ISSUE 05
FALL 2019

Seek

THE ROCKEFELLER UNIVERSITY

Life forces

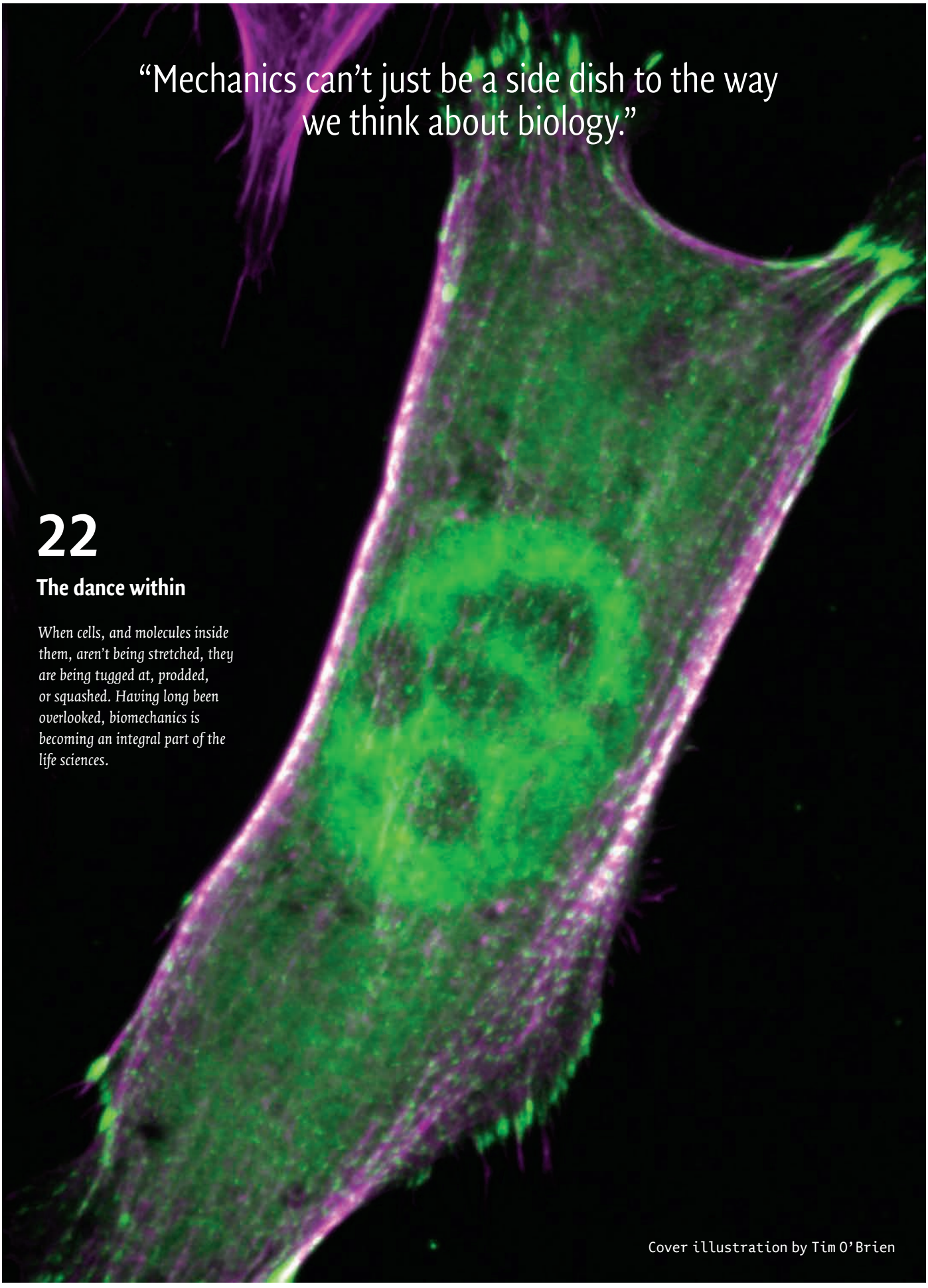
How cells—and even tinier bits of biology—get by in a world of constant motion

ALSO

Malignant metabolism

Overcoming overspecialization

What's time to a fly?



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The dance within

When cells, and molecules inside them, aren’t being stretched, they are being tugged at, prodded, or squashed. Having long been overlooked, biomechanics is becoming an integral part of the life sciences.

Cover illustration by Tim O’Brien

LABORATORY OF STRUCTURAL BIOPHYSICS AND MECHANOBIOLOGY, THE ROCKEFELLER UNIVERSITY

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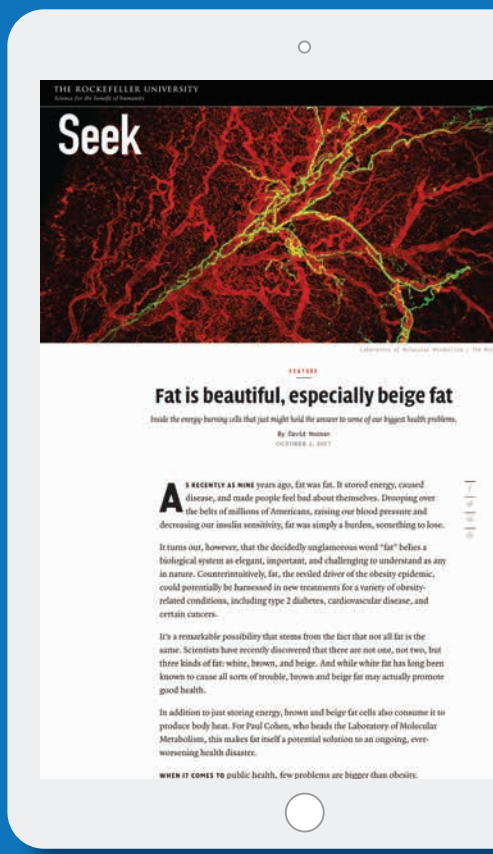

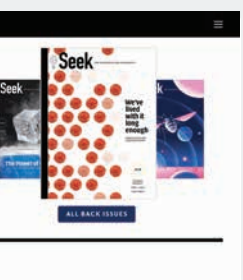

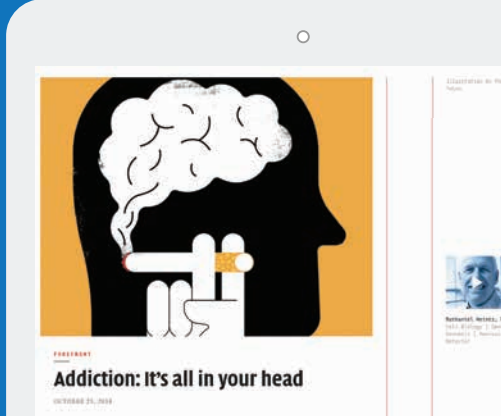

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Photograph by Matthew Septimus

