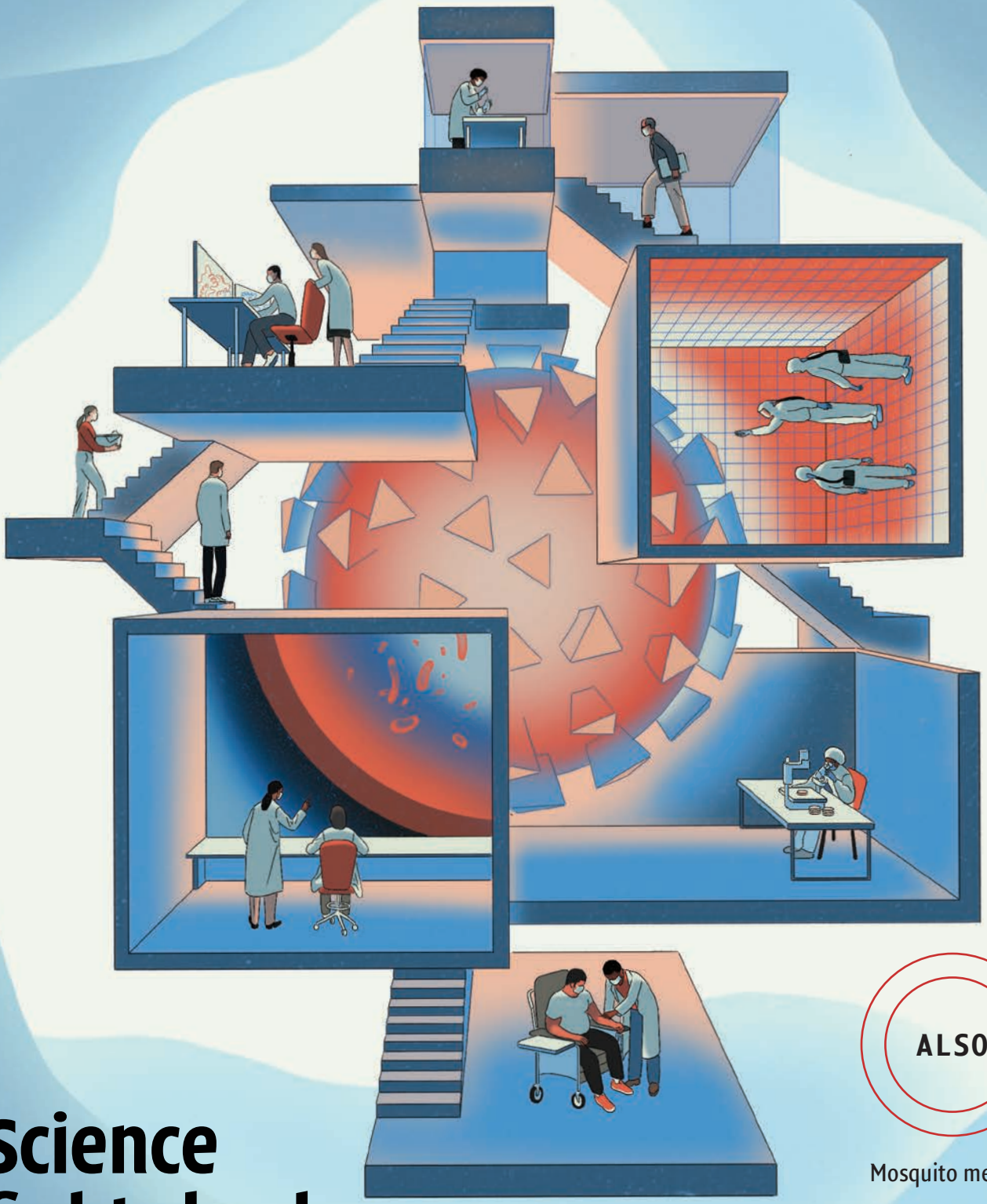
ISSUE 06
FALL 2020

Seek

THE ROCKEFELLER UNIVERSITY



Science fights back

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Mosquito menace

The brain inside your gut

Addiction then and now

“The summer months were a whirlwind.”

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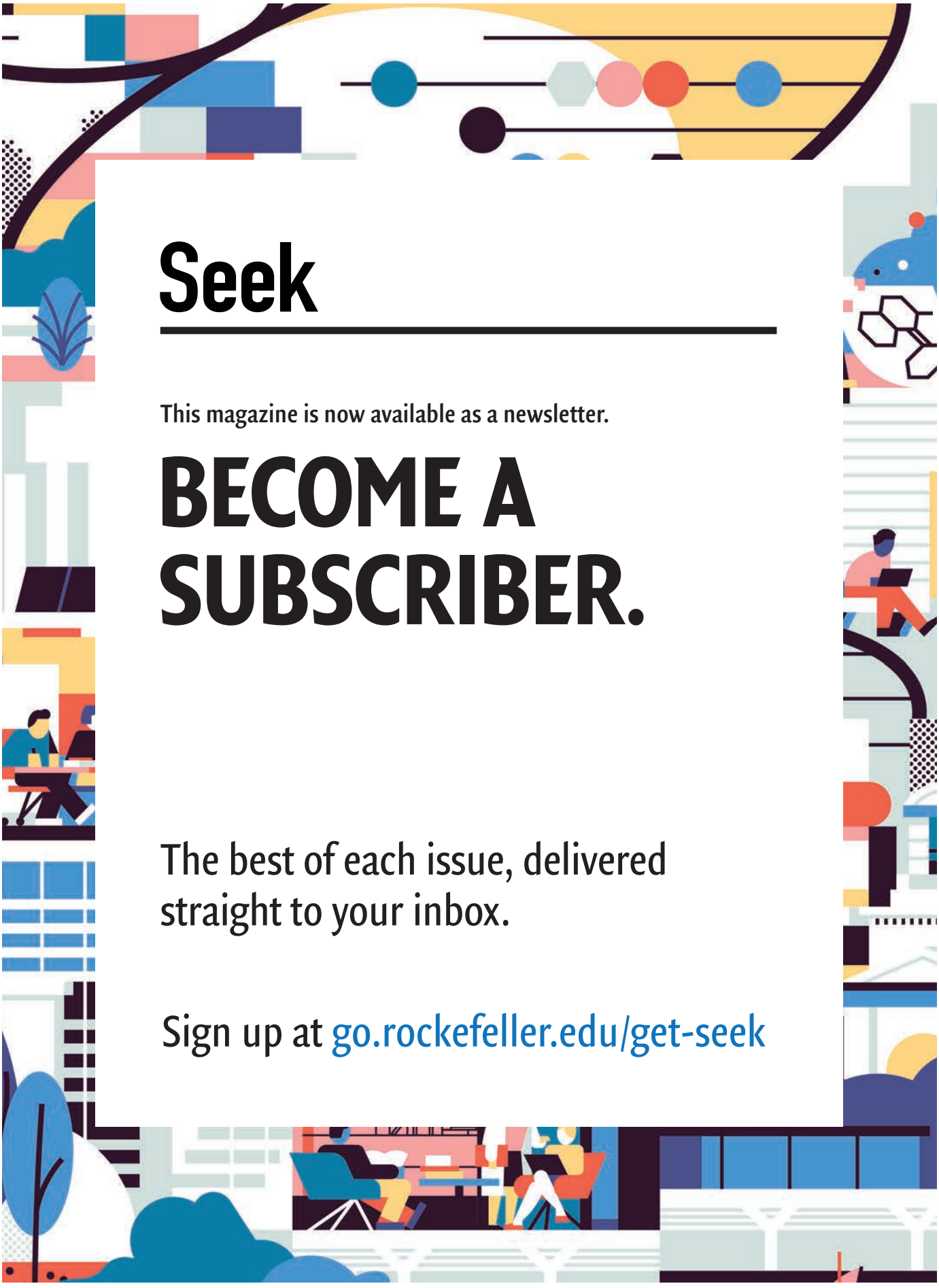
An intense new chapter

In early 2020, researchers everywhere united, scrambling to address a singular, urgent problem: a virus that was devastating the world. How they work and collaborate might never again be the same—it might be better.

Illustration by Jun Cen



ALEKSANDAR SAVIĆ

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In a better version of New York City, all kids would have access to inspiring science education. Jeanne Garbarino is the biochemist and science-outreach professional whose job is to make it happen.

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Top-tier biosafety. This lab is Hotel California for the tuberculosis bacterium, West Nile virus, SARS-CoV-2, and other deadly pathogens—they can never leave. For scientists, it's the only place to study these highly infectious agents without infecting themselves or others. The 5,600 square-foot suite, known as a biosafety level 3 facility (BSL-3), uses high-volume HEPA filters and negative pressure to contain airborne pathogens. Constructed last year, it is one of only a handful of BSL-3 labs in New York City, and has proved to be a crucial resource for Rockefeller scientists studying the novel coronavirus (read more about their work on page 22).

PHOTO BY FRANK VERONSKY

Reported by Lori Chertoff, Katherine Fenz, Bahar Gholipour, Eva Kiesler, Joshua Krisch, and Zachary Veilleux.

FOREFRONT

CELLULAR DECAY

When zombies take over the brain

DEATH IS A complex affair, at least for cells. There are several ways in which a cell can die: It might commit a form of suicide known as apoptosis, for example, or self-digest in necrosis. Further complicating matters is the fact that some cells may appear dead as doorknobs although they're actually in a limbo between life and death—a state from which they might at some point return as transformed versions of their old selves.

An intriguing example of such cellular zombies was recently discovered in the lab of Paul Greengard, a Nobel laureate and Rockefeller's *Vincent Astor Professor,* who passed away last year. A team of scientists was trying to figure out what goes wrong in the brains of people with Parkinson's disease. The researchers had long struggled to understand why dopamine-producing neurons in the midbrain perish, leading to debilitating movement

Illustration by Tianhua Mao

DATA

Neurodegeneration happens in all people, all the time. On average, an adult loses 3,250 neurons every hour.

problems characteristic of Parkinson's.

In retrospect, they may have been asking the wrong question. As the scientists reported in *Cell Stem Cell*, at least some of these midbrain neurons appear not to be dead after all, but rather to be resting in a zombie-like state known as senescence. And the results suggest that a zombie neuron may be even more damaging to the central nervous system than a dead one: By releasing inflammatory chemicals, the undead cells spread senescence to surrounding healthy neurons and make those neighbors shut down as well.

Research associate Markus Riessland says the discovery was especially surprising given that senescence is almost unheard of among neurons, although it does occur frequently in other parts of the body.

"Our findings shed new light on how Parkinson's disease progresses," he says, "and might provide new opportunities for treatment." For example, Riessland and his colleagues suspect that so-called senolytic drugs, which are known to remove senescent cells, might make it possible to slow the brain's deterioration. ◎

MARIO MORGADO

Fish use a vibration-sensing organ similar to the ear to detect predators' movements in the water around them.

Erzberger and Hudspeth with tanks of zebrafish.

IN DEVELOPMENT

Some cells are multilingual

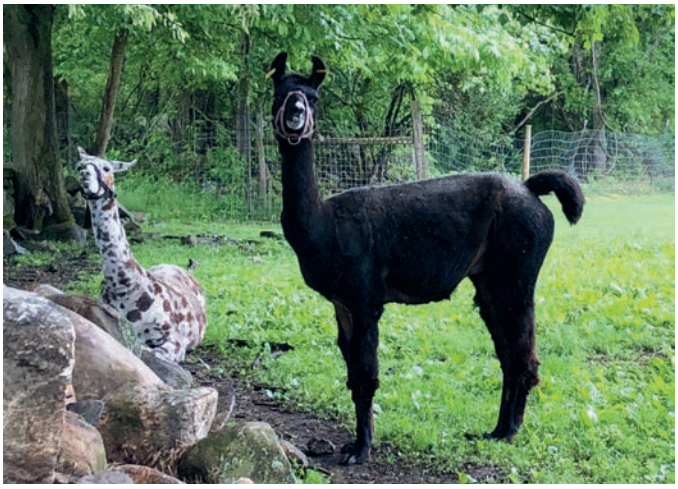
WHEN EMBRYONIC STRUCTURES take shape, their cells must navigate with painstaking choreography. One wrong step, and entire sheets of tissue may warp. The hair cells of the inner ear, the sensory organ used for hearing and balance, are a striking example of such precision: They neatly line up in two rows facing each other, like cadets preparing for a drill.

"The cells have no blueprint for where to go, they just figure it out themselves by talking to each other," says postdoc Anna Erzberger. It sounds simple, but it's not.

Together with colleagues in the group of A. James Hudspeth, the *F. M. Kirby Professor*, Erzberger has studied the developmental process that plays out in the fish equivalent of an inner ear. As it turns out, immature hair cells use more than one language to communicate.

When one cell divides into two, the daughters first engage in biochemical signaling—long held to be the singular mode of cellular discourse—to establish their individual identities. But soon after, they switch to mechanical lingo, enabling a kind of course correction. At this stage, the two cells may randomly find themselves occupying either the "right" or the "wrong" spot relative to one another—and in the latter case, they swap places. Propelled by surface-tension forces, the two cells gingerly dance past each other to assume the correct orientation.

"Traditionally, scientists have looked only to changes in genes and proteins to explain how developmental events happen," says Erzberger, who coauthored a paper on the findings published in *Nature Physics* in May. "But biochemistry is only part of the story, and the missing link is often mechanics." ◎



COVID-19

A ride out of the pandemic?

"IT SEEMS VERY strange that we should be picking, of all things, llamas," says Michael P. Rout, referring to his latest project with Brian T. Chait, the *Camille and Henry Dreyfus Professor.* "But for reasons we don't really understand, llamas make antibodies with fantastic properties."

Llama antibodies are smaller than those of humans but just as potent, and also easy and cheap to produce. The two scientists, with help from their two llamas, Rocky and Marley, are exploring antibody-based COVID-19 treatments with advantages that similar drugs based on human antibodies don't have, such as the potential to scale up globally. ◎

DATA 22 Number of pandemics in recorded history, including COVID-19, with a global estimated death toll of at least one million.

B-CELL BASICS

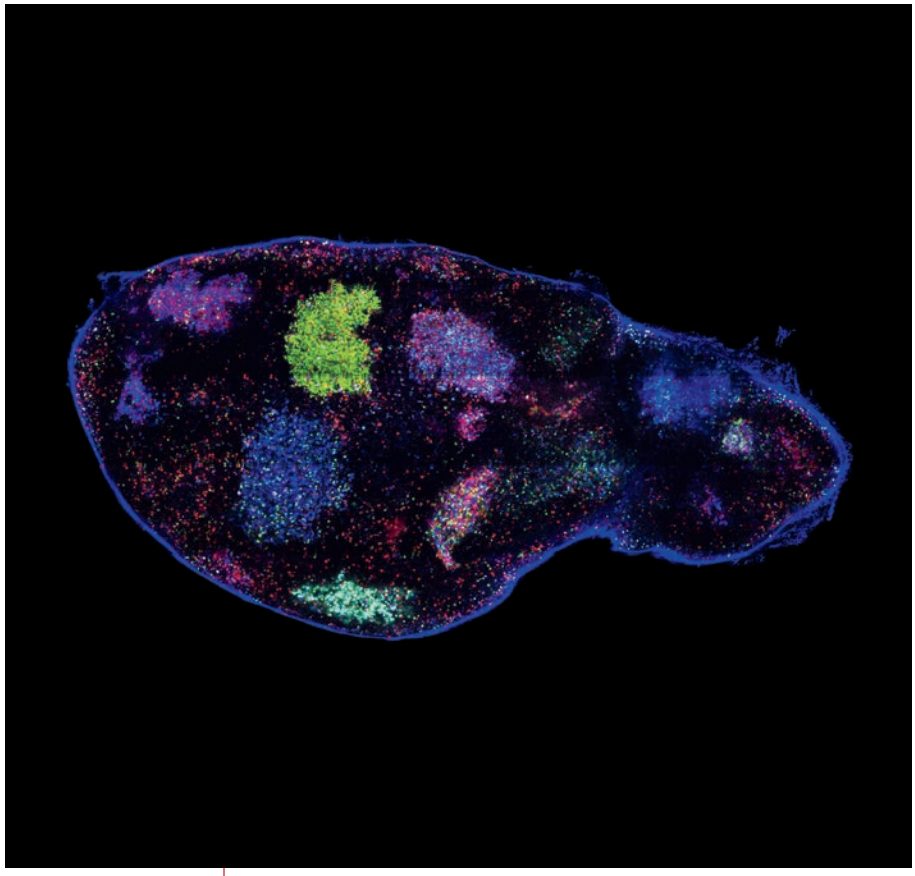
We need to get better at making vaccines, and not just because of COVID

NEW PANDEMICS REQUIRE new vaccines, but so do old plagues. For example, scientists have tried for decades to develop a universal flu vaccine that works for every version of the virus, but this goal remains elusive. Last year, influenza killed more than 60,000 Americans.

But new opportunities are on the horizon—and according to Gabriel D. Victora, the *Laurie and Peter Grauer Assistant Professor*, some might come from learning how antibody-producing B cells move in and out of germinal centers. Located in lymph nodes, germinal centers are what Victora calls "boot camps" for activated B cells. "The cells go in as amateurs and come out as skilled professionals making antibodies that bind more tightly to their targets," he says.

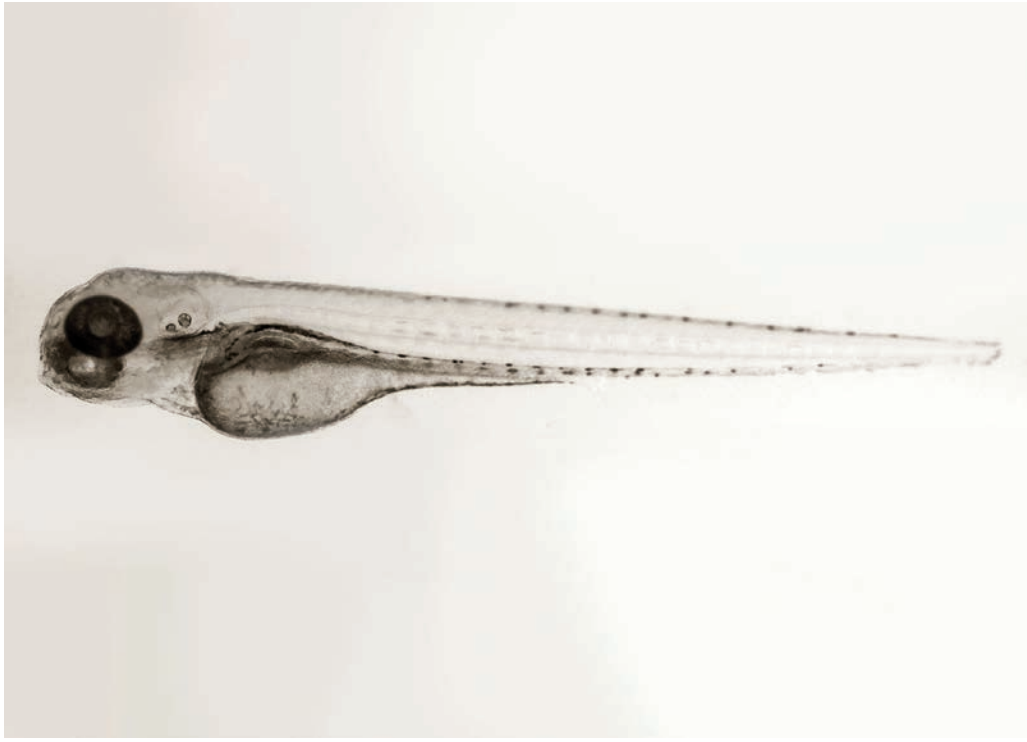
In recent work published in *Cell*, Victora's team found that those educated B cells don't easily return to camp the second time they're exposed to an invader—which might make it hard to develop effective vaccines against highly variable viruses. "If we can find the bottlenecks, and learn how to circumvent them, that might lead to improved vaccination strategies," he says.

The implications may extend to viruses other than the flu, such as HIV and hepatitis C—and perhaps also to coronaviruses. ◎



Activated B cells cluster in germinal centers (blue, green, and purple) inside a mouse lymph node.

CAPRALOGICS; THE ROCKEFELLER UNIVERSITY / LABORATORY OF LYMPHOCYTE DYNAMICS



10 MILLION

DATA

The number of neurons in an adult zebrafish. Cats have about 25 times as many; lobsters have 100 times fewer.

How brains make decisions is one of neuroscience's greatest enigmas.

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IMAGING INNOVATIONS

This fish is about to flip

IT'S NOT PLEASANT to swim when the pool is too hot.

In the lab of Alipasha Vaziri, a gang of zebrafish larvae has found an elegant solution to this problem: By simply flipping their tails to one side, they can cool down the water around them. The direction is important—every once in a while, the fish will try flipping the other way. It never helps.

Outside the fish tank is a team of researchers who, unbeknownst to the fish, are guilty of warming the water in the first place, with lasers, and of letting it cool to reward fishes that have learned the "correct" way to flip. In repeating this drill, they've been teaching the fish a new, goal-oriented behavior. And once the animals have been trained, they become part of an intricate set of experiments designed to shed light on one of neuroscience's greatest enigmas: how brains make decisions.

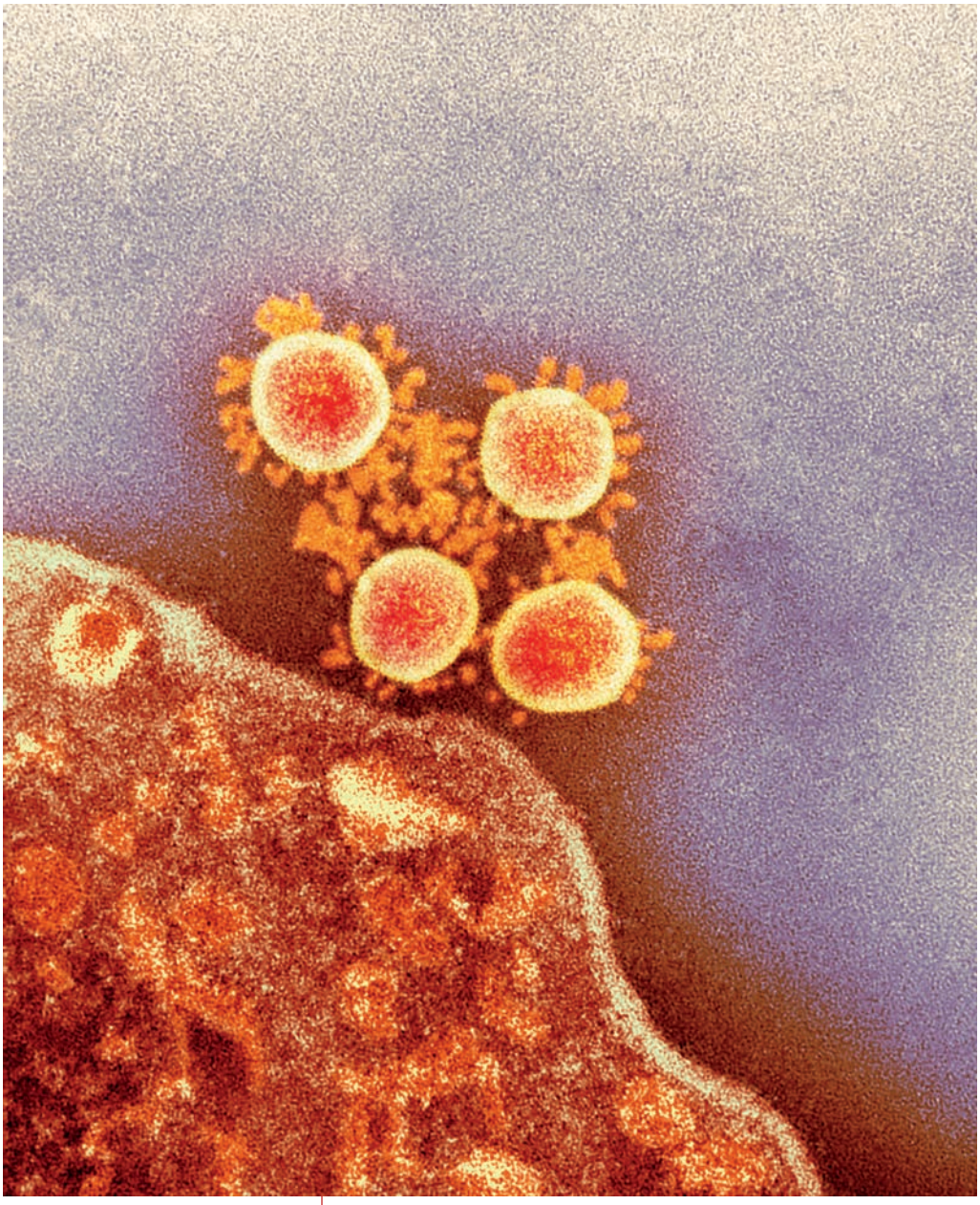
When a fish responds to rising temperature, it flips in the correct direction about eight times out of ten. The researchers closely monitor each tail flip while simultaneously detecting the activity of neurons in the animals' brains. The whole episode takes about 20 seconds, but the scientists are homing in on a shorter interval right after the water-warming laser is switched on and before the fish moves—the key moment when the left-or-right choice is made.

"The goal is to understand how decisions unfold," says Vaziri.

In their findings, recently published in *Cell*, the scientists describe the activity state of about 5,000 neurons across the entire fish brain. They identified a number of activity patterns—some related to the brain's sensing the heat, some to its coordinating tail flips, and others to the decision-making process. They also found that about 10 seconds before a fish moves, those patterns will foreshadow whether it's about to make the correct or incorrect turn.

In fact, just by observing the brain-activity profiles, the scientists could usually guess beforehand when the fish would move its tail, and whether it would gear left or right.

If predicting an animal's next move seems remarkable, so is the technology the scientists built in order to conduct these experiments. Tracking how neurons across multiple brain regions respond and cooperate is anything but trivial, and Vaziri's team made it possible by pairing advanced statistical methods with a novel light-field microscopy technique developed in the lab.



SARS-CoV-2 particles isolated from a COVID-19 patient are docking onto a host cell (lower left). The virus uses its spike proteins (orange) to attach to the cell and break into it.

DATA

A single nasal swab from a person infected with SARS-CoV-2 can contain 1 billion copies of viral RNA.

THE CORONAVIRUS

A mediocre mutator

IT'S A NIGHTMARE pandemic scenario: The drugs and vaccines being developed for COVID-19 are rendered useless by a SARS-CoV-2 mutation, and the scientists working on these treatments go back to square one. What if, like HIV or influenza, the coronavirus will be able to tweak its genome to dodge medical defenses and stay a step ahead of science? The possibility has been keeping people awake at night ever since the virus first escaped Wuhan.

But new research has delivered hopeful results, suggesting that SARS-CoV-2 may not be the master escape artist those other viruses are. A team of Rockefeller scientists found that, although the virus could potentially accumulate mutations affecting its spike protein—the key viral molecule recognized by antibodies—there are ways to prevent such mutants from resisting future treatments.

Scientists in the labs of Paul Bieniasz, Michel C. Nussenzweig, and Charles M. Rice are developing therapies for COVID-19 based on antibodies harvested from patients who successfully overcame the coronavirus. They are banking that these antibodies—amplified in the lab using cloning techniques—will bind to the spikes, preventing the virus from entering human cells (read more about their work in "Inside the Response," page 22).

Whether such drugs will remain effective over time depends on the likelihood that mutations will change the sequence and structure of the viral spike. So the team designed a series of experiments to see whether the spike could acquire resistance to the therapeutic antibodies. In findings published in August on the preprint server BioRxiv, they combined a faux coronavirus expressing the SARS-CoV-2 spike protein

NATIONAL INFECTION SERVICE / SCIENCE PHOTO LIBRARY

with antibodies, and grew the virus in human cells in a dish, then observed changes in the spike protein.

Of a vast pool of potential viral mutants, a small fraction was selected that dodged the antibodies and was able to infect cells. Predictably, these escapees carried slight genetic modifications in the spike protein, "the very types of mutations that could potentially make the virus resistant to antibody treatment," says Theodora Hatziioannou, a research associate professor in the Bieniasz lab.

But although some resistant mutants arose in the presence of individual antibodies, none were detected when a cocktail of two different antibodies targeting distinct spike regions was used. That is reassuring, Hatziioannou says, as it suggests that a drug formulation combining two or more antibodies would be unlikely to fail.

The scientists are also working to determine the probability that spike-protein mutations will undermine the effectiveness of a future vaccine. Quantifying that risk is more complicated, Hatziioannou says, since vaccines are typically designed to make the body produce its own antibodies, as opposed to introducing a specific kind of antibody into a patient's bloodstream. Success would therefore depend on what type of antibody response a given vaccine candidate elicits and how that response varies among people.

Further clues will begin to emerge as data from large-scale phase III clinical trials of developmental vaccines, now under way internationally, become available. ◎

"Scientists may have to fundamentally rethink how some aspects of our brains are organized."

Illustration by Chris Kindred

MIND MAPPING

Attention needs more attention

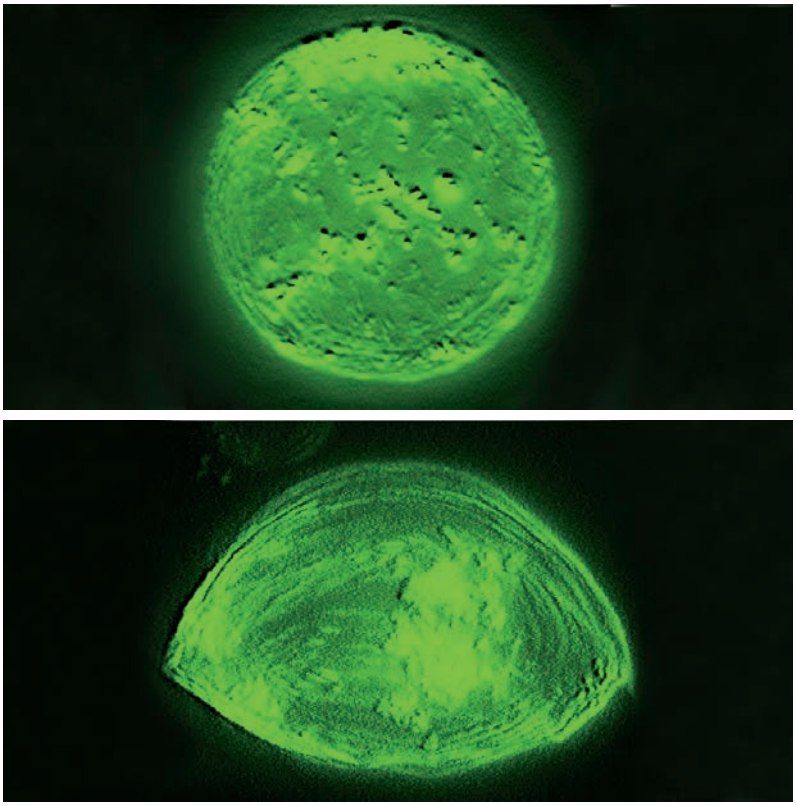
LIFE CAN SOMETIMES feel overwhelming—and it literally is. Every second, a tremendous soup of sensory information floods the human brain: sights, sounds, and sensations, all clamoring to be known. If not for the brain's capacity for selective attention, the world would forever look like chaos.

Selective attention allows the brain to decide which sensory input to prioritize at any given moment (as you're reading these words, for example, it's giving premium processing status to the sight of letters). It's an essential task whose biological machinery resides in a handful of areas, all confined to the brain's parietal and frontal lobes—or so scientists have long thought.

A few months ago, however, two neuroscientists reported their discovery of a new area that appears to control selective attention. In their behavioral experiments, in which subjects were tasked with watching moving dots on a screen, this area kept activating. Further tests revealed that its neurons closely track precisely which part of the screen is being attended to—the signature characteristic of an attention-governing brain region.

The discovery has introduced new mysteries. For one thing, the new area is located in an unlikely place—the dorsal part of the posterior inferotemporal cortex—that has not previously been linked to attention. It suggests that the classical account of selective attention isn't the full story, says Rockefeller professor Winrich Freiwald, who published the findings in the *Proceedings of the National Academy of Sciences* together with a colleague at the University of Bremen.

"Scientists may have to fundamentally rethink how some aspects of our brains are organized," Freiwald says. ◎



Synthetic cells have mastered the art of stretching, a prerequisite for self-replication.

TROUBLESHOOTING

Primordial shapeshifters

IT'S THE HOLY grail of synthetic biologists: creating a living cell from scratch. So far they've managed to make simple prototypes—essentially tiny fat balloons with a soup of genetic material inside, capable of reading genetic code, producing proteins, and transporting molecules around. Yet these artificial blobs lack an essential feature shared by all living things: the ability to generate more copies of themselves.

Self-replication is arguably the most sophisticated of biological phenomena and has long seemed nearly impossible to engineer. But clues are starting to emerge thanks in part to Albert J. Libchaber, the *Detlev W. Bronk Professor Emeritus*, who became interested in the process by which a cell deforms from a sphere into an oval—a first step required for it to split into two. "It's not easy to divide a perfect sphere," he says.

Together with Vincent Noireaux, a postdoc in the lab now at the University of Minnesota, Libchaber found a secret ingredient that can help cell prototypes elongate: polyethylene glycol, a sticky molecule found in skin creams and soap bubbles. Previously, the scientists had tried stretching their spherical creations with MreB, a protein that builds a bacterium's inner scaffolding, which molds the cell into its trademark rod-like shape. But MreB on its own did nothing to flatten Libchaber's cell replicas; only after polyethylene glycol was added did it turn into a dynamic polymer capable of inducing the sphere-to-oval transformation.

The findings, published in the *Proceedings of the National Academy of Sciences*, bring scientists a step closer to creating a self-reproducing molecular contraption: a truly living cell made from 100 percent dead ingredients. ◎

WEIRD ANIMALS

What Darwin never guessed

THE ORIGIN OF species usually goes like this: One group of stickleback fish lives at sea, the other goes to freshwater, and voila—one species becomes two. For centuries, evolution has been thought to generally march in the same direction, toward new traits and more-specialized adaptations. But recently, scientists at Rockefeller and George Washington University found a quirky exception.

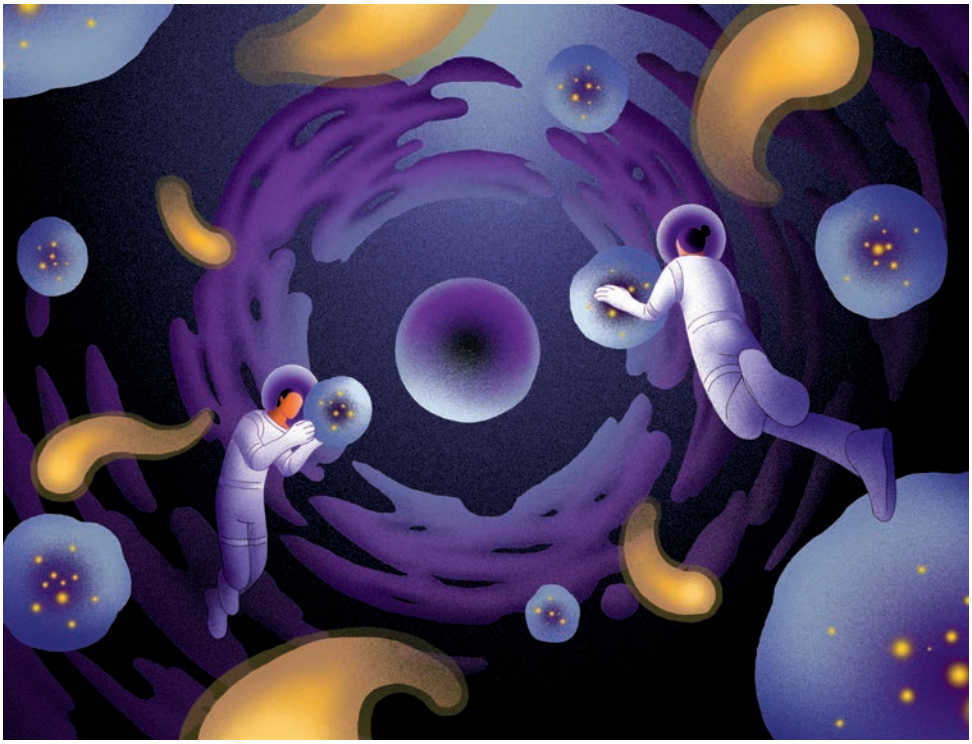
Turtle ants live in trees, in tunnels previously excavated by beetles. To keep intruders out, ant soldiers use their large heads to plug the tunnels. But when an ant colony moves to a new habitat, the soldiers may have to adapt to larger or smaller holes dug by a different beetle species, and the size and shape of their heads evolves for a snug fit. Surprisingly, researchers found that this aspect of ant evolution has gone both forward and backward—sometimes creating novel head shapes, other times reverting to more primitive ones.

"You would think that once a species is specialized, it's stuck in that narrow niche," says Daniel Kronauer, the *Stanley S. and Sydney R. Shuman Associate Professor*, whose team published the findings in the *Proceedings of the National Academy of Sciences*. "But turtle ants have a very dynamic evolutionary trajectory with a lot of back and forth." ◎

Turtle ant soldiers display a wide range of head shapes and sizes.

SCOTT POWELL

Return of the cytonaut



"CELLS LIVE IN a watery world, even when the organisms of which they are part do not," wrote Christian de Duve in his 1984 book, *A Guided Tour of the Living Cell*. Most human cells, for instance, are immersed in fluids that render their vast inner space jelly-like. Floating within this cytoplasmic soup are mitochondria, ribosomes, vacuoles, and many other so-called organelles—tiny instruments that carry out a cell's basic functions.

Inspired by the films of Jacques Cousteau, de Duve wanted his readers to embark on the journey with the mindset of a "cytonaut" ready to explore "a strange world, fascinating, mysterious, but very far removed from our everyday experience." The late cell biologist was himself a pioneer who, together with Albert Claude and George E. Palade, spent the 1940s and 1950s detailing the first functional map of the cell—work for which the three Rockefeller scientists later shared a Nobel Prize.

A must-see along the tour is the lysosome, a bubble-shaped organelle that de Duve was the first to set eyes on in 1955, and whose acidic interior was subsequently found to serve various purposes, such as breaking down cellular debris. Yet it wasn't until early this year that scientists discovered that our cells need this sour little sac to process iron, an essential nutrient, into a form they can metabolize in order to survive. This may, in fact, be the most important of the lysosome's functions.

Graduate student Ross Weber made the discovery in a lab not far from the one de Duve once inhabited. There, in an experiment that had to be controlled with minute precision, he manipulated cells to make their lysosomes less acidic. For reasons that have long been unknown, cells will stop dividing and die if the pH within lysosomes rises above a certain threshold.

Today Weber and other members of the lab, led by Kivanç Birsoy, have a possible explanation for this phenomenon. Their experiments show that cells with more-alkaline lysosomes suffer iron depletion—and as a result, they lose their ability to produce essential molecules such as DNA. "Lysosomes participate in a lot of different cell functions like signaling, metabolism, and recycling," says Birsoy, who is Rockefeller's *Chapman Perelman Assistant Professor*, "but processing iron seems to be the only thing cells really cannot do without them."

He hopes the new research, published in *Molecular Cell*, might lead to the development of novel cancer therapies. Several types of tumor cells are known to be sensitive to elevated lysosome pH, and the new findings suggest it's the ensuing iron deficiency that deals these tumor cells a fatal blow. This could mean that depleting tumors of iron offers an effective way to kill them, says Birsoy. This is the latest possibility to come out of his lab's extensive effort to develop new treatments that starve tumors for nutrients they cannot produce on their own.

The team also plans to explore whether the new findings could be relevant to other conditions linked to the loss of lysosome acidity, including a group of rare metabolic disorders and neurodegenerative diseases. "We believe there are a lot of exciting possibilities out there," Birsoy says.

Moreover, the lysosome isn't the only organelle whose inner secrets might yield ideas for new medicines. Mitochondria, for example, the cell's peanut-shaped powerhouses, are the targets of several promising cancer treatments. And who knows what other treasures await 21st-century cytonauts as they plunge deeper into the cellular sea. ◎

Illustration by Wenkai Mao

Q&A

The long overdue science of addictions

With Mary Jeanne Kreek

FRANK VERONSKY

IT WAS CALLED a trailblazing medical experiment, but few scientists and physicians wanted anything to do with it. Launched in the early 1960s, it would have been illegal just a few years earlier, and the idea was still controversial.

Some of the patients, a group of men in their 20s and 30s, had already been in and out of jail a number of times. Once ordinary New Yorkers with respectable jobs—among them a musician, a truck driver, and an office clerk—they were now longtime heroin addicts, often dismissively labeled as "psychopaths" or "junkies." The medical establishment believed their addiction lay beyond a doctor's responsibility, and if they had been treated in a hospital before, they likely had been there as a prisoner.

At The Rockefeller University Hospital, however, the men found themselves in rooms with unlocked doors. There, every day for several months, Mary Jeanne Kreek, then a second-year medical resident, gave them an oral dose of methadone—a special type of painkiller that Kreek and her mentors believed could treat the men's addiction by stunting their hunger for heroin. And she cared for them with the bedside manners she would show any other patient.

Kreek's early work helped launch the methadone clinic, helping millions of people with heroin addiction.

The experiment was among the very first to use a pharmaceutical intervention to treat addiction—and it worked. Many of the men eventually stopped taking heroin and continued with long-term methadone maintenance therapy. They returned to school, obtained jobs, and in some cases reconciled with their families. "As measured by social performance," the investigators wrote in one of their first reports of the research, "these patients have ceased to be addicts."

The 1964 study led to the development of methadone maintenance therapy, the most common treatment for heroin and other opioid addictions, today used to treat over 1.4 million people worldwide. And for Kreek herself, it launched a lifelong career at the vanguard of research on addiction diseases related to opioids, alcohol, cocaine, and other substances.

In the years since, her work has continued to both expand our understanding of addiction and shift society's attitudes toward victims. Substance abuse is now seen less as a moral weakness and more as the symptom of a medical condition—a disease in need of more research and better treatments. Today the field is rife with new tools, and researchers are closer than ever to unraveling a mystery that has long baffled humanity, perhaps ever since the first Mesopotamians began picking opium poppies 5,000 years ago: What gives some substances the power to warp the brain and take such strong command over the mind and behavior?

We asked Kreek, Rockefeller's *Patrick E. and Beatrice M. Haggerty Professor* and head of the Laboratory of the Biology of Addictive Diseases, to tell us more about the past, present, and future of the field.

What made the 1964 study so groundbreaking?

When we started the study and brought in active heroin users to The Rockefeller University Hospital, some of our colleagues didn't understand why we were doing it. People with addiction were thought to suffer from personality issues and were usually referred to psychiatric care. But such treatment wasn't working, and over 90 percent of heroin addicts would relapse after a year. So Vincent P. Dole, who was my mentor and an accomplished scientist in the fields of hypertension

and obesity, thought the underlying problem had to be something different.

We realized early on that heroin users had a strong "hunger" for the drug—not because they wanted to get high but because they would not feel normal without it. Addiction is less about seeking pleasure than about avoiding feeling ill. This was the first clue that we were looking at something more similar to an endocrine disorder than a personality problem. And it led us to try to find a suitable pharmacological intervention, just like how you would go about developing treatments for other medical disorders.

"Addiction is less about seeking pleasure than about avoiding feeling ill."

What else have scientists learned about addiction by studying the underlying biology?

We now know, based on years of research in rodent models, that addictions are diseases of the brain with behavioral consequences. A specific addiction occurs because exposure to a drug changes the brain in multiple ways. For example, after chronic exposure to an opioid, we have seen dramatic changes in the nucleus accumbens, an area responsible for the brain's reward system, and in regions involved in memory and learning, including the caudate, putamen, and hippocampus. Affected neurons undergo profound shifts in gene expression that change the availability of the receptor targeted by an opioid, all of which affects the brain's basic functioning.

We have also learned that the extent and nature of such changes can vary from person to person—which explains why some people are more susceptible to addiction than others. This vulnerability has been shown to be due in part to genetic differences.

Some critics say methadone therapy is just replacing one opioid with another. Is that true?

It is very misleading. Both heroin and methadone are opioids, but they act differently in the brain. Heroin, like most other opioids, has a short duration of action. As a result, it acts on its receptor, the mu opioid receptor, like a jackhammer, turning it on and off so rapidly that neural circuits become disrupted. In contrast, methadone and a similar medication, buprenorphine, are long-acting in humans. Their effect on the receptor is steady, which helps to stabilize the disrupted physiology. By sustained action at the receptor, these medications also block the usual "high" feeling caused by heroin, should patients continue to consume it.

Could the same approach be used to treat other addictions?

That's our hope. We know that certain molecules, so-called kappa opioid receptor agonists, can inhibit responses to cocaine in animals by acting similarly to methadone, albeit on a different opioid receptor subtype. We have studied them in rats and mice that learn to self-administer the drug by pressing a lever; when we give these animals a kappa agonist, they stop trying to self-administer cocaine.

We now have over 400 novel compounds that were designed by people in my lab or collaborating chemists. We're studying each to identify any that could be developed into a safe and effective drug.

We are also working to develop a similar treatment for alcoholism based on a kappa agonist drug, nalfurafine, which was developed in Japan for treatment of itching skin in individuals with kidney disease. We're currently studying it in rodents, either alone or in combination with naltrexone, an already approved mu opioid antagonist that other groups have shown is modestly effective for treating alcoholism. Given that both compounds have been used safely in humans, I'm hopeful that this strategy will become available as treatment for alcohol addiction within the next five years.

To what degree does one's life trajectory play a role in addiction?

The environment does play a role, but not in the way we used to think. If you're never introduced to a drug, you won't become addicted—however, genetics is what ultimately drives the development of addiction.

We know this because of studies in my lab and others using mice engineered with specific gene variants mirroring those that have been implicated in addiction in humans. In one case, we found that a single-nucleotide polymorphism (a difference in a single DNA building block) made one group of mice self-administer twice as much heroin as their wild-type counterparts. It was not because of their family, it was not their environment. It was not peer pressure. It was a subtle change in DNA.

Have attitudes to addiction changed in light of such findings?

There have been improvements, but the stigma prevails and there are still systemic impediments to treatment. For starters, regulations overseeing methadone maintenance therapy are still bizarrely tough. To be able to prescribe it, doctors need to have special training and be part of a government-regulated clinic with a certain number of counselors and medical staff for patients. Paradoxically, no such restrictions apply for prescribing other opiates for pain relief—in fact, doctors were long encouraged to prescribe them, which contributed to the opioid crisis we face today.

We still have some way to go before addictions are truly understood as diseases. Few medical schools teach their students that this is in their domain of obligation—that they should be both identifying and treating addiction in their patients. ◎

130

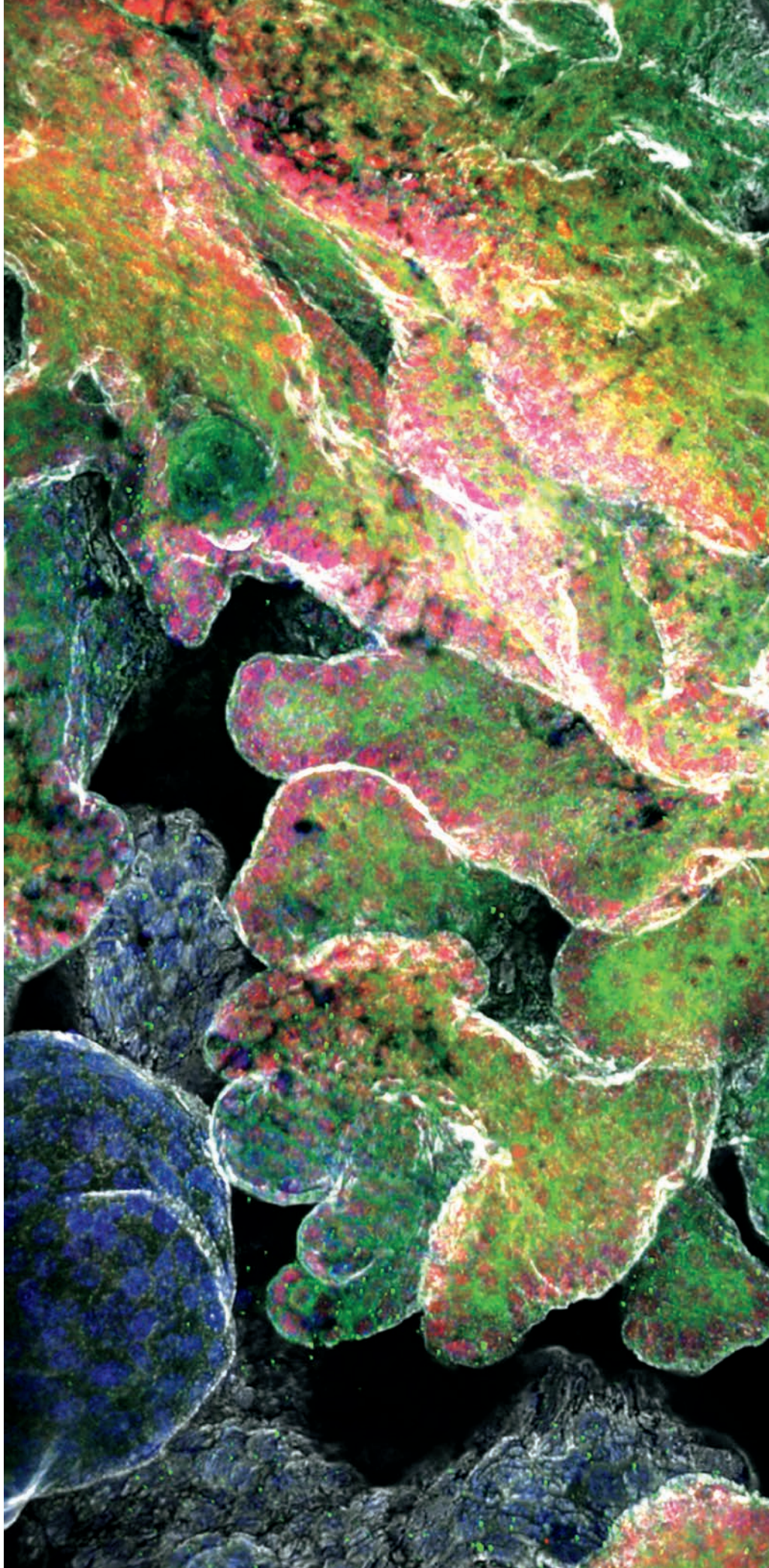
DATA

The average number of deaths per day in the U.S. attributable to opioid overdose.

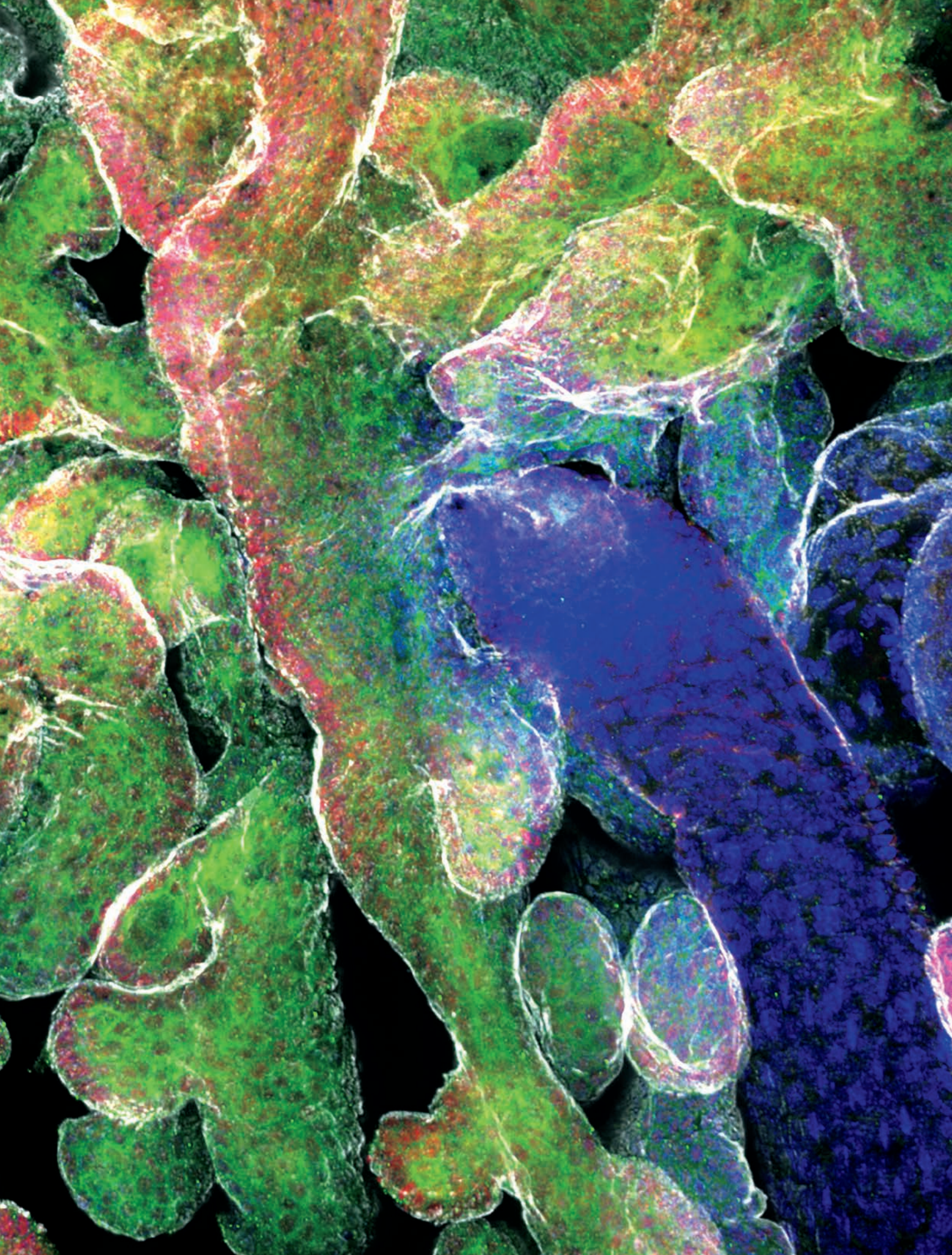
Benign buds

TWO OF THE most common forms of skin cancer arise from the same source—epidermal stem cells—but take different paths in life. Basal cell carcinomas start off as bud-shaped cell clusters and tend to humbly stay put. This makes them less aggressive than their cancerous cousins, squamous cell carcinomas, which originate as tiny folds before burrowing into deeper layers of the skin to form tumors capable of spreading throughout the body.

A team led by Elaine Fuchs, the *Rebecca C. Lancefield Professor*, captured this image while trying to understand what makes some precancerous tumors turn malignant while others remain relatively benign. It turns out that the mechanical properties in the tissue are key factors determining whether epidermal stem cells (green) grow up to become the docile buds seen here—or insidious folds in the skin, just waiting to metastasize. ◎



THE ROCKEFELLER UNIVERSITY / ROBIN CHEMERS NEUSTEIN
LABORATORY OF MAMMALIAN CELL BIOLOGY AND DEVELOPMENT



It takes a certain kind of person to make kids from all backgrounds feel at home in the world of science. And sometimes you have to dance on the internet.

Jeanne Garbarino

By Caitlin Shure

She cruises from bench to bench, observing the goings-on of her lab. Currently, Jeanne Garbarino's high schoolers are combing the inside of their cheeks for chunks of genetic material that they'll submit to a PCR machine—a step that will later allow them to scrutinize their own genes. The exercise is part of a program, helmed by Garbarino, that invites students from local schools to spend a day on Rockefeller's campus. She is doling out supplies and advice when a few of her scientists-in-training abruptly switch course: They would like to record a dance routine for TikTok. It's not part of the experiment, but Garbarino obliges.

In her role as director of RockEDU Science Outreach, Garbarino welcomes spontaneity—both because she wants her visiting students to enjoy themselves and because occasional silliness is part of the learning process. And so she dutifully dances alongside the teenage girls presently occupying the university's classroom lab. A discussion of bioethics will follow, as will pizza.

"I'm a 12-year-old in a 41-year-old woman's body," says Garbarino. "I think that's what makes me good at this."

But in fact, Garbarino is good at her job for many reasons. For starters, she possesses an infectious affection for the material. She discusses biology not in the manner of a stodgy professor instructing pupils but like a close friend sharing highlights of her favorite TV drama. She's a nerd, but she's also thoroughly cool.

Outgoing and outspoken, Garbarino has made a name for herself and for RockEDU, an outreach initiative that runs a variety of programs to promote scientific literacy and appreciation in K-12 students. More than a series of lessons, the program aims to dissolve the barriers between science and the rest of society. (Although in-person programs have been suspended since the spring because of COVID-19, RockEDU has temporarily shifted many of its programs online, combining Zoom sessions with at-home experiments conducted with supplies mailed to students' homes.)

It's a job that requires a huge amount of multitasking: In a given day, Garbarino might train mentors, write a grant, match students to laboratories, tackle a budget, and conduct a science workshop. But the best parts of the job are those that lead to the kind of science-infused silliness that appeals to Garbarino's inner 12-year-old. They are also the type of activities that, when she was actually 12, she would have loved.

Garbarino became accustomed to making executive decisions at an early age. She received her first set of house keys in third grade, right around the same time she started babysitting for local kids. Dinner was set at 6 p.m., but beyond that she was free to roam the neighborhood as she saw fit. And in Norwood, the Bronx community where Garbarino grew up, ample adventures awaited within walking distance.

Proudly groomed in the pre-internet era, Garbarino regularly corralled neighborhood friends to play handball, peruse candy shops, or shred the local skating ramp. She performed the role of big sister to myriad children, whether related by blood or by block. In this role, she honed her leadership skills and learned the importance of community support. It was a childhood that, Garbarino says, she wouldn't trade for anything.

Although rich in camaraderie, Norwood didn't offer the educational opportunities a future scientist might hope for. A working-class neighborhood, it was what

Photographs by Mario Morgado

Garbarino would now refer to as "under-resourced," meaning it didn't provide the experiences and tools that more privileged students take for granted. So when she developed an early and intense interest in science, Garbarino looked outside the classroom to sate her intellectual hunger.

"I would walk to the public library on East 205th Street and copy pages out of the encyclopedia for hours at a time," she says. "Yeah, I pretty much loved science from birth."

Still, it wasn't until college that Garbarino formally pursued this passion. At SUNY Geneseo, a state college about 40 miles south of Rochester, she was drawn to biochemistry and began working part-time in a lab devoted to cholesterol metabolism.

She learned to pipette, run electrophoresis gels, and conduct the other basic sorcery that one performs as an undergraduate researcher. She knew she wanted to become a scientist.

Accordingly, during her senior year she did her best to cobble together a grad school application. "I wasn't sure what I was doing and I had nobody helping me," Garbarino recalls. "I just wrote a letter. It was probably terrible."

Terrible or not, the application landed her an interview at Columbia University, in the Department of Nutritional and Metabolic Biology. Though she had learned her way around a lab, Garbarino had no clue how to conduct herself during an interview. The moment she arrived, she felt out of place; and her interviewer, molecular cardiologist Jeanine M. D'Armiento, sensed her discomfort. She questioned Garbarino about her background, eventually asking whether she had family members in science or similar fields.

"My parents sell tickets for Metro North," Garbarino answered. D'Armiento responded in kind: "Jeanne, my dad is a bus driver."

Columbia did not accept Garbarino that year. But D'Armiento offered her a job as lab technician. The ensuing months were a crash course in laboratory etiquette and a gauntlet of tough love.

"Dr. D'Armiento let me know when I wasn't meeting the bar. She pushed me and made me learn the concept of accountability," Garbarino says. "I will never stop being grateful for that."

When Garbarino reapplied the following year, Columbia accepted her with an apology.

> "Our goal is not to create an army of researchers but to show that science is a part of our society. We want to instill trust in science and scientists."

KEENLY AWARE OF the importance of strong mentorship—particularly in the sciences—Garbarino now strives to provide both practical learning and emotional encouragement to her trainees. Over the past eight years, she has groomed a robust network of RockEDU mentors who offer guidance to young students from diverse backgrounds. One of several programs under the RockEDU umbrella, an initiative called LAB Jumpstart teaches laboratory skills to kids from underresourced communities. The program also pairs students with "advocates" who provide extracurricular advice, ranging from how to write a professional e-mail to tips on the top campus snacks.

"That extra mentorship helps the students believe that an institution like Rockefeller can be a home for them," says Garbarino. "It also helps them develop their own identities in science and see that this environment is for all types of people."

Other RockEDU programs focus on K-12 educators and on science curriculum development. But Garbarino's mission isn't just to educate or even to inspire; she wants to restructure the conversation around science, dispelling the notion that biomedical research, and the institutions that practice it, are elitist and inaccessible. Such perceptions, she says, foster public skepticism of science and have real implications for policy. In this sense, RockEDU aims to function not just as training ground for future researchers, but also as a vehicle for cultivating scientifically informed citizens.

"Our goal is not to create an army of researchers, but to show that science is a part of our society. We want to instill trust in the scientific process and in the scientists who participate in it," says Garbarino.

For this reason, the RockEDU curriculum includes explorations of science's role in the world. Students studying their DNA, for instance, will also debate the social and ethical implications of widespread genetic testing: Is it advisable to submit your genes to an online ancestry company? Who should have access to this data? Is it appropriate to use gene-editing technology in humans?

RockEDU's flagship event, Science Saturday, annually draws more than 1,000 New Yorkers in non-pandemic times, filling an entire building with hands-on exhibits designed and run by Rockefeller scientists. By establishing connections between researchers and city residents, such programs emphasize that science is not the purview of a certain category of person but of all cultures and communities.

AT COLUMBIA, GARBARINO gradually came to appreciate her own place in the world of science. After rotating through a range of research areas, she narrowed her focus to metabolic mechanisms in yeast. Specifically, she investigated the process by which excess fat kills the organism—a phenomenon called lipotoxicity

Garbarino (right) helping students from her LAB Jumpstart program build a Geiger counter.

MARIO MORGADO

that may be relevant to understanding some human medical conditions.

"In yeast, I could examine things at a very narrow scale. I loved looking at how biochemical pathways were working and which genes were getting turned on and off," says Garbarino. "I just loved probing, tinkering, and exploring."

Garbarino's parents were less jazzed. Civil servants with government pensions, they saw their daughter living on a measly student stipend, with little job security, and they worried.

"My mom had a hard childhood—she was homeless several times in her life—so it was difficult for her to understand why I would take the luxury of continuing my education," Garbarino says. "That tension sometimes got in the way of being able to talk about why I was doing what I did."

For kids from underresourced communities, the barriers to pursuing science are more profound than a dearth of classroom microscopes. Students contend with cultural obstacles that persist even as one breaks into the highest echelons of academia. So while Garbarino was on the cusp of obtaining her doctorate, her parents were questioning why she still didn't have a real job.

After receiving her Ph.D., she began a postdoctoral fellowship at Rockefeller in the lab of Jan L. Breslow, head of the Laboratory of Biochemical Genetics and Metabolism, where she studied how cholesterol moves around inside cells. Simultaneously, Garbarino began exploring alternative ways of applying her scientific mind. She regularly contributed to Rockefeller's student-led campus newsletter, launched a science blog, and created a discussion series.

Through these projects, Garbarino became deeply interested in how to convey scientific ideas to nonscientists—and more broadly, how to expand the perimeters of the scientific community. She visited local schools, took students on lab tours, and volunteered for every outreach opportunity that presented itself. And that, she says, is where she found her sweet spot. During the final stretch of her postdoc, Garbarino asked Breslow for advice on how to translate her passion for outreach into a real job—ideally one at Rockefeller. Responding like a true scientist, Breslow counseled: "Write a proposal."

A few months later, Garbarino found herself in the office of Rockefeller's then president, Marc Tessier-Lavigne. Proposal in hand, she underscored the need to portray the human side of research and described outreach as not just a source of education but a form of community building. "I told him: This is the kind of program that Rockefeller needs, and I want to be the one to lead it," she says. Two days later, Garbarino became the new director of science outreach, taking over a program that, even on campus, had largely flown beneath the radar.

Today, Garbarino's scientific training continues to inform her approach. Each experiment is guided by a theoretical model that she created to optimize the educational experience. At the core of the model sit two groups: people with formal expertise in science and newcomers who want to engage with it more deeply. A successful outreach program, says Garbarino, is one that meets the goals of both groups.

A Rockefeller postdoc, for instance, might want to enhance her teaching skills; and a young student from the Bronx might want to better understand how genes give rise to disease. Garbarino's job is to develop a program that satisfies both. In theory, the task is simple. In practice, however, it involves a dizzying array of logistics.

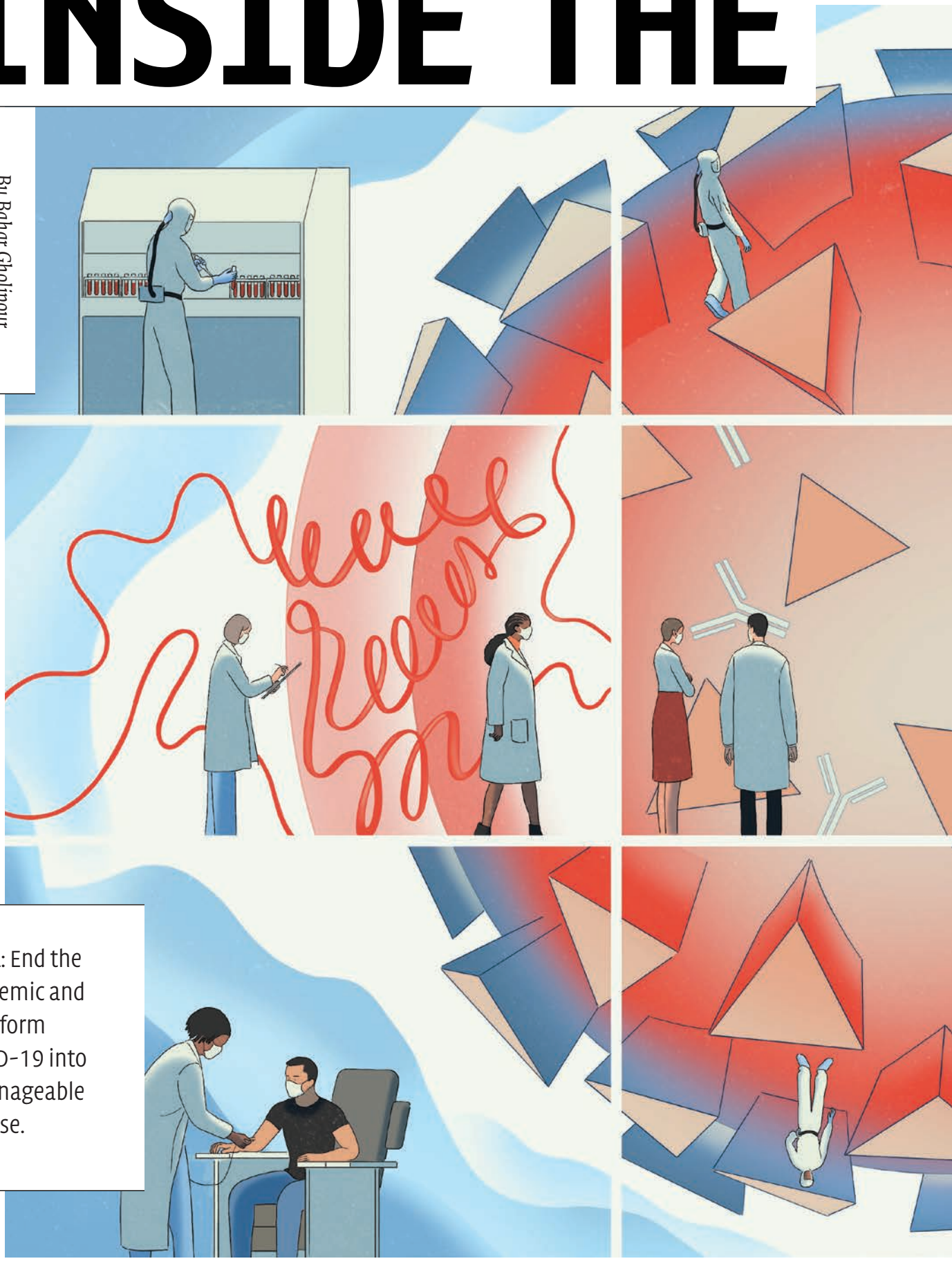
"Even when you're being very careful, a program could fail miserably," she says. "But from that failure, you learn and adapt." In this respect, she notes, outreach is a science in and of itself: It often requires successive rounds of iteration and failure before things run smoothly.

With Garbarino's meticulous scientific approach RockEDU has expanded considerably. The program now reaches thousands of students each year through in-house, in-school, and online activities—making good on its mission to welcome an expanded cohort into the scientific community. As a former Rockefeller postdoc and a grown-up kid from the Bronx, Garbarino embodies the two groups that her model strives to serve. And RockEDU, in turn, serves Garbarino's own unique interests.

"Through outreach I can marry my love of science with my love of people," she says. "It's kind of perfect." ◎

INSIDE THE

By Bahar Gholipour



GOAL: End the pandemic and transform COVID-19 into a manageable disease.

RESPONSE

Illustration by Jun Cen

APPROACH:
Employ every technique in the 21st-century science playbook.

"This will happen again, for sure. We need more emphasis on infectious disease research so that next time the scientific community can respond even faster."

It was the end of March. The Rockefeller campus was quiet but for the sound of birds and the lone crackle of a lab-waste cart, dragged along an empty hallway. In the gardens, blossoms were beginning to emerge but humans were a rare sight. The scene mirrored the larger surroundings, a city of eight million that seemed to have suddenly frozen in time, save for ambulances zipping by.

Yet despite this seeming tranquility, some labs were bustling. Virtually overnight, teams were putting together entirely new projects and beginning to conduct experiments under the added complication of social-distancing guidelines, with one crucial goal: to help alter the course of a pandemic that had brought the world to a standstill.

It usually takes years or even decades for basic-science insights to ripen into medical innovations, but in this age of the COVID-19 pandemic, a new mode of discovery is emerging. Unified in their purpose, scientists are collaborating across disciplinary and national boundaries in a tremendous race to understand a new virus. Their joint scope is vast: Some lines of investigation could help COVID-19 sufferers in the near future; others take a longer view, seeking to understand lasting medical effects of the disease and preparing for new viral outbreaks yet to come. The projects aim to attack the virus from every angle, understand how it behaves and thrives, figure out why some people get more severely sick from it than others, and devise new methods and tools to assess potential treatments.

Considering how much death and destruction SARS-CoV-2 has already caused, the challenges ahead are daunting. Yet there are good reasons for optimism given how far bioscience has come since the last time humanity was hit by a pandemic of this intensity. With the 1918 flu, it took 15 years just to identify the culprit pathogen. The disease was widely believed to be bacterial until Richard Shope, a Rockefeller virologist, isolated the H1N1 influenza virus in 1933.

Scientists are once again faced with a mysterious pathogen that has so far defied treatment. This time, however, they are equipped with tools of extraordinary power and precision, and knowledge garnered over decades of intensive study. Their challenge is to redirect their expertise—whether in immunology, genetics, biochemistry, or other fields—to a single problem, a diabolical virus that has killed over a million people and devastated societies worldwide.

Here we'll take a look at three rapidly unfolding COVID-19 research projects born in the midst of a statewide lockdown.

Michel C. Nussenzweig

From one pandemic to another

IF MICHEL NUSSENZWEIG expected the new year to be busy, it was mainly because of a virus that's been around for nearly 40 years. In January, the university had handed off the yields of a decade-long HIV research project to a pharmaceutical company to collaborate on developing a new, landmark drug based on HIV antibodies. In no time, however, a new challenge was on Nussenzweig's desk: The lab needed to clone more antibodies, this time for an emerging coronavirus that day by day was looking more like a severe threat with pandemic potential. The idea was to quickly develop treatments that, like the new HIV drugs, would harness the immune system's natural virus-fighting powers—specifically by identifying and copying exceptionally potent antibodies found in patients who had successfully recovered from the infection.

Nussenzweig, the *Zanvil A. Cohn and Ralph M. Steinman Professor*, pushed off at once, working with immunologists, virologists, and medical scientists spanning several labs within and beyond Rockefeller. Step one was to get their hands on hundreds of SARS-CoV-2-targeting antibodies and to sift through that stockpile to identify those variants that neutralize the virus most effectively by blocking its entry into cells.

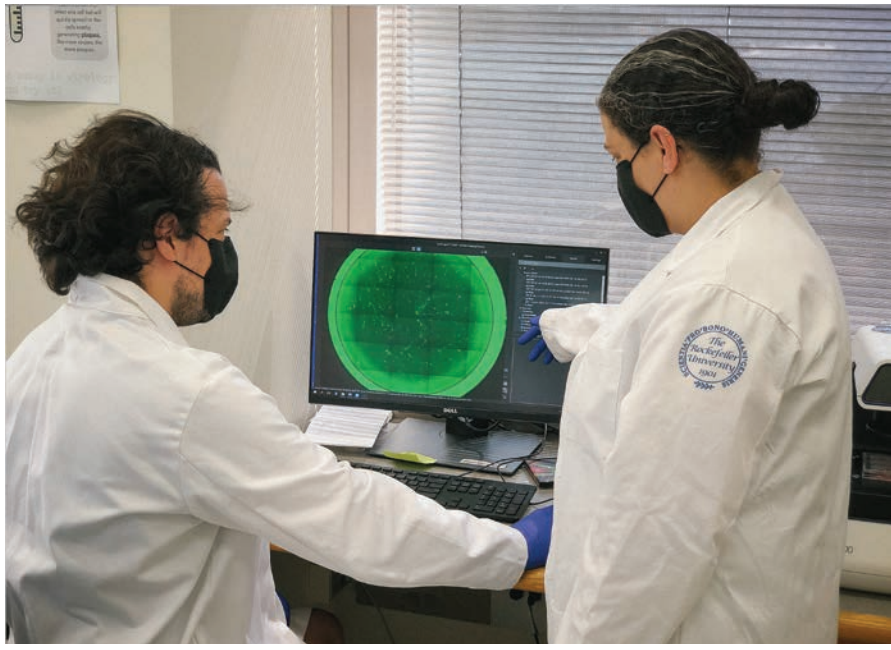
It was a needle-in-a-haystack proposition since most antibodies are, at best, capable of only a blunt, imprecise attack on the virus, like hitting it with a baseball bat. Potent neutralizing antibodies, on the other hand, are what Nussenzweig describes as "precision guided missiles with nuclear warheads"—capable of delivering a decisive and fatal blow to the virus. Their potency means that, instead of having to mimic the whole spectrum of antibody responses, researchers can manufacture just one or two antibodies in large quantities, to be used as a drug that people can take during the early stages of infection. This antibody injection would, hopefully, give the immune system a head start in fighting the virus before it can gain a foothold.

To find those prized antibodies, the scientists needed blood from people who had successfully fought off the infection—and they needed it fast.

Fortuitously, Jill Horowitz, a member of Nussenzweig's team, lives in New Rochelle, a New York City suburb where the country's first sizable outbreaks emerged. Horowitz immediately got to work recruiting recovered patients willing to help: She arranged a town hall in the synagogue where the virus had struck, she went on the local radio, she handed out flyers in the shopping mall. "In that early stage, it was crucial to recruit as many people as possible as quickly as possible," Horowitz says. After that kick-start, the recruitment team led by Rhonda Kost, in The Rockefeller University Hospital, reached recovered individuals from across the greater New York City area.

Their efforts paid off: In a few short weeks, flocks of COVID-19 survivors visited campus to donate blood plasma, from which Nussenzweig's team extracted antibody-producing immune cells using a tried-and-true technique they had developed for their HIV research. (Read more about the lab's work on HIV in "An end in sight" in the Fall 2018 issue of Seek.)

Next, the researchers needed to find which of these individuals produce the exceptional antibodies—and here they came up against another roadblock. The procedure normally entails growing the virus in the lab, bathing it with each antibody, and assessing which antibody has the best neutralizing capacity. It's a

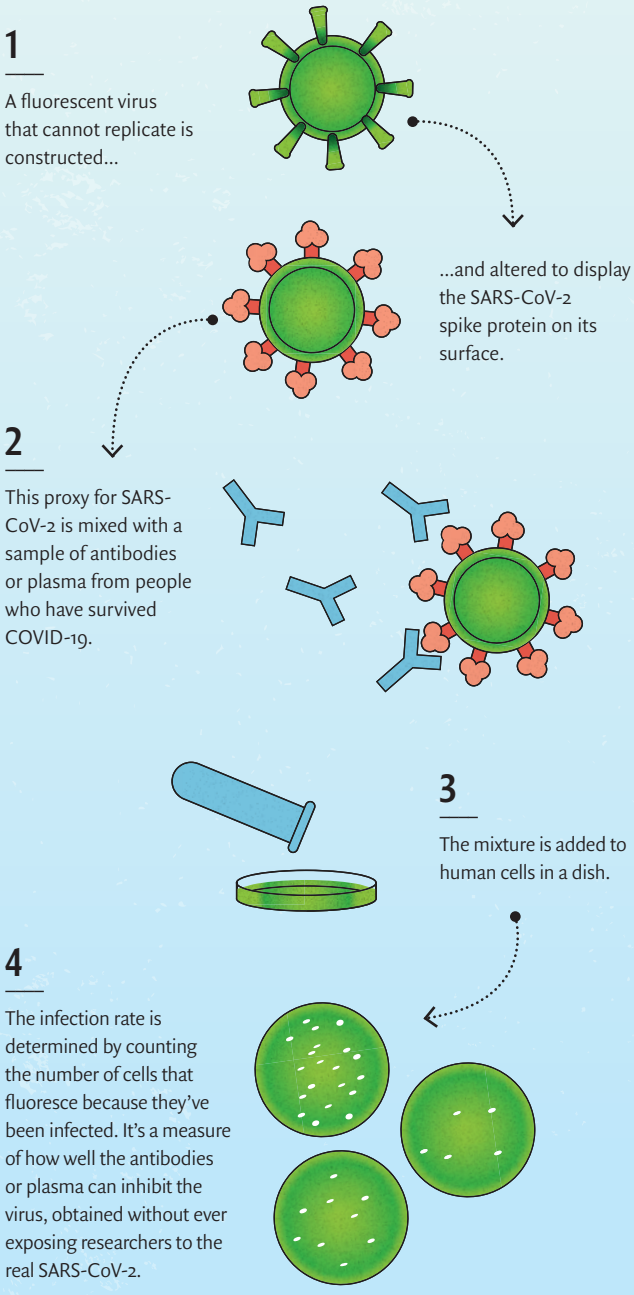


Postdocs Fabian Schmidt and Yiska Weisblum in the Bieniasz lab in August.

BAHAR GHOLIPOUR; MARIO MORGADO

The faux coronavirus

Carrying out research on a dangerous virus requires a highly specialized laboratory and strict safety protocols, so progress tends to be slow. But thanks to a method developed at Rockefeller, researchers everywhere can now test promising antibodies safely and swiftly.



labor-intensive and time-consuming procedure, especially when you're dealing with a virus as contagious as SARS-CoV-2, which must be handled in a biosafety level 3 laboratory (see "Top-tier biosafety," page 5). To circumvent this step, Nussenzweig turned to his colleagues Paul Bieniasz and Theodora Hatziioannou, who swiftly came up with a work-around: a faux coronavirus that serves as a stand-in for the real thing in lab experiments but is much more convenient to work with.

This pseudo-coronavirus is made up of a different virus, typically vesicular stomatitis virus, that has been rendered unable to replicate. It is then tweaked to express the SARS-CoV-2 spike protein, which is what the coronavirus uses to gain entry to cells. "We basically decorate another virus with the spike protein and use it as a proxy for SARS-CoV-2 infection," Hatziioannou explains. Working with virologist Charles M. Rice, the *Maurice R. and Corinne P. Greenberg Professor*, she and Bieniasz found that, for their purposes, the pseudo-virus worked just as well as the real one (see "The faux coronavirus," left).

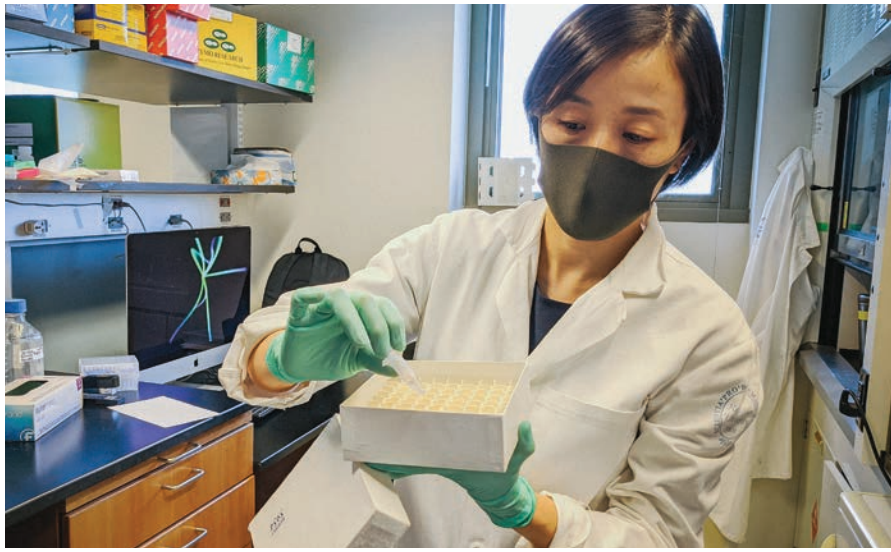
A picture of the immune system's response to SARS-CoV-2 soon started to emerge. The scientists found that the spectrum of plasma antibodies varied widely among infected people, but about one percent of donors had sky-high levels of antibodies with neutralizing superpowers.

"To find individuals with such potent antibodies was a great relief," says Davide Robbiani, a research associate professor in Nussenzweig's lab. "We expected to see everyone respond differently, but there was no guarantee that we would find exceptional responders like we had in the past with HIV-1. And the fact that they do exist among people who recovered from COVID-19 was positive news for the development of antibody-based drugs."

By early May, merely a month after the city went into lockdown, the team had zeroed in on three unique antibodies that had all the features of a good

Jean-Laurent Casanova

MARIO MORGADO



Zhang in the Casanova lab in June.

drug candidate. Although they came from different patients, these antibodies share a key feature: They bind to a critical region of the spike protein, the so-called receptor-binding domain, presumably blocking it from docking onto the host-cell receptor to gain entry. And they could block the virus even at extremely low concentrations.

What's more, these antibodies bind to the receptor from different angles, suggesting that a combination of them could work together to put an airtight seal on the spike protein and make it harder for the virus to escape the therapy by mutating.

The summer months were a whirlwind of advancing the three antibodies down the development path, where steps normally done in sequence were instead happening in parallel. As animal studies were conducted, for example, a pharmaceutical partner began to manufacture the antibodies needed for the human trials, and plans and infrastructure were put in place for producing huge quantities of the antibodies, standing by to be deployed if the clinical trials succeed.

"It is an extraordinary effort—and it's gratifying to be able to condense all the expertise we gained over a decade of HIV-1 work and pour it into a much larger project, much faster," says Marina Caskey, a clinical investigator who has been designing the human trials, both small ones conducted at the university and larger multi-institutional trials scheduled to begin in December in some of the country's hot-zone areas.

This fast-tracked experience in antibody research and development might also set the stage for future responses to emerging pathogens. "This will happen again, for sure," Nussenzweig says. "It's now clear that we need to put a lot more emphasis on dedicated infectious disease research, so that next time, the scientific community can respond even faster."

98,941

Number of scientific papers on COVID-19 published in the first nine months of 2020.

It's not just the virus. It's also us.

BAHAR GHOLIPOUR; MARIO MORGADO

WHILE AIRPORTS WERE deserted of human passengers, plastic vials containing human blood and DNA samples were being ferried around the world in record numbers. Many were collected from COVID-19 survivors who were relatively young and had no underlying conditions. When these patients ended up in hospital ICUs, they defied a common narrative about the disease: that symptoms would be mild in those who weren't elderly or immune suppressed.

But on the seventh floor of The Rockefeller University Hospital, where hundreds of these blood samples would eventually arrive, researchers were not at all surprised. "We see this pattern in every single infectious disease we have studied," says Qian Zhang, a research associate in Jean-Laurent Casanova's lab. "There is always a subgroup of people who get severely sick."

Zhang and her colleagues believe that the samples they've collected from COVID-19 outliers might hold important insights—clues to understanding the disease that scientists won't necessarily find by examining the average patient population. In recent decades, knowledge gained from the lab's study of similar outlier cases has led to new treatments for mycobacterial disease, herpes simplex virus infections, and other infectious diseases. And in all these cases, the reason the disease became unusually severe could be traced to a traditionally overlooked place: the patients themselves.

"Infectious diseases are not just about the pathogen. There is always an interplay between the pathogen and the host's immunity," says Casanova, head of the St. Giles Laboratory of Human Genetics of Infectious Diseases.

His lab's approach involves searching people's DNA for alterations that cause subtle defects in the immune system—cracks that pathogens might exploit. In many cases, those who carry this kind of alteration won't know it. They might be susceptible only to a specific pathogen—and as long as they don't encounter that pathogen, the mutation will go unnoticed.

$2.2B

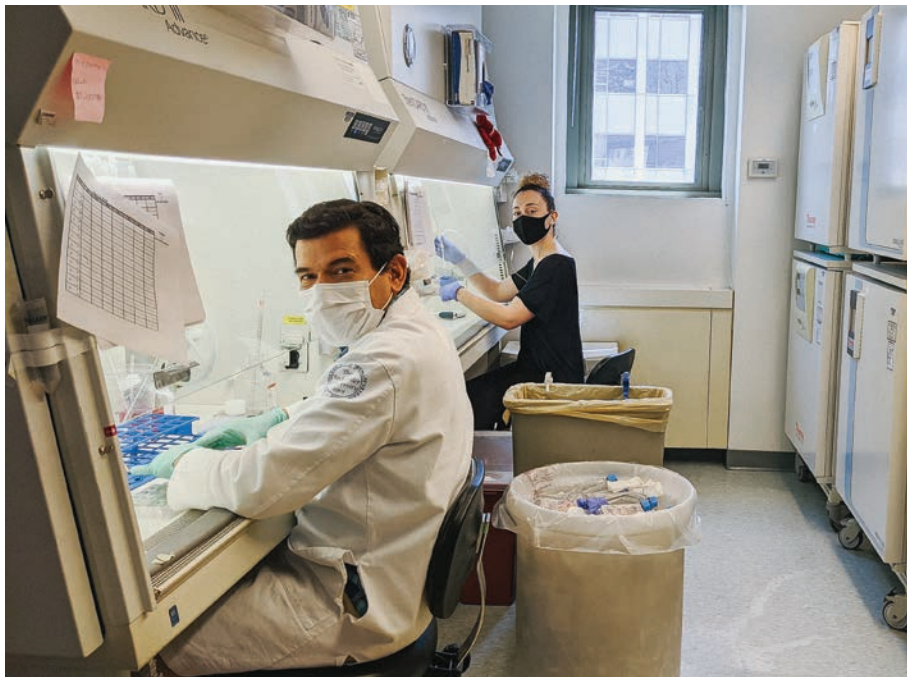
NIH grant money awarded for COVID-19 research in the first nine months of 2020.

In early January, when Casanova first heard about an emerging infectious disease in China, he wasted no time looking for such ticking-bomb mutations. As many other scientists scrambled to shift their focus to the new and mysterious disease, he already had a plan—the same plan he has successfully applied to many other illnesses. "I immediately got in touch with colleagues in Asia and asked for samples from their most severe patients," he says. And just as quickly as the virus swept the world, Casanova's project ballooned into an international collaboration, called the COVID Human Genetic Effort, spanning more than 30 labs and numerous collaborating hospitals around the world. Co-leading the group with Helen Su of the National Institute of Allergy and Infectious Diseases, Casanova has since enrolled thousands of patients who were hospitalized for COVID-19. "The approach is to try to enroll as many patients as possible, in as many hospitals as possible," Casanova says. "That's the only way to detect a signal when you are searching for a rare genetic variation."

Recently, the team published two major discoveries pinpointing causes of severe COVID-19 in subsets of cases. Among the several hundred patients studied so far, the researchers have found that about four percent carry genetic mutations affecting type 1 interferons, proteins crucial for the immune system's response to the virus. Normally, cells secrete these proteins at the start of an infection, but the researchers detected little or no interferons in the blood of patients with these mutations. Another 10 percent of patients were found to have misguided antibodies that were attacking not the virus but the immune system itself—specifically type 1 interferons.

Taken together, the results suggest that deficiencies in a specific immune mechanism are behind a significant number of COVID cases that become severe. "Never before for any infectious disease have we been able to decipher the root of the problem for such a large proportion of the severely affected patients," Casanova says.

There is still more to learn. Because mutations that make people uniquely vulnerable to infectious diseases are rare, it will take time to gather conclusive data about the many causes of such vulnerabilities, Casanova says. Still, he is hopeful that even the early findings will have practical implications. For example, type 1 interferon already exists as a drug and could potentially, he says, benefit people who develop life-threatening COVID-19 but can't produce it on their own.



Visiting Professor Andres Arias and former grad student Marie Materna in the Casanova lab in June.

Casanova's team is also looking for mutations in a second group of people who seem to be resistant to SARS-CoV-2 infection, including spouses of infected individuals who test negative and remain symptom-free. "Whether a genetic alteration makes a person more vulnerable or more resistant to infection, it has something important to teach us about how the virus interacts with the immune system," Casanova says. "And ultimately, such knowledge could lead to treatments for anyone who's been infected."

The chemistry conundrum

FROM A SCIENTIFIC point of view, SARS-CoV-2 represents more than a threat to humanity. It's also a marvel of biochemistry: a mere strand of RNA wrapped in a protein shell that, despite its simplicity, is capable of preying on organisms as complex

BAHAR GHOLIPOUR

Sean F. Brady

SARS-CoV-2 is both a threat to humanity and a marvel of biochemistry, slim but feisty.

as ourselves. Its biological machinery may be slim, but it's incredibly feisty.

Once the virus finds its way into human cells, it immediately gets to work replicating itself. A suite of enzymes and proteins works to read and write the SARS-CoV-2 RNA into thousands more copies; pack each copy into a new shell; and send the viral particles bursting out of the cell like confetti out of a popped balloon.

Disrupting any step in this process could potentially sabotage the virus's replication scheme, and researchers around the world are now hunting for compounds that will glom on to critical viral enzymes and thwart their activity. Among them is Sean F. Brady, the *Evnin Professor*, who's looking for such would-be drugs by surveying DNA from soil samples.

Dirt may seem like an odd place to look for solutions to the current catastrophe, but for Brady there is no better. For years, he has successfully exploited soil in preparation for a different crisis that, despite receiving far less publicity than COVID-19, poses an equally serious threat: the rise of antibiotic-resistant bacteria such as *M. tuberculosis* and *C. difficile*.

A spoonful of soil contains thousands of species of bacteria, which together produce a plethora of replication-slowing compounds—natural antimicrobials that the bacteria release as they compete with other microbes for nutrients and space. Brady has pioneered a unique method to find these chemical weapons by extracting bacterial DNA from soil, searching it for antimicrobial-producing genes, and reverse-engineering those compounds in the lab (read more about Brady's approach in "Drugs from dirt" in the Fall 2017 issue of Seek).

At the outset of the COVID-19 crisis, Brady redeployed the same technique to search for bacterial compounds with antiviral properties. "The whole premise is that we go out to find nature's solutions to microbial problems, whether it's a bacterial infection or a viral one," he says.

To find potential antivirals, the team went back to their vast libraries of bacterial DNA extracted from soil, searching for signatures in the sequenced DNA that suggest a group of genes might make a certain type of molecule. The team is particularly interested in finding genes producing inhibitors of the RNA-dependent RNA polymerase, the key enzyme in SARS-CoV-2's replication apparatus.

In the short few months since taking this new direction, the scientists have identified several compounds showing antiviral activity in lab experiments. They are also pursuing candidate drugs isolated not from soil bacteria, but from our own microbiome. "Just like bugs growing in the environment, the bugs that grow inside us make molecules that have structures similar to antivirals," Brady says. "But are they truly antivirals? We don't know yet."

Elsewhere on campus, Tarun Kapoor, the *Pels Family Professor* is scheming to target another essential item in SARS-CoV-2's replication toolbox: the helicase. Vital to all organisms, helicases are like molecular motors that move along strands of DNA—or in the case of coronavirus, RNA—unzipping them in preparation for the genetic information to be copied.

Like Brady, Kapoor hopes to find drugs for COVID-19 by leveraging decades of research in other fields. He worked on developing new drugs to stop cancer cells from replicating—a strategy he's now adapting for SARS-CoV-2. His team has already identified the virus's helicase and a suite of compounds that may be able to inhibit it. Both Kapoor and Brady are now working with Rice to test their compounds and identify those poised to stop viral replication.

Success in any of these avenues could go beyond curbing the current crisis. In only the past 20 years, no less than three coronaviruses—SARS, MERS, and now SARS-CoV-2—have jumped from animals to humans, causing considerable suffering and economic damage, and there is no shortage of coronaviruses lurking in nature.

"What's remarkable is that the helicase in SARS-CoV-2 is 99 percent identical to the helicase in the virus that caused the SARS epidemic in 2002," Kapoor says. "Coronaviruses are likely to show up more and more in the human population, so learning how to target the replication machinery of this one could potentially prepare us for future versions." ◎

3,532

Number of COVID-19 clinical trials launched in the first nine months of 2020.

JACOB PRITCHARD

This isn't *Drosophila*

BY ALEXANDER GELFAND

A lab is on a mission to defang* Aedes aegypti, *one of the world's most dangerous mosquitoes. Step one: Make her a decent lab animal.

"A lot of people in the field said, 'You're an idiot. *Aedes aegypti* is a joke mosquito.'"

ESLIE VOSSHALL'S office on the fourth floor of Smith Hall is bright and welcoming, filled with contemporary art and flooded with sunlight. It is also a stone's throw from a room containing tens of thousands of the deadliest animals on the planet: mosquitoes.

Female mosquitoes require blood to produce their eggs; and as anyone who has ever been eaten alive at a barbecue might suspect, some of them strongly prefer that of human beings. In addition to making mosquitoes a nuisance, this preference for human blood also makes them one of the most important disease vectors in the world: By passing microbes from person to person, these tiny pests kill more people every year than any other animal—including *Homo sapiens* itself. In 2015, 580,000 humans perished through homicide and war, while 830,000 died from mosquito-borne diseases.

Vosshall is on a mission to defang these lethal creatures. Since 2008, she has focused her research on *Aedes aegypti*, a mosquito that transmits such debilitating and potentially fatal viral diseases as yellow fever, dengue, chikungunya, and Zika to 400 million people annually.

Of course, humans have sought effective ways to repel, eradicate, and neutralize mosquitoes for centuries. But Vosshall brings something new to the field: a comprehensive strategy complete with cutting-edge techniques designed to pinpoint the very essence of the mosquito's menace—the genes and neural circuits that compel these bloodsuckers to seek us out and bite us.

"Our mission is to understand everything we can about the female mosquito: how she finds us, how she bites us, and how we can stop her," Vosshall says.

By zeroing in on some of the fundamental mechanisms driving *Aedes*'s host-seeking and blood-feeding behaviors, she and her team have already identified potential new interventions. Their work includes efforts to understand and interfere with the animal's senses as well as its appetite.

PREVIOUS SPREAD: ALEX WILD

Younger (left) and Vosshall.

JOHN ABBOTT

Yet when Vosshall first began investigating *Aedes*, plenty of mosquito experts thought she was making a mistake.

And there were times when she more or less agreed with them.

PLANET EARTH is rife with mosquitoes. By some estimates, they're the third largest animal population, outnumbered only by termites and ants; there are at least 3,500 species worldwide. The most infamous of these, *Anopheles*, spreads malaria—a disease that by itself threatens half the world's population and kills hundreds of thousands of people every year.

Traditionally, mosquito researchers have mainly studied *Anopheles,* so Vosshall's decision a decade ago to focus instead on *Aedes* was met with skepticism.

"A lot of people in the field said, 'You're an idiot. *Aedes aegypti* is a joke mosquito,'" Vosshall recalls from the lab's insectary, a temperature- and humidity-controlled room where swarms of mosquitoes flit about inside mesh-covered cages.

But after a deep dive into mosquito-research literature, Vosshall became convinced that *Aedes* would be easier to work with in the lab. And she was right; for reasons that no one can quite explain, the genetic and molecular techniques she has developed to study mosquitoes have turned out to work far better on *Aedes* than they do on *Anopheles*.

What's more, the threat posed by *Aedes* has only increased with time. The past decade has seen an uptick in Eastern equine encephalitis, an *Aedes*-borne virus that kills 30 percent of those infected and leaves survivors with lifelong neurological problems. The Zika virus, which causes devastating birth defects in babies born to infected mothers, was declared an international public health emergency in 2016. And experts now warn that climate change will vastly expand the range of both *Ae. aegypti* and *Ae. albopictus*, a close relative with the potential to carry the same diseases over an even wider swath of the globe. (Unsettlingly, the latest predictions have the two mosquitoes menacing 49 percent of the world's population by 2050.)

Finding out what's going through a mosquito's mind could mean better repellents, better traps, or perhaps something we haven't even thought of yet.

Few today would argue that Vosshall made a poor choice, though she herself may occasionally have had cause to regret it. She began her career working with a far more tractable insect: *Drosophila melanogaster*, the common fruit fly, whose genetics have been subject to research and manipulation for over a century. In this obliging model animal, Vosshall made important discoveries about the neuroscience of olfaction, a topic she has also explored among humans.

Although Vosshall knew that *Ae. aegypti* would be a far more challenging subject than *Drosophila,* the mosquito nonetheless presented her with difficulties she could not have anticipated. Some of these had to do with the extraordinary complexity of the animal's host-seeking behaviors, which proved devilishly hard to unpack. And some had to do with unforeseen technological challenges that initially prevented Vosshall from conducting the kinds of experiments that might have unpacked them.

Mosquitoes excel at sniffing out their prey; a mélange of odors in our breath and sweat will alert them to our presence from 100 feet away. Yet while the insect's olfactory system is a remarkably sophisticated phenomenon in itself, it is but one part of an even more complicated mosaic of sensory inputs that draws mosquitoes to us. Research by Vosshall and others has shown that the insects rely on a wide range of cues to track us: Odor, heat, and vision are all integrated in the mosquito brain to paint a giant bull's-eye on our backs, with the carbon dioxide in our breath acting like a kind of all-purpose sensory umami that enhances other cues through its mere presence.

Previously, mosquito researchers had relied primarily on observational and behavioral experiments to investigate such phenomena: slathering a chemical on a volunteer's arm to see if it would repel the animals, for instance, or laying out some nice, warm blood with and without CO_2 present to see if it would entice the bloodthirsty pests. But Vosshall wanted to create genetically modified mosquitoes that lacked specific traits, such as a proper sense of smell or the ability to sense CO_2,

JOHN ABBOTT

Mosquitoes don't usually sit for portraits—and their restless nature makes experiments challenging as well. Cooling them off can help.

to determine precisely how those traits help *Aedes* find us—and whether selectively knocking them out might be enough to throw them off our scent.

Toward that end, the lab pioneered a set of techniques for genetically engineering mosquitoes in the lab, adapting tools such as the powerful genome editor CRISPR for use on *Aedes*. Although the process took several years, Vosshall and her team were eventually able to run experiments that had simply not been possible before: creating mutant mosquitoes that didn't prefer humans to other warm-blooded animals, for example, or that could not detect CO_2.

Even then, however, certain tasks remained difficult, if not totally unfeasible.

The existing map of *Aedes*'s genome—a crucial tool for analyzing, exploiting, and manipulating its genes—was a mess, an incomplete jumble in 36,000 pieces. And modifying individual genes without having the full genome was like trying to rewire a circuit board without a blueprint: The risk of making mistakes was very high.

"It made everything much harder," Vosshall says. "It made some things impossible."

Frustrated, Vosshall took to Twitter, imploring researchers to help her lab assemble a better genome, and soon found herself coordinating an international effort. In 2018, she and her colleagues published a vastly improved *Aedes* genome.

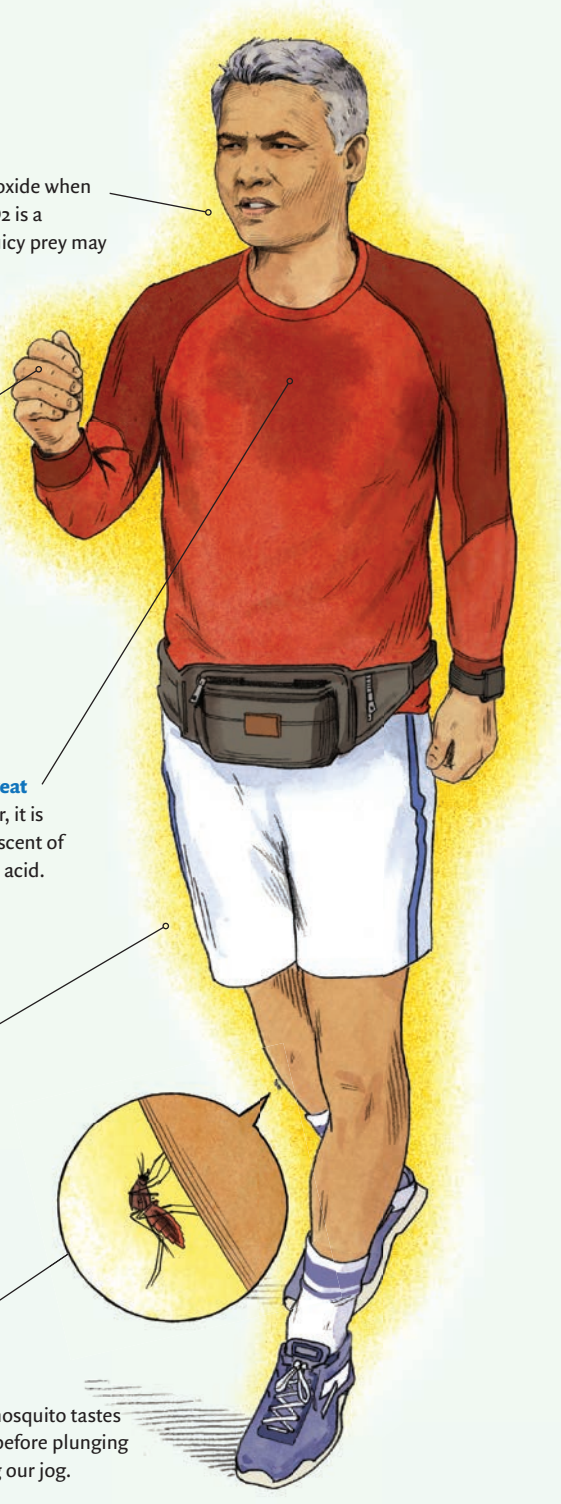
"That was game-changing," says postdoc Meg Younger, who is trying to figure out how *Aedes* integrates various sensory cues to home in on us.

Among other things, explains Younger, the new and improved genome made it far easier to track the activity of cells in the mosquito brain. Younger used the lab's genome-editing methods to tag individual populations of neurons with a marker that makes the neurons fluoresce when they activate.

By wafting different odors over a live mosquito and peering into its head with a custom-made microscope, Younger

How mosquitoes find us

Developing effective mosquito interventions has proven challenging in part because the insects' host-seeking behavior is so complex. Humans unwittingly display a bouquet of sensory cues, making us easy targets for mosquitoes:



1

Our CO_2
All animals emit carbon dioxide when they breathe. A whiff of CO_2 is a mosquito's first hint that juicy prey may be nearby.

2

Our movements
Though not the mosquito's strongest sense, vision still plays a role as the mosquito senses our movements and tracks toward us.

3

Our (uniquely human) sweat
As the mosquito gets closer, it is drawn to us by the unique scent of human sweat, rich in lactic acid.

4

Our body heat
As the mosquito prepares to land it senses our body heat, which confirms that we are alive and full of fresh blood.

5

Our taste
When it finally lands, the mosquito tastes us with sensors on its feet before plunging in its proboscis and ruining our jog.

Illustration by Joe McKendry

DEET feet

ALTHOUGH IT'S BEEN in use since the 1950s, scientists still don't know exactly how DEET works. Besides, it is far from perfect: The unpleasantly oily emulsion lasts only six hours after it's been applied, and it's not entirely effective in turning insects away.

Yet DEET is the best repellent available, making it a hot subject of investigation. Discovering what makes it so singularly repulsive to mosquitoes would advance our understanding of their sensory systems and fuel efforts to develop better repellents.

There may not be a simple answer. More than a decade ago, Vosshall showed that DEET scrambles the olfactory systems of both flies and mosquitoes, spoiling their ability to detect odors that would lead them to us. Other scientists revealed that mosquitoes are also put off by the bitter taste the chemical leaves in their needle-like probosci when they bite. Then Vosshall and her team noticed that the creatures were repelled not only by way of smell or taste, but also through contact: Mosquitoes engineered to lack a normal sense of smell were still attracted to DEET-slathered humans but would leap away in disgust after landing on them.

Last year, Vosshall, doctoral student Olivia Goldman, and former Ph.D. student Emily Dennis, who is now a postdoc at Princeton, demonstrated that *Aedes* also tastes DEET through its tarsi, the lowermost portions of its legs. Now Goldman plans to conduct further studies to identify the particular cells in mosquito tarsi that are activated by contact with the chemical, and then establish which specific receptors in those cells produce the DEET contact response—information that could one day be used to develop a whole new breed of contact-based repellents.

can see which neurons are responding in the animal's olfactory organs—and where the signals from those neurons are processed in its brain.

Younger has a collection of some 700 odors to play with—bequests from Vosshall's years of research on olfaction in both fruit flies and humans, all stored in a large and extraordinarily fragrant "odor cabinet." She's interested in any odor that evokes a particularly strong neural response: Substances that turn *Aedes* off could potentially be used as repellents to keep her away from us, while delicious-smelling molecules could serve as attractant to lure her into traps.

Younger plans to then explore how *Aedes* combines different cues to track its prey. And she would eventually like to image the animal's brain in real time as it seeks a blood meal—an exercise that could reveal what is going through a female mosquito's mind as she buzzes toward her target, and perhaps lead to entirely novel ways of diverting her. That could mean mosquito repellents that work better than DEET—something others in the lab are already at work on—or better traps, or perhaps something we haven't even thought of yet (learn more about the team's research on repellents in "DEET feet").

"I really think it's possible to get mosquitoes to stop biting people," Younger says. "We just need to know more about how they work."

MANIPULATING THE FEMALE mosquito's senses is not the only way to render her innocuous, however. After all, she wouldn't come looking for us in the first place if she weren't so hungry for our blood.

As it turns out, hunger follows similar biochemical signaling pathways in both humans and mosquitoes; namely, ones involving molecules called neuropeptides. And just last year, Vosshall and Laura Duvall, a former postdoc who now leads her own lab at Columbia University, exploited that similarity to startling effect.

In humans, neuropeptides regulate hunger by activating so-called NPY receptors, which have become a popular target for appetite-suppressant drugs. Mosquito researchers, meanwhile, have long known they could inhibit *Aedes*'s craving for blood by injecting neuropeptides that activate the insect's own NPY-like receptors. In 2019, Vosshall and Duvall made the surprising discovery that human anti-obesity drugs that target NPY receptors, fed to mosquitoes in a saline solution cocktail, caused the insect's attraction to humans to plummet.

Alas, indiscriminately flooding the environment with huge quantities of human drugs is not a viable public-health strategy. To work in the real world, we'd need something to inhibit hunger in mosquitoes without affecting human appetite.

Happily, Duvall was able to identify an alternative compound that works specifically on mosquitoes—a three-and-a-half-year-long endeavor that involved culturing all 49 of the animal's

Illustration by Andrea Mongia

Duvall tending to mosquito larvae.

JOHN ABBOTT

NPY-like receptors in the lab, singling out the one that was sensitive to human diet drugs, and testing its response to hundreds of thousands of other molecules. The most potent of these turned out to be compound 18, a mosquito-specific diet drug that has no effect whatsoever on human NPY receptors. Feeding a female mosquito a specially formulated milk shake containing compound 18 will kill her appetite for several days.

With support from the Robertson Therapeutic Development Fund, a Rockefeller initiative to fund early-stage drug development, Duvall and Vosshall plan to work with medicinal chemists to turn compound 18 into something that could be put in a backyard mosquito feeder—perhaps one containing a super-attractive bait developed with help from Younger's olfactory research. Just a sip and *Aedes* would instantly lose her appetite for days, like a python that has swallowed a goat.

It's unlikely, says Vosshall, that any one method of mosquito control, even one as ingenious as this, will suffice; mosquitoes are too wily, too adept at seeking us out and biting us. Instead, a multipronged approach will probably be required. Eventually we'll need something that builds on each of several lines of mosquito research going on in the labs of Vosshall, Duvall, and others. And since anything that works against one species could conceivably work against others—and might even work against other blood-sucking, disease-spreading creatures such as ticks—it would be hard to overestimate the potential impact of these multifarious gene-driven efforts to get *Aedes* off our backs.

"The deadliest animal on Earth is, far and away, the mosquito," Vosshall says. "But it will ultimately become manageable." ◎

INTERVIEW

Humans, we are learning, wouldn't really be human without a little help from the trillions of bacteria we host—many of which interface directly with our own cells. We asked Daniel Mucida about the microbes within.

There's a reason for those gut feelings

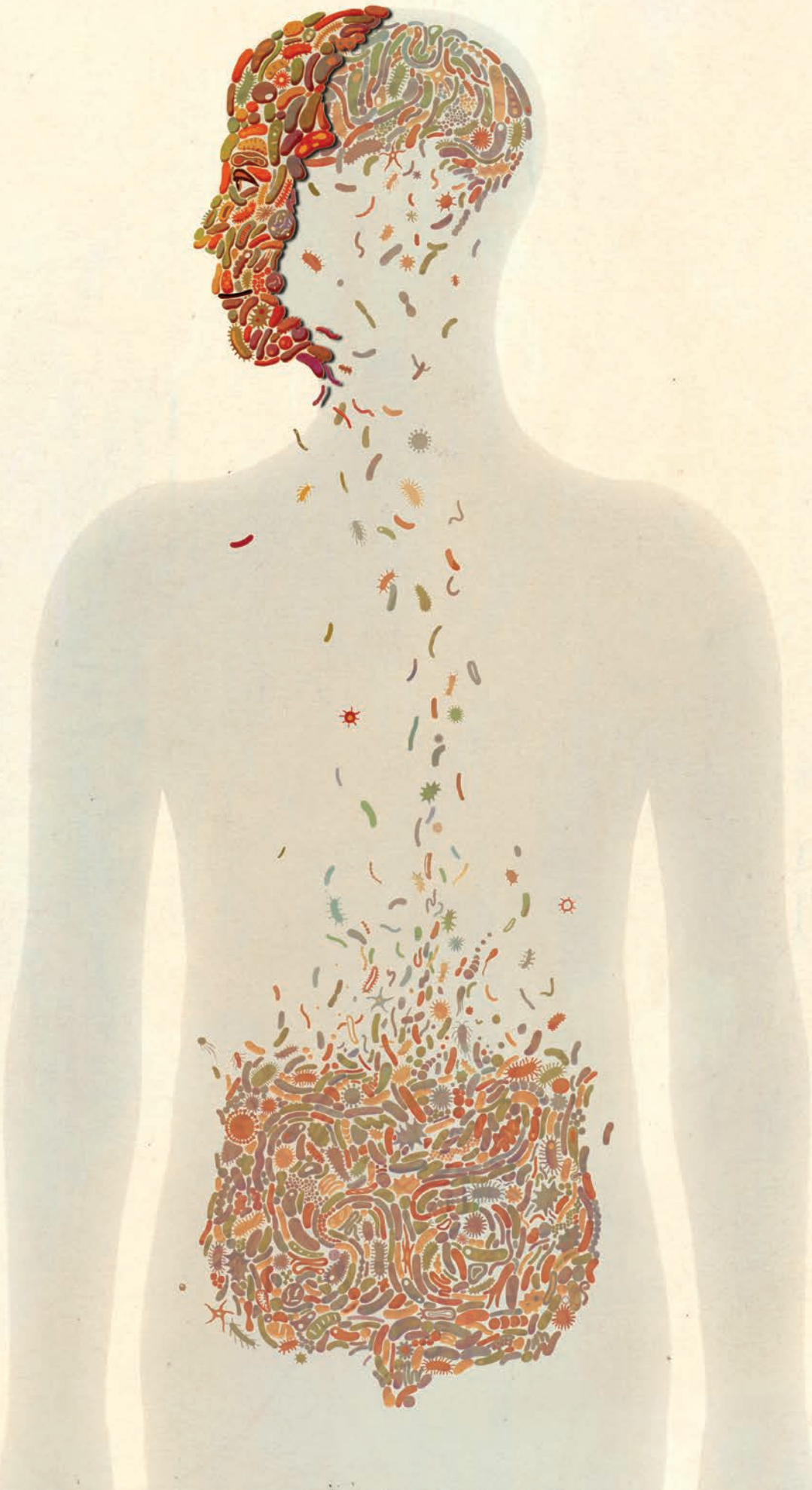
By Zachary Veilleux

We tend not to give much credit to the 10 trillion bacteria that line our digestive tracts. Rather, we think of them as docile passengers that, other than perhaps cleaning up scraps of partially digested food, mainly go about their business.

The reality is more complicated. We are as married to our gut microbes as we are to our spouses—with them, in sickness and in health, until death do us part. And as with husbands and wives, our very happiness may well depend on having the right ones.

It turns out that gut bacteria do more than just metabolize our metabolites. They play critical roles in nutrition, weight regulation, and immunity—and there's growing evidence that their influence goes further. Researchers have found that these organisms directly affect neural activity in the intestines, helping coordinate the processes of digestion and perhaps even affecting behavior, mood, and cognition.

Illustration by Dadu Shin



There may be a direct correlation between what you eat and how your neurons behave.

Daniel Mucida, head of the Laboratory of Mucosal Immunology, came to the gut for the immunology—the digestive system is the body's most active site of immune activity. But he stayed for the neuroscience. It's hard to study immunity, he says, unless you also account for the activity of cells belonging to other tissues or systems—including neurons, which sense changes in the environment and pass messages between cells.

We spoke to Mucida about the possibility that our resident *E. coli* are seeping into our thoughts.

What do bacteria living in the intestine and the colon have to do with the neural activity happening far away in the brain?
It's a common misconception that neural processes occur only in the brain. Yes, the brain is where cognition happens, but every site in the body has neural activity. Unlike most organs, however, the gut has whole nerve cells based in it, not just their extensions. You actually have about as many neurons in your intestine as in your entire spinal cord.

This is why the gut is sometimes referred to as a second brain. It's able to control complex processes on its own, without input from the brain—including the way food passes through the system, how nutrients are absorbed, and when digestive enzymes are released. The brain is free to focus on other things.

And in many ways, gut neurons—we call them enteric neurons—behave similarly to those in the brain. For instance, it turns out that neurotransmitters such as serotonin and dopamine, which are known to regulate things like mood, emotions, and anxiety, are secreted in the gut as well as in the brain. In fact, about 95 percent of your serotonin is in the gut.

Mood, anxiety—these are things we often talk about feeling in our "gut."
Yes, they are things that people colloquially ascribe to the gut, and there may be a reason for that. Does the release of serotonin in the gut make you feel something in your gut? At this point we're not even close to answering this question.

What we do know, based on research in my lab and others, is that there is close coordination between the neurons of the gut and those of the brain. Messages are passed between them. We believe the gut neurons are there to handle the moment-to-moment processing required to maintain digestion, under the broad supervision of the brain.

So how do bacteria fit into this picture?
We are learning that the commensal bacteria of the gut are much more integrated into other physiological systems than previously thought. One of my lab's interests is to understand how they help protect us from disease, and we have found that healthy, helpful microbes can directly coordinate an immune response. When a bacterial pathogen shows up, they secrete enzymes that stimulate our immune cells.

Similarly, Paul Muller, a recent grad student in the lab, and collaborators, found that our commensal bacteria play an active role in coordinating neurological processes. These bacteria are able to activate a specific neural circuit that connects the gut to the brain. How they do it is not yet clear, but it's something we're looking at.

That would give bacteria a lot of power over our neurological processes.
Indeed, we keep finding that bacteria influence the body on many levels. For example, we are intrigued by the prospect that your gut microbiota might affect your appetite and body weight. We have seen in our germ-free animals—mice that are raised in sterile conditions and lack a bacterial environment—that certain neural circuits fail to activate. But when you add microbes to these mice you can activate these circuits and, in some cases, change the animals' behavior.

For example, we recently showed that gut microbes regulate a circuit that controls blood sugar levels and appetite. When mice don't have these microbes, their blood glucose levels are reduced; when you add the

The body contains 200 human cell types, and over 40,000 species of bacteria.

bacteria back in, glucose levels are restored. We are intrigued by the possibility that the makeup of your gut microbiota could affect your metabolism and eating habits, and maybe also how susceptible you are to pathogens, or diseases, that depend on these dynamic changes in metabolism.

How else can the gut influence behavior?
There are some indications that the gut microbiome plays a role in mood disorders and other psychiatric conditions. For example, we know that some microbes can produce substances that mimic human neurotransmitters like serotonin and bind to the same receptors. These can likely influence mood and behavior, and it's easy to imagine they might be acting on neurons in people who are prone to anxiety, depression, or neurodegenerative conditions. But, despite some recent advances, this is still an open question.

Likewise, it has been observed that infection during pregnancy increases the chance that the baby will develop an autism-spectrum disorder. And in mice, there is evidence that the makeup of the microbiome of the mother when there is an infection will influence what type of immune-derived molecules—cytokines—develop in the brain of the fetus. These cytokines can influence the development of neurons. In these mouse models, if you change the microbiota of the mother you can actually prevent the development of autism in the offspring.

So how do you change your microbiota?
The most obvious way is through diet. For one thing, the composition of fibers, proteins, fats, and sugars in your meals absolutely does affect what kind of microbes will flourish in your gut. If you change your microbes, you change your metabolism and immune cell composition, leading to altered neuro-immune communications. There are also protein-derived antigens in food that may directly influence the activity of immune cells.

But there's also a third, very intriguing, possibility. There may be components of the diet that can be directly sensed by the gut nervous system. This would imply a direct correlation between what you eat and how your neurons behave. Some of these relationships are known—capsaicin, for example, the active component of chili peppers, binds to the cation channel TRPV1—but the role of nutrition is understudied in both neuroscience and immunology. In the interface between the two fields, a lot of interesting questions remain unexplored, such as how dietary components that trigger food allergy in susceptible people can interfere with neuronal activity and animal behavior.

What happens when important gut bacteria die?
Normally, the gut is able to maintain a balanced system. There is likely some mechanism in place to keep certain species in check. But you can see how there might be a connection between dysfunction in the body and diseases we think of as infectious in nature, such as *C. difficile*. And it's worth mentioning that some of these diseases disproportionally affect people with psychological disorders and mental illness. It's dangerous to assert directionality here—what's causing what?—but that's something we hope can be better defined as the field matures.

How do we get to these answers?
The field is still very much in its infancy, but I think it's important to ask questions about the human body as a whole. Separating biology into fields such as microbiology, immunology, and neuroscience will only get us so far given how closely interrelated these systems are. Immunologists can no longer study the immune system in isolation; immune cells are influenced by everything else that is happening in and on the tissue, including the complex society of microorganisms residing there.

And it's a great time to be an immunologist. Because we have collaborations with neuroscientists, microbiologists, cancer biologists, and others, my lab has been able to go in many surprising directions. ◎

FRANK VERONSKY

Scope and scalpel in one

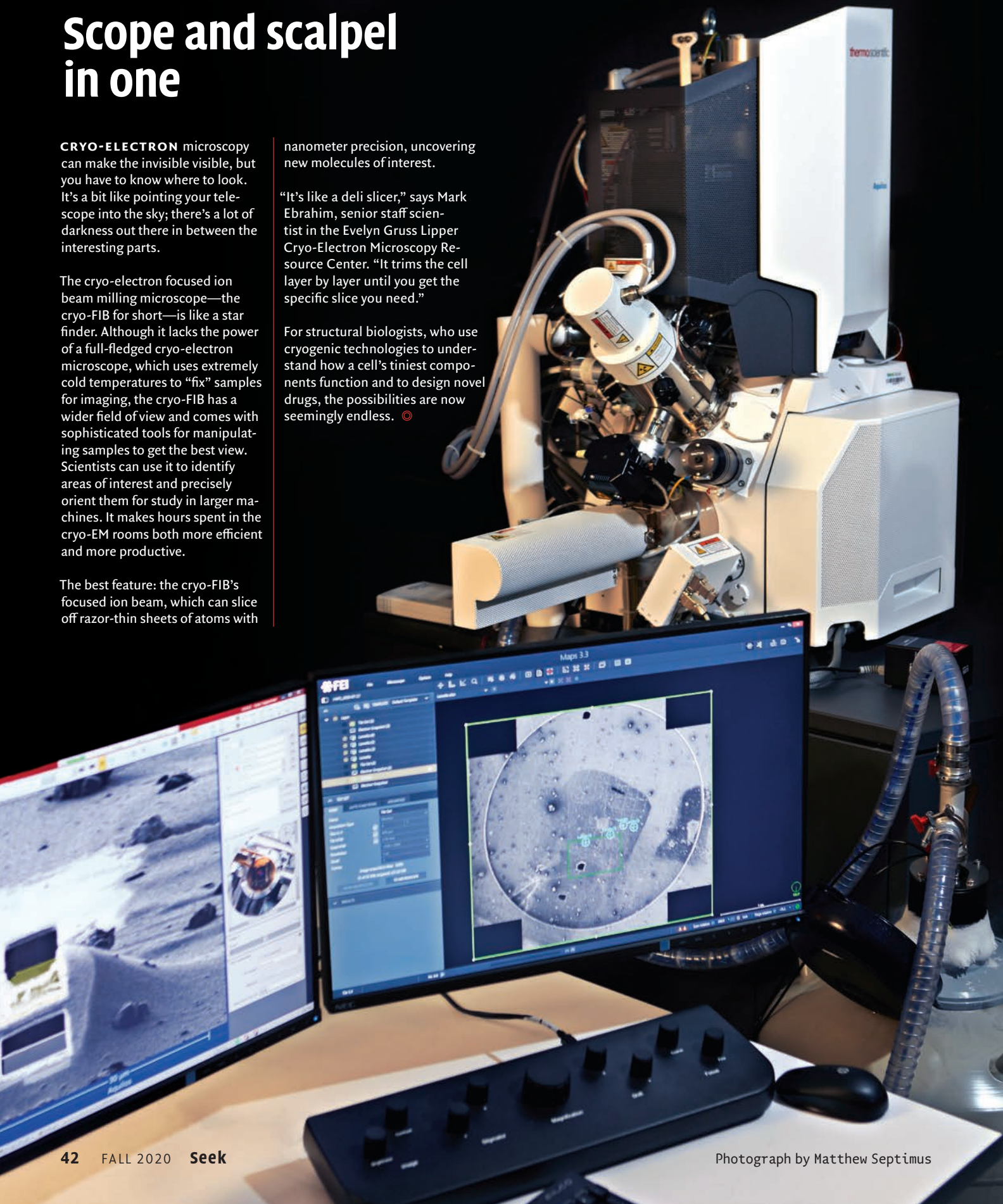
CRYO-ELECTRON microscopy can make the invisible visible, but you have to know where to look. It's a bit like pointing your telescope into the sky; there's a lot of darkness out there in between the interesting parts.

The cryo-electron focused ion beam milling microscope—the cryo-FIB for short—is like a star finder. Although it lacks the power of a full-fledged cryo-electron microscope, which uses extremely cold temperatures to "fix" samples for imaging, the cryo-FIB has a wider field of view and comes with sophisticated tools for manipulating samples to get the best view. Scientists can use it to identify areas of interest and precisely orient them for study in larger machines. It makes hours spent in the cryo-EM rooms both more efficient and more productive.

The best feature: the cryo-FIB's focused ion beam, which can slice off razor-thin sheets of atoms with nanometer precision, uncovering new molecules of interest.

"It's like a deli slicer," says Mark Ebrahim, senior staff scientist in the Evelyn Gruss Lipper Cryo-Electron Microscopy Resource Center. "It trims the cell layer by layer until you get the specific slice you need."

For structural biologists, who use cryogenic technologies to understand how a cell's tiniest components function and to design novel drugs, the possibilities are now seemingly endless.



Photograph by Matthew Septimus

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