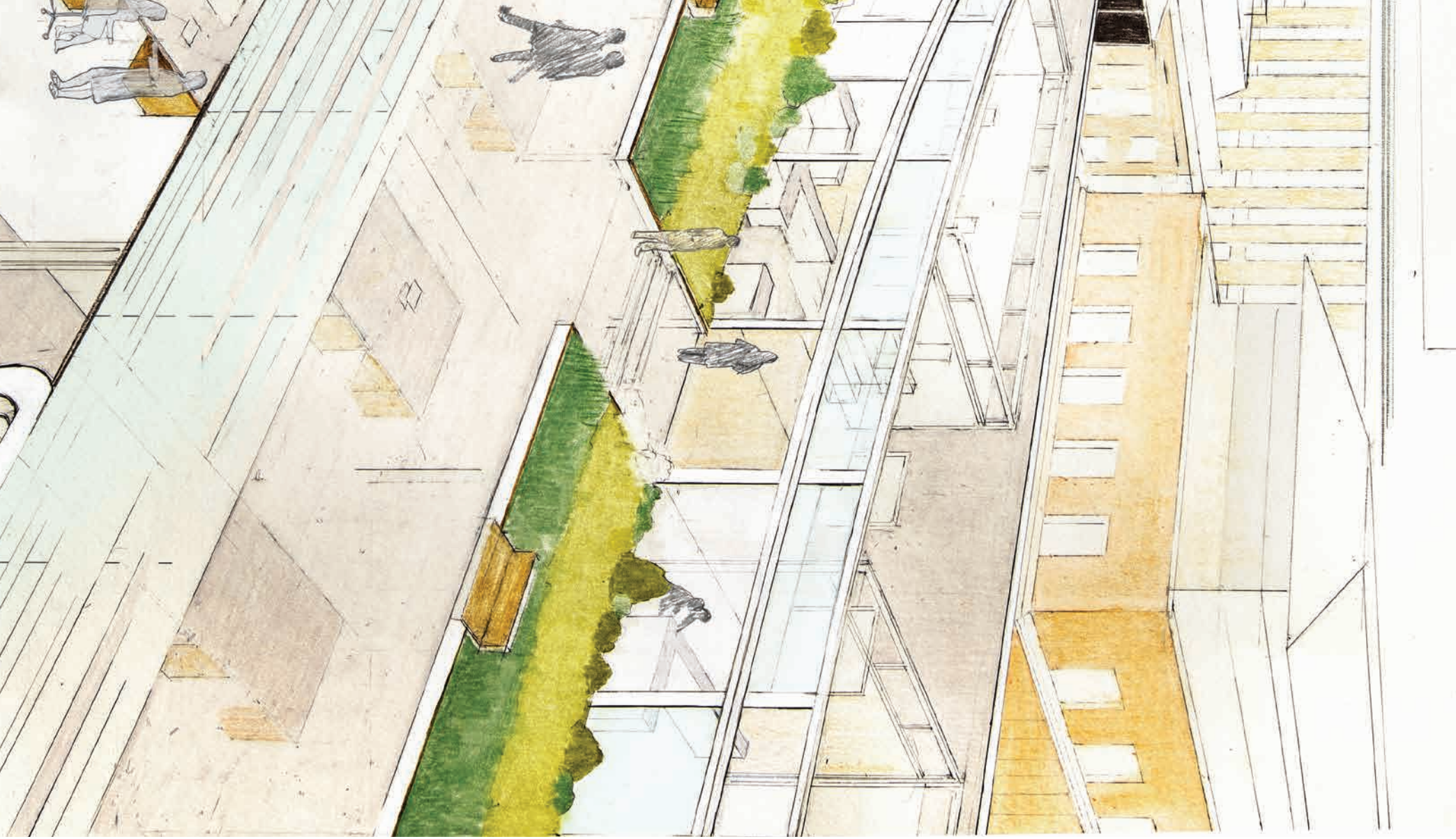
"Normally an ant will walk up to a Sharpie line and immediately turn around," says Leonora Olivos-Cisneros, a research specialist. "But mutants with olfactory deficiencies will walk right over it. No other substance works as well." (Inks from other sources have no effect, suggesting that the ants are reacting to what they smell, not to what they see.)

Because the exact ingredients of Sharpie ink are proprietary, it's difficult to determine which chemical is repulsing the ants. "Even if we don't know the components, we know it works," says Olivos-Cisneros.

"Red works best," she adds. ◎

Photograph by Daniel Kronauer





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