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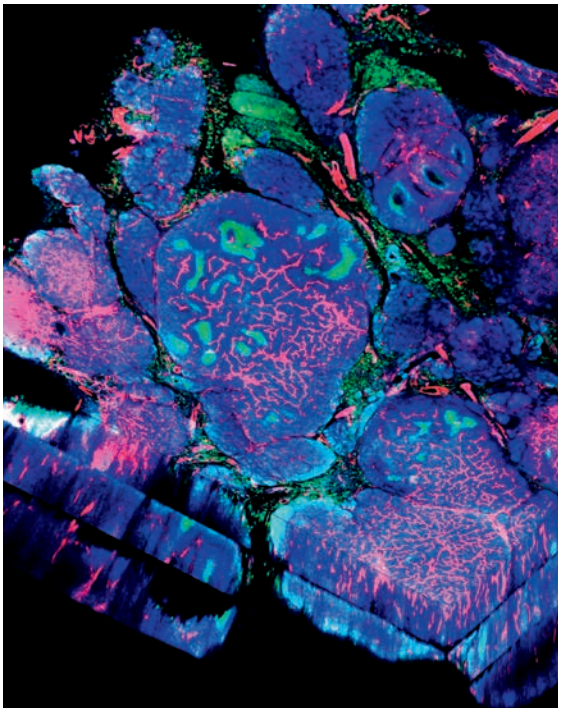

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"The Rockefeller University" by Leonie Bos

LEFT TO RIGHT: MATTHEW SEPTIMUS, SCIENCE PHOTO LIBRARY, FRANK VERONSKY, IKER AYESTARAN

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In touch with history. Several decades of science were conducted in Rockefeller's Smith and Flexner Halls before their interiors were gutted in a 2010 renovation. A new interactive installation, the Scientist Explorer, honors the 137 men and women with labs in the buildings—from the first who arrived in 1917 to those currently on the faculty. Occupants and visitors of today's Collaborative Research Center, which connects the two buildings, can use the circular touchscreen to explore the work of both neighbors and predecessors.

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

FOREFRONT

ANTICIPATION

Experiences, memories, and the elusive element of time

THE WAY WE act and react is often informed by our past—specifically, by good or bad experiences that help us project what may transpire in the future. A classic example is the Russian psychologist who rang a bell before feeding his dog—eventually the dog learned to salivate at the sound even in the absence of dinner.

But Pavlov's story tends to glaze over an important factor in this behavioral equation. Today's neuroscientists have reasons to suspect that associative learning isn't merely the outcome of a cue being linked to a reward—the order of these events matters, too.

Consider a scenario where the bell normally rings after, not before, the arrival of dog biscuits. To the canine diner, the sound won't then represent bliss, but the *end* of bliss; and it will presumably produce memories of sadness rather than of appetite. All of which

Illustration by Iker Ayestaran

suggests that the brain doesn't just file experiences of different kinds in its memory bank—it somehow assigns time stamps to these experiences as well.

Time is a weird thing from a biological perspective, far more abstract than sounds or objects. You can't see, hear, touch, or taste it, yet the brain seems quite capable of tracking it. Precisely how this chronicling occurs in the context of learning is something that researchers in the lab of Vanessa Ruta, the *Gabrielle H. Reem and Herbert J. Kayden Associate Professor*, are very keen to understand.

The lab doesn't have much faith in the dog as a model system, however. For these scientists, man's best friend is *Drosophila melanogaster*, the humble fruit fly. Recently, Ruta's team set up a modern version of Pavlov's experiment in which they exposed flies to an odor rather than to a sound; and instead of rewarding the animals with a treat, they used optogenetic technology to directly stimulate reward-signaling neurons in the flies' brains.

The results were clear. When the flies were given a reward signal immediately after receiving a puff of the smell, they became attracted to that scent; but when the reward came before the smell, they shunned it instead. "The difference in time is only one or two seconds, yet the flies form completely opposing associations," says graduate fellow Annie Handler.

She and her colleagues identified a set of brain cells whose activation enables the fly to know the sequence of events. In addition, they found that flies that had learned to covet the smell could quickly be retrained to detest it, and vice versa. In other words, flies are like us in that their memories are not set in stone.

"There are so many things that we could remember on a daily basis, so we hold on to the memories that turn out to be predictive; and we toss out associations that are incorrect or irrelevant," says Ruta. "When you live in a dynamic environment—which both flies and humans do—that seems like a very good strategy." ◎

MARIO MORGADO

Spermatic innovators

SPERM SCIENCE HAS a curious past, supported at times less by fact than by the (predominantly male) imagination. In the late 17th century, when Dutch scientists caught the first glimpse of the tadpole-like cells under the microscope, they decided that each one carried within its head a miniature human being that would grow into a baby—positing that the egg cell, discovered decades earlier, played but a minor role in human reproduction.

This myth was eventually debunked, but others followed, including the still-popular idea that ejaculated spermatocytes purposefully swim toward the egg, propelled by an ancient drive to outcompete sperm from other males. In reality, these cells are much less heroic: They don't even swim very far but passively drift across the uterus, buoyed along by soft motions in the female tissue.

In short, we have yet to see the evidence of machismo manifesting at the micro scale.

This isn't to say sperm are completely without agency, however. They do have at least one impressive talent: an unsurpassed knack for building novel genes. In this sense, the testes are not mere sperm factories but also laboratories churning out fresh DNA content—undeniably a seminal mission given that new genes are the raw material for the evolution of species.

Recently, scientists took a major step toward understanding how nature's attempts at innovation play out during the development of sperm. Working with fruit flies, a team in the laboratory of Li Zhao created a detailed map of DNA mutations arising in each sperm and the activity of new genes arising from those mutations.

"It offers an unprecedented perspective on a process that enables living things to adapt and evolve, and that ultimately contributes to the diversity of life on Earth," Zhao says about the research, published in *eLife* earlier this fall.

Her team is interested in so-called de novo genes that emerge from scratch rather than through duplication of existing genes. The fly sperm turned out to be a treasure trove—in it, the scientists identified 184 previously unknown de novo genes. Zhao suspects that some of these genes may play a role in spermatocytogenesis, the process in which sperm form from precursor cells. "Precisely what de novo genes are doing to move sperm development along is an exciting open question," she says. ◎

Fat, miscalibrated

Losing one's leptin makes it hard to stay slim.

NATURE HAS ITS way of keeping things in balance. When it comes to body weight, the key regulator is leptin, a hormone secreted by fat cells. When fat storage increases, leptin informs the brain to lower appetite—and vice versa. That's how the body balances its fat stores and food intake, keeping them within a fine range.

In some people, however, the system miscalculates. For the past 25 years, since leptin was first discovered by Rockefeller's Jeffrey M. Friedman, scientists have wanted to understand exactly how changes in the hormone's function may lead to obesity, an ever-worsening public health problem that now affects more than 650 million adults worldwide. Some have suggested that the disease is caused by problems in leptin's faithful reporting of fat levels to the brain; others have argued that it is in fact due to the brain's failure to respond to the hormone.

It turns out this internal calibrator can go kaput in different ways in different people.

In a study published in *Nature Medicine* earlier this year, Friedman, the *Marilyn M. Simpson Professor*, and his collaborators suggest that at least 10 percent of obese people may be genetically incapable of producing sufficient leptin at all. No matter how much fat is stored in the body, their leptin levels remain low.

"These people have less leptin from an early age, making them a little bit hungrier than everyone else," says Olof Dallner, a research associate and the lead author of the study.

The researchers traced the problem to a type of RNA that seems to regulate how much leptin is produced. When the team engineered mice without this specific RNA, and fed them a high-fat diet, the mice kept accumulating fat to the point of becoming obese, but their leptin levels nevertheless remained low. Another group of unaltered mice munching on the same unhealthy diet became a little chubby, too—but this group produced normal amounts of leptin, which appears to have kept them from becoming outright obese.

DATA

A typical leptin-deficient mouse weighs 1.94 times more than the average lab mouse.

There's compelling evidence that these findings might pertain to humans, too. When the team looked at the genetic profiles of more than 46,000 people, they found that alterations in the human version of the same RNA are linked with lower leptin levels. Some people, this work suggests, may have a subtype of obesity that's potentially treatable with leptin therapy. That was indeed the case with the low-leptin mice: When the animals received injections of leptin, they lost weight.

All of this is good news for people with leptin-curbing mutations. But most obese people gain weight not because of too little leptin but because their brain has stopped responding to it. For this group, there may be other avenues for therapy—for example, targeting the brain networks that control not just how much we eat, but also how much energy we burn.

In a recent study published in *Cell*, Friedman's team identified a group of neurons in the brain stem that do just that. In mice, turning the neurons off triggers the burning of fat to produce body heat, and also decreases hunger. It suggests that these multitalented cells could be powerful levers for managing body weight—especially if they could be targeted with drugs.

ZACHARY VEILLEUX

DRUG INCUBATOR

Camouflaged targets

Sakmar and Lorenzen in the lab.

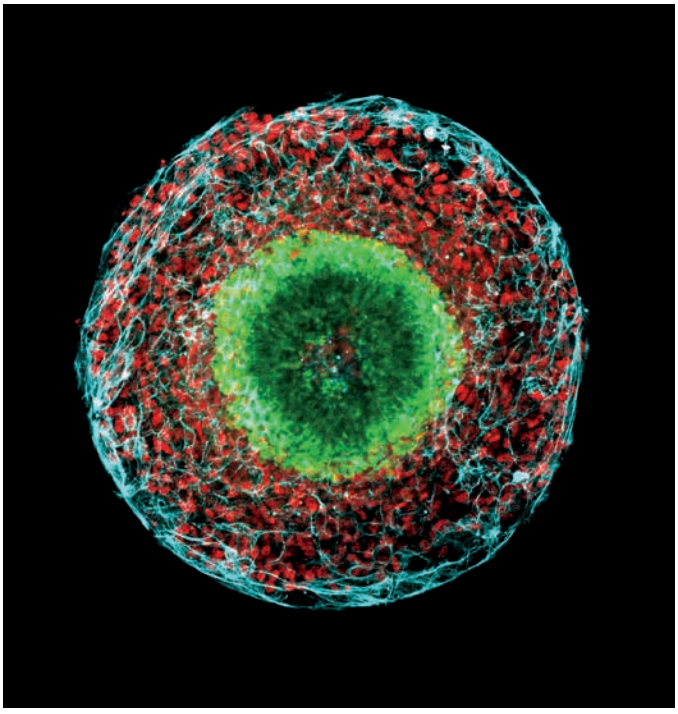
NEARLY ONE-THIRD OF all medications act on the same type of molecule, called a G protein coupled receptor. In humans, there are an average of about 800 GPCRs on the surface of each cell, and it might come as a surprise that even in such a well-studied and successful family, there are still over a hundred receptors that remain a mystery. Scientists have not been able to pinpoint their precise function.

And that hasn't been for lack of trying—with their promising pedigree, GPCRs have been the focus of intense drug discovery research. The next drug target for migraine, osteoporosis, or brain cancer could be a GPCR, if only you could find a molecule that would unlock the receptor. More often than not, it seems that nothing does.

"One hypothesis is that some component is missing," says Thomas P. Sakmar, the *Richard M. and Isabel P. Furlaud Professor.*

That missing component, it turns out, could be the receptors' little-known accessory proteins. Graduate student Emily Lorenzen, who recently developed a high-throughput technique to study GPCRs, was surprised to discover that many of these receptors may get outfitted with accessory proteins inside cells. This means that a receptor's overall shape and function might often be different in the test tube—where the receptor is naked—than inside the body.

The findings, described in *Science Advances*, may explain why some drugs that show promise in the lab go on to fail in human trials. If a drug is designed to bind to a naked receptor, it might miss its target inside cells or tissues, where the receptor is camouflaged with its accessory protein. With the receptors' double appearance revealed, researchers hope the path to drug discovery will be smoother. ◎



MARIO MORGADO (TOP), LABORATORY OF STEM CELL BIOLOGY AND MOLECULAR EMBRYOLOGY, THE ROCKEFELLER UNIVERSITY

IN DEVELOPMENT

Huntington's goes way back

MOST PEOPLE WITH Huntington's disease don't show symptoms until age 30 or older. But a new technology has made it possible to trace the condition back to the biological events that instigate it—and those events, it turns out, happen long before birth.

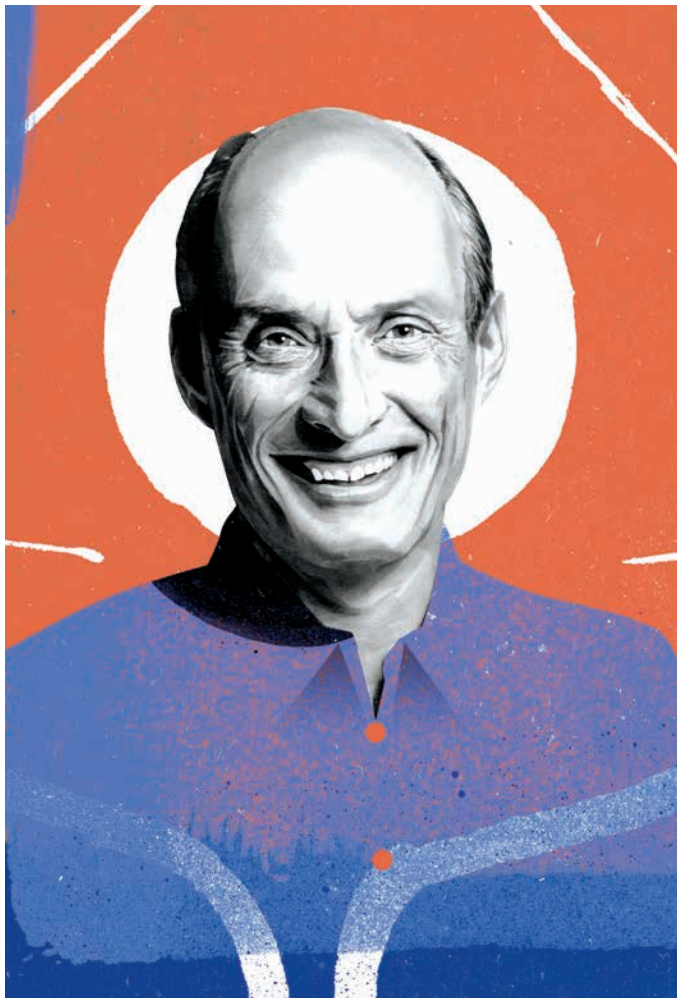
The discovery is very meaningful, says Ali H. Brivanlou, who led the research, since it may focus new therapies on the causes, not the consequences, of Huntington's.

Research in the field has long relied on animal models, and it wasn't until Brivanlou's lab developed an alternative system based on human cells that they saw evidence of the disease arising during neurulation, one of the earliest stages of embryonic development. The new system, the neuroloid, is a tiny, self-organizing cell-culture colony that mimics the brain.

"It really opens a door to identifying the mechanisms that govern brain development, understanding how they go awry in disease, and testing drugs that set these mechanisms back on the right course," says Brivanlou, who is Rockefeller's *Robert and Harriet Heilbrunn Professor.* ◎

END OF AN ERA

In showing that neuroscience isn't all about voltage, Paul Greengard electrified it



IN 1953, THE year Paul Greengard graduated as a biophysicist, scientists felt they had a pretty good idea of how the nervous system works. They saw the brain as an elaborate data-processing machine, maybe a compact version of the trailer-size IBM 650 launched that same year. Like computer chips, brain cells communicated via electrical signals, though those signals were transmitted via neural extensions and synapses rather than through copper wire. And although the brain's apparatus was astonishingly complex, its fundamental processes were driven by plain voltage.

Greengard, however, had a hunch that things were not quite so simple. He focused instead on what he called slow synaptic transmission, a second mode of nerve-cell communication in which neurotransmitters such as dopamine or serotonin carry messages from one part of the brain to the other, ultimately producing durable changes in an organism's mood, alertness, or sensory perception. By the early 1980s, he had shown that this chemical mode of cell-to-cell signaling actually represents the lion's share of neuronal communication. It was work that helped jump-start modern neuroscience, and it eventually earned Greengard a Nobel Prize.

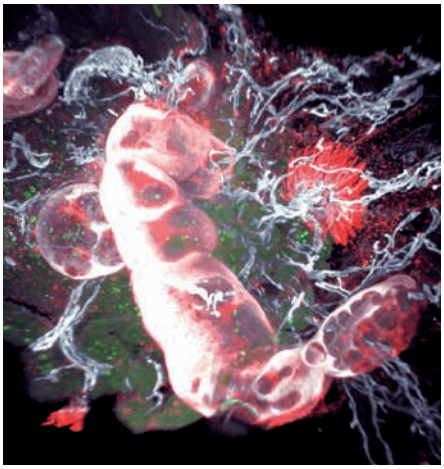
"Paul's discoveries laid out a new paradigm," Rockefeller's president Richard P. Lifton said shortly after Greengard died in April, at age 93. "Today, abnormalities in signaling among neurons are recognized to underlie many disorders," from Parkinson's disease and schizophrenia to depression and substance abuse. ◎

DATA 30nm

The average distance a neurotransmitter must travel as it moves across the synapse connecting two neurons.

EATING

Your gut has a plan



THE TENS OF trillions of microorganisms that inhabit the gut are, generally speaking, a friendly bunch. They help digest food, protect us from infections, and even support certain brain functions. But occasional bad actors can be found even in the best societies—and in the gut microbiota, such delinquents tend to be disease-causing food pathogens like *Salmonella*.

Whenever food enters the intestine, the immune system pulls off an impressive balancing act. It stays vigilant against potential arriving pathogens while at the same time keeping its cool: It tolerates the overwhelming majority of good bacteria and allows nutrients to be absorbed. Such a delicate feat calls for a good strategy—and new research shows that the gut's immunological approach is embedded in its very topography.

In a study published in *Nature*, scientists in the lab of Daniel Mucida found that the gut consists of segments that pace the immune cells' reactions to each arriving swallow. Cells capable of generating tolerance against the vast majority of luminal encounters occupy the first compartments, where nutrients are absorbed, and they are backed up by cells with better resistance capacity at the end, where invaders are eliminated.

"At first glance the intestine appears uniform throughout," says Mucida. "But we've found a sophisticated functional system lurking beneath the surface." These findings might inform the development of oral vaccines as well as drugs for gastrointestinal disorders, he says, and give scientists a finer understanding of a snack's journey along the gastrointestinal tract. ◎

LABORATORY OF MUCOSAL IMMUNOLOGY, THE ROCKEFELLER UNIVERSITY

Illustration by HelloVon

PHOTOGRAPHY

Out of the jungle, onto the art scene

HE CLEARLY HAS a thing about ants. When Daniel Kronauer isn't using them for research purposes, he stalks them with his camera, paparazzi style. "Knowing the biology of ants so well, I'm able to anticipate their behaviors and find myself in the right place at the right time," he says.

Kronauer is head of Rockefeller's Laboratory of Social Evolution and Behavior, and his unique photos give a ground-level view of life as an ant. His shot of a cathedral-shaped bivouac—built by and consisting of nomadic army ants in the rain forest of Costa Rica—reveals an astonishing complexity of ant teamwork. The photo earned Kronauer an award in London's Natural History Museum's prestigious Wildlife Photographer of the Year competition, in the invertebrate-behavior category, and is now part of an exhibit touring various international venues.

DANIEL KRONAUER

Army ants interlink their bodies to build a nest, allowing them to relocate the entire colony daily.

ANTIVIRAL VANGUARD

The problem with Zika

Rather than protecting the body from Zika, special antibodies may in fact help the virus enter maternal cells.

FOR SCIENTISTS working on a Zika vaccine, there's an ugly new twist. A Rockefeller team has found that some pregnant women who've been infected with the virus develop antibodies that correlate with an increased risk of babies being born with microcephaly, a Zika-linked condition in which the head is underdeveloped.

"A safe vaccine would need to induce the immune system to selectively produce antibodies that are protective, avoiding those that potentially enhance the risk of microcephaly," says Davide F. Robbiani, a research associate professor in the lab of Michel C. Nussenzweig. This means that vaccine developers must figure out not only how to make the immune system react against the virus but also how to steer its response.

Robbiani and his colleagues, who published their findings in the *Journal of Experimental Medicine*, discovered the problematic antibodies when analyzing blood samples from about 150 pregnant women with the virus, all collected in Brazil during the country's 2015 Zika outbreak. Further studies in animals suggested that, rather than protecting the body from Zika, these antibodies may in fact help the virus enter maternal cells. ◎

SYNAPSE PROBLEMS

Stuck in a groove

FOR A MILLIMETER-LONG roundworm with only 302 neurons, *C. elegans* is surprisingly curious. Constantly on the move, it inches its environment, exploring every corner and poking its head into every nook. So Menachem Katz was surprised when his roundworms stopped their leisurely stroll and instead moved frantically back and forth, like the stuck hand of a clock.

The change of routine came after Katz, a research associate in the lab of Shai Shaham, the *Richard E. Salomon Family Professor*, tweaked the worms' version of astrocytes, our star-shaped brain cells known to support neurons. *C. elegans* has only four such cells, and Katz had taken them all out, prompting the worms into a course reversal loop. "It's as if once they start the action, they can't stop repeating it," says Katz.

The idea was to see what happens when, in the absence of housekeeping astrocytes, the nervous system is unable to clear up the excess neurochemical glutamate from the junctions between neurons. In research published in *Nature Communications*, Katz and his team showed that the worms' repetitive behavior is indeed caused by glutamate flooding the neurons, overstimulating them in wave after wave.

These findings mean a model organism as simple as *C. elegans* could be used to study the role of glutamate signaling in repetitive behaviors, opening the possibility of meaningful new experiments. In mice, for example, glutamate spillovers are linked to excessive grooming. Other studies have found mutations affecting glutamate signaling in people with obsessive-compulsive disorder and autism spectrum disorders, both of which can cause repetitive behavior. "It turns out, this model may hold up in more complex nervous systems," Katz says. ◎

Katz examines dishes of *C. elegans* worms.

MATTHEW SEPTIMUS

9,025

DATA

The number of people who contracted tuberculosis in the United States in 2018, representing 0.09 percent of all cases worldwide.

PRECAUTION

TB and travel

Some people have mutations that make them especially vulnerable to mycobacteria, and they are more common than previously thought.

ONE IN FIVE citizens of the world hosts *Mycobacterium tuberculosis*, the bacterium that causes TB. If you've lived your whole life in the West, you're likely not one of them, and your risk of encountering the germ in the future is extremely low.

Unless, of course, you happen to be someone who travels far and wide—to Brazil, Botswana, Bangladesh, or any of the three dozen countries where TB is rampant. In that case, your risk of contracting the disease is determined by your DNA, among other things. Some people have mutations that make them especially vulnerable to mycobacterial infection, and according to a recent study, those mutations are a lot more common than previously thought.

Earlier this year, Jean-Laurent Casanova and his team reported that one in 600 Europeans carry mutations in the gene TYK2, making their immune systems less capable of fending off the disease. It's not a problem for those who stay in Europe, Casanova says, since "their risk of getting TB is effectively zero." But for those with certain travel itineraries, it's a risk factor.

Genetic testing can reveal the mutation and may suggest when precaution is warranted. The scientists found that TYK2-associated vulnerability to TB is caused by low levels of gamma interferon, a blood protein that usually protects the body from the disease. "It's probable that treatment with gamma interferon, a medicine that has been available for 30 years, could be an effective therapy for these people," says Casanova, who is head of the St. Giles Laboratory of Human Genetics of Infectious Diseases. ◎

Illustration by Carmen Segovia

Q&A

The world's most powerful molecule has a PR problem

With Robert B. Darnell

Darnell has spent decades studying RNA in the context of brain diseases and cancer.

WITH ITS ICONIC shape and voluminous genetic script, DNA is the darling of nucleic acids. Since 1944, when Rockefeller scientists first identified it as the substance of hereditary information in cells, DNA has been center stage in biology, heralded as the blueprint of everything that organisms are or have the power to become. So popular is the splendid spiral that it has come to be visual shorthand for life itself, embodied in everything from fine art to postage stamps and $10 gift-shop bracelets.

Yet DNA isn't necessarily the most interesting of molecules. To realize its potential, which usually means to make proteins, it must first be copied into fragments of a less famous molecule: ribonucleic acid, or RNA. RNA's main job is to messenger DNA's instructions to the cellular machinery that makes proteins.

But RNA is not merely a messenger. In recent decades, researchers have been surprised to discover how many different types of RNA there are, and the myriad ways in which they help cells manage their basic operations. RNA is even believed to have instigated life on Earth, long before DNA and proteins came into the picture. And it is turning out to be a worthy subject for clinical science. For example, the level of certain RNAs in a patient's tissue might help predict disease outcomes, offer important insight into the nature of the disease, and in some cases even open doors to new treatments.

Clinician-scientist Robert B. Darnell, Rockefeller's *Robert and Harriet Heilbrunn Professor* and the founding director of the New York Genome Center, has spent decades investigating RNA and the proteins that help regulate it in the context of brain diseases and cancer. We asked him to tell us more about the mysterious molecule to which we, along with 8.7 million other species, owe our existence.

What should people know about RNA?

All your cells have the same DNA, which is basically an inventory of all the things our cells are theoretically able to do. RNA, on the other hand, is customized to the situation. Its job is to determine what any given cell actually ends up doing at a specific time or under specific circumstances. When we talk about gene expression, the process by which a piece of DNA gets activated to produce a protein, we're often really talking about RNA. There's a whole layer of regulation that alters both the quality and the quantity of that protein, much of which involves RNA.

Furthermore, many genes are modular, meaning they can be assembled in different ways at the RNA level. The result of this process is that a single gene may produce not just one, but hundreds of versions of a protein that differ in their structure and function. It's a way in which evolution has allowed organisms to become increasingly sophisticated. Generally speaking, bacteria make as many proteins as they have genes, but humans, thanks to alternative splicing, make many more. RNAs are the driving force of our biological complexity.

But RNA gets really fascinating when we consider its feat as the very origin of life on Earth. In a likely scenario, the earliest life form was a membrane surrounding a piece of RNA capable of doing two things: carrying its own genetic recipe and acting as an enzyme to make new copies of that recipe—in other words, it could replicate itself.

If RNA came first, what was the purpose of DNA?

At some point, replicating RNAs needed a more reliable system to safeguard their genetic content from damage. Many scientists

FRANK VERONSKY

believe that an early cell solved this problem by making backup copies of the RNA sequence in the form of DNA, which is more robust. That's how cells ended up with two versions of the genetic code: a DNA version that ensured data safety and an RNA version that allowed the data to be used in a flexible manner.

Another evolutionary breakthrough, of course, was the addition of proteins. Early organisms that used RNA to make proteins had a big advantage over those that didn't. RNA is made up of only four basic building blocks while proteins are built from 20, which means proteins can assume more elegant and functional shapes.

Back to the present—how does RNA influence complex life process like those involved in human cognition?

The human brain is the most complex biological system we know. It consists of many billions of cells, and each can make thousands of connections with other cells, with millions of connections being modified every second. The brain's ability to produce highly sophisticated functions like cognition is believed, at least in part, to result from mind-boggling intricacy at the RNA level.

It's not uncommon for genes expressed in the brain to produce hundreds of protein variants; and there are other ways in which RNA helps fine-tune gene regulation in response to various stimuli and environmental factors. For example, when a neuron makes a particular RNA, factors that bind to that RNA can modify how quickly it will be translated into a protein or degraded, or they might dictate the location within the cell to which the RNA will be sent. Through such regulation, it is believed that RNA has the power to induce local changes in a neuron's connectivity, thereby strengthening or suppressing the responses to particular synapses firing.

"RNAs are the driving force of biological complexity."

Does all this complexity also complicate our understanding of human disease?

Absolutely. For many common disorders, it has been challenging to establish which genes are responsible, and this is particularly true for brain diseases. Take autism spectrum disorders, for example. Initial genetic studies yielded lists of mutations thought to contribute to these conditions, but it turns out that these mutations don't account for most patients' symptoms.

One reason for this is that most such genetic research has focused on a subset of patients' DNA, the approximately two percent of the genome that codes for proteins. For autism, even the best among such studies have failed to identify clinically relevant mutations in two patients out of three. The remaining 98 percent of DNA remains largely unexplored—in fact, some people call it the genome's "dark matter."

DATA

As much as five percent of the weight of a human cell is RNA.

But we now know that much of this noncoding sequence in fact codes for RNAs. And when you consider just how much influence RNAs have on genes, it starts to look a lot more important.

Newer methods are being developed to sift through entire genomes and predict disease-linked mutations within these noncoding sequences. These are extremely data-heavy studies that require machine-learning algorithms as well as more refined biochemical methods such as CLIP, an approach our lab pioneered. CLIP allows scientists to extract RNA from live brain tissue or from frozen clinical samples and purify the precise points of interactions between those RNAs and the proteins that regulate them.

Recently, we combined CLIP and a similar, DNA-based technology with machine learning to study close to 1,800 families in which one child has autism, and we discovered mutations in the so-called junk DNA that may spur the disease by acting on regulatory RNA or DNA binding proteins. We hope these findings will lay a pathway for how to fill the gaps in our understanding of autism and other complex genetic disorders.

Could the same technology be used with other diseases?

Yes. In mouse studies, we recently discovered that stroke induces a dramatic reduction in the levels of a particular RNA called miR-29. By studying this RNA's function, we were able to identify a potential drug target for treating a common type of stroke-induced brain damage. We are also applying the method to study memory and fragile X syndrome, and we're working with other labs to discover noncoding mutations relevant for other brain disorders, viral infections, and different forms of cancer.

We are optimistic that this RNA-centered approach has great potential to further our understanding of all kinds of previously intractable diseases, and potentially come up with new treatments. It's also promising to be a powerful tool in the laboratory. For example, we will be using it to study the regulation of how synapses connect to neurons with the goal of better understanding both how the brain works normally and how it deteriorates in disease.

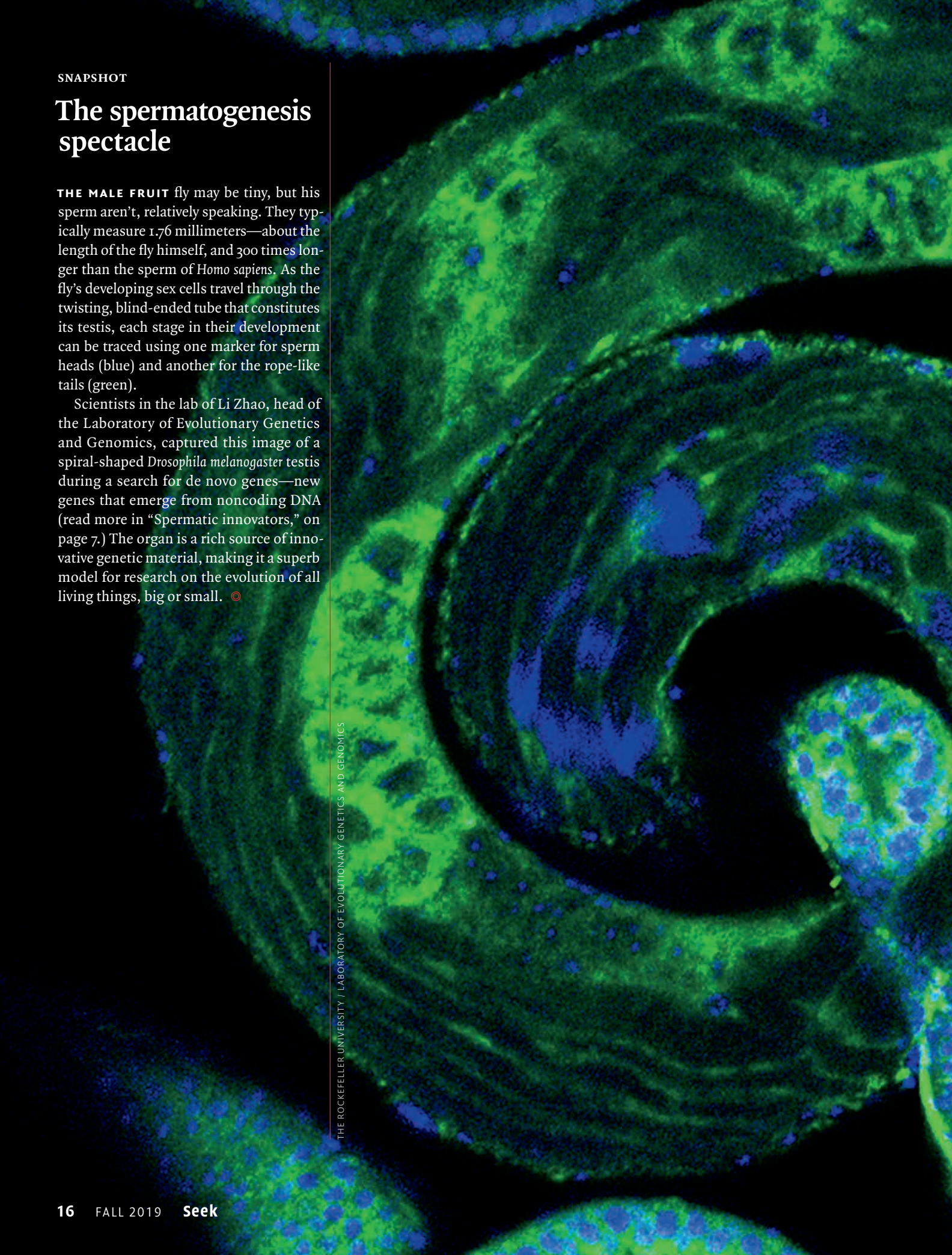
Ultimately, mapping sites of RNA regulation and understanding it in greater detail could be a gateway to connecting what we're learning in the lab to what we're seeing in the clinic, including how genes and environmental factors contribute to disease. Integrating all this knowledge has been, and will remain, a huge challenge for bioscience. But with the ability to understand and target precise spots of the genome's dark matter, we might be able to come up with clinically actionable ways to target those spots. ◎

SNAPSHOT

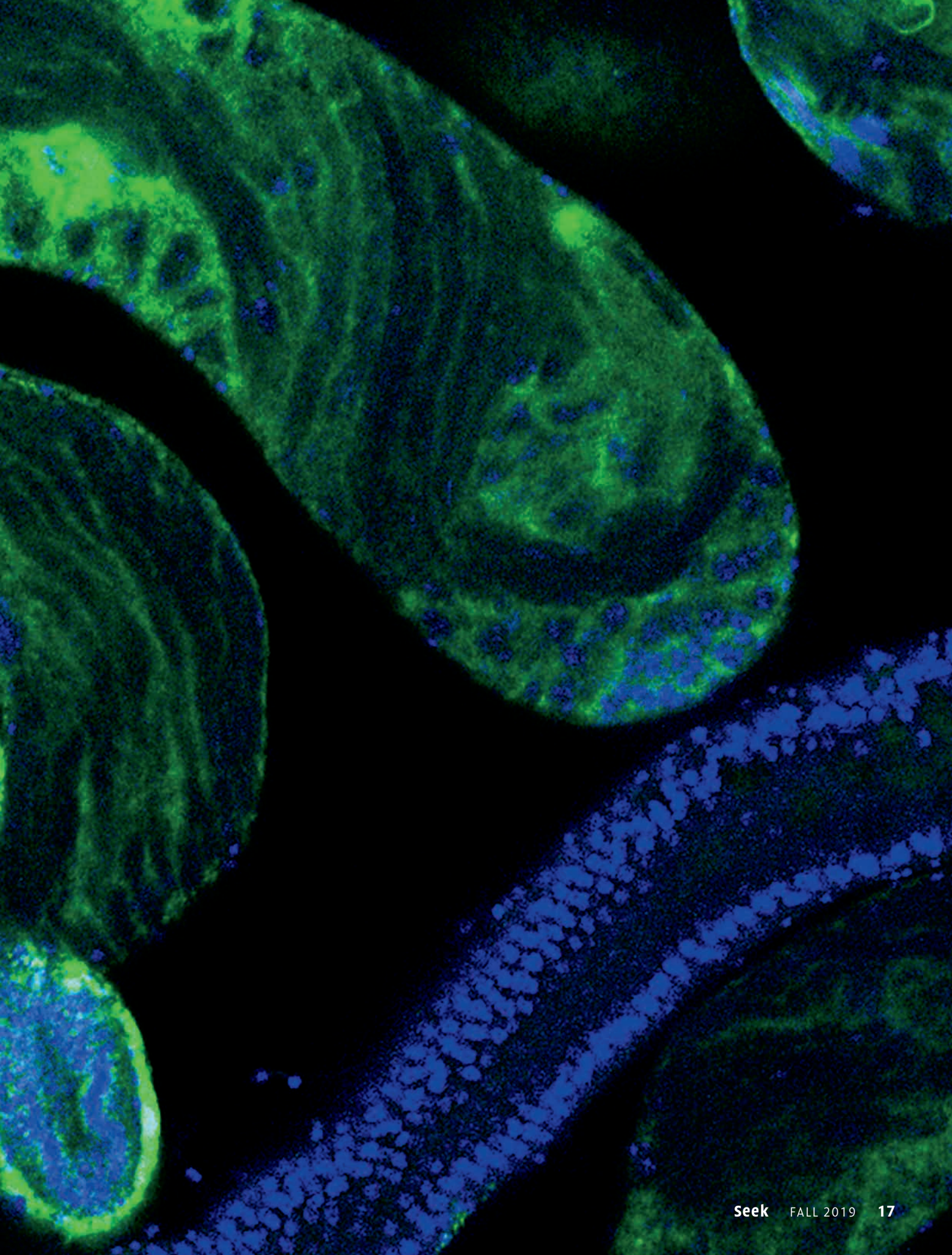
The spermatogenesis spectacle

THE MALE FRUIT fly may be tiny, but his sperm aren't, relatively speaking. They typically measure 1.76 millimeters—about the length of the fly himself, and 300 times longer than the sperm of *Homo sapiens*. As the fly's developing sex cells travel through the twisting, blind-ended tube that constitutes its testis, each stage in their development can be traced using one marker for sperm heads (blue) and another for the rope-like tails (green).

Scientists in the lab of Li Zhao, head of the Laboratory of Evolutionary Genetics and Genomics, captured this image of a spiral-shaped *Drosophila melanogaster* testis during a search for de novo genes—new genes that emerge from noncoding DNA (read more in "Spermatic innovators," on page 7.) The organ is a rich source of innovative genetic material, making it a superb model for research on the evolution of all living things, big or small.



THE ROCKEFELLER UNIVERSITY / LABORATORY OF EVOLUTIONARY GENETICS AND GENOMICS



From the largest whales to the smallest germs, living things have evolved some remarkable ways to get around. Meet the physicist whose studies of locomotion are taking her places.

Jasmine Nirody

By Caitlin Shure

JASMINE NIRODY SCOURED her dorm room. She searched under tables and chairs, in corners and crevices, to no avail. Her snakes were officially missing.

"How did they get out?" she wondered. But in a sense, she knew the answer.

Then an undergraduate at New York University, Nirody had adopted the animals after using them in a senior thesis project to investigate how snakes move—in particular, how they maneuver across surfaces of varying textures. In the wild, the animals propel themselves off bumps and cracks in naturally uneven terrain, such as a forest floor. Nirody and her colleagues discovered that snakes have a failsafe that allows them to wiggle on even the slickest of surfaces: their scales are ridged such that they can generate friction anywhere they go.

Of course, these findings weren't particularly helpful to Nirody as she searched for her truant pets. All she knew was that they had the ability to slither almost anywhere—down the hallway of her dorm, onto the streets of Manhattan, and possibly into Washington Square Park to stun unsuspecting tourists.

She never recovered the three snakes.

Now a Rockefeller fellow in physics and biology, Nirody has moved on to study microscopic animals less prone to escape. Formally called tardigrades, the organisms also go by the name water bears—because when enlarged several orders of magnitude they really do look like adorable, if alien, bears.

Barely visible to the naked eye, tardigrades are the smallest organisms with legs, and therefore are the smallest organisms to walk. Nirody will show a video of their mesmerizing movement to anyone who swings by her office.

Her interest in the tiny perambulators? Same as her earlier interest in the snakes: She wants to know how they move. Not just the general gist of their ability to push their legs off the ground, but the minute details of the friction and inertia involved. She wants to understand the physics of it.

"When mammals walk, we're very concerned about gravity," Nirody says. "But these guys are more worried about the opposite problem—about floating away. So the question is: How do they adapt to these challenges?"

This line of research dovetails with others that Nirody is pursuing about how specific animals navigate their respective environments, or how a single organism might alter its behavior to accommodate a changing landscape.

Later, she says, this knowledge will help us build robots. Just as birds inspired us to build airplanes, so snakes, geckos, and even the tiny tardigrade, Nirody believes, may spur new innovations.

NIRODY DIDN'T HAVE pets as a child. The reasons were partly logistical: Her family moved around—from Mumbai to Florida, then to New Jersey—and transporting animals along with everything else seemed complicated. Moreover, she had somewhat nontraditional tastes in pets. She begged her parents for a turtle or a lizard, but the idea of a domesticated reptile terrified her mother. A cat or a dog might have been an easier sell, but Nirody wasn't interested.

"I don't really like mammals," she states bluntly. "They're just hairy."

With her household at an animal impasse, Nirody directed her attention outside. She became enamored of bugs and keenly interested in how they move. In this respect, Nirody attributes to her

Photograph by Matthew Septimus

younger self a fascination with mechanics. Like most kids, she wanted to know how things work.

Yet being a child, and lacking serious exposure to the world of basic science, she didn't realize that her curious instincts were also a viable career. She assumed that becoming a medical doctor was the closest she could get. So after studying math—at the time of her snake experiment, she was a math major at NYU—she enrolled in medical school.

Once there, she spent her nights researching, coding, and taking on side projects that weren't on the curriculum. At one point, it dawned on her that even though she was officially training to be a doctor, she was really becoming a researcher.

"I began to understand that there is a way to make a living answering the questions that interest me," she says.

So she switched schools.

THE ABILITY TO navigate diverse landscapes is key to an organism's survival. If you can only amble on dry land, for example, you'll be in trouble if you encounter a patch of mud.

Humans are capable of a transitioning between a few modes of mobility—from running on asphalt to trudging on sand to swimming in the ocean, for example. Still, there is a lot we *can't* do locomotion-wise. We can't scale trees in the manner of lizards. We can't skate on the surface of water, like insects. And we're really just mediocre swimmers.

So to acquire a more expansive understanding of the movement techniques that exist in nature, Nirody seeks distinctly nonhuman, nonmammal subjects—precisely the type of organisms that she's always been drawn to.

After experiencing the rigidity of medical school, Nirody knew she wanted to pursue a career path that would allow her to follow her evolving interests and to ask a broad range of questions. She enrolled in a graduate program in biophysics at the University of California, Berkeley.

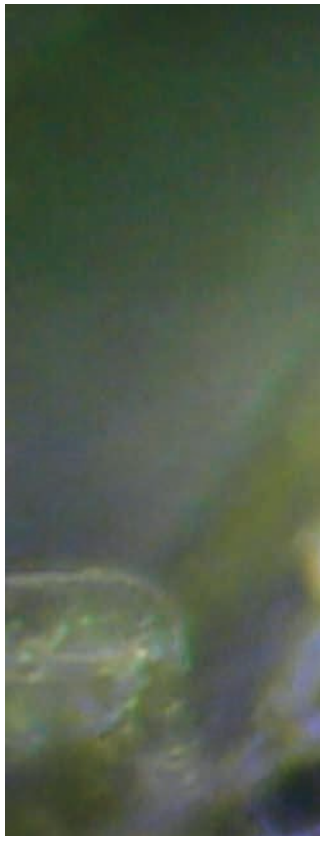
> "If you polled all the organisms on earth, flagellated swimming would be by far the favorite means of locomotion. So I figured I should go with the majority vote."

There, she met the mathematical biologist George Oster, who served as both her adviser and as a model for the kind of scientist she wanted to become.

"He found ways to make himself useful in a lot of different areas," she says. "Because if you have a physics background, you can pop your head into a biological or engineering field and take a look at the math, and then just pop your head back out again."

Over the course of her graduate studies, Nirody popped in and out of an impressive diversity of fields. Rotating through labs, she first studied color patterns in seashells, then the mathematics of genetic ancestry, then cockroach locomotion.

Cockroaches weren't for her—"I do have my limits in terms of what animals I can spend time around," she says—so she ended up working on bacteria. Specifically, she investigated a mode of bacterial movement known as flagellated swimming. A flagellum is a wispy appendage that extends from a bacterium's body, whipping back and forth to propel the microbe through water or other fluids. This techinque is



The tardigrade, a half millimeter long at most, is the smallest animal to walk on legs.

SCIENCE PHOTO LIBRARY

incredibly efficient, and is a dominant mode of movement in nature.

"If you polled all the organisms on earth, flagellated swimming would be by far the favorite means of locomotion," says Nirody. "So I figured if I was interested in locomotion, I should go with the majority vote."

She devoted most of her Ph.D. work to understanding the motor that drives flagella to spin around. This system, she learned, functions somewhat like a wheel and axle. At the microscopic scale of bacteria, however, wheels lack sufficient mass to accumulate momentum and need constant nudging to stay in motion. So rather than spin continuously, the microbial motor rotates in incremental steps.

Resolving the mechanics of this little system answered the type of fundamental how-does-it-work question that had always compelled Nirody. And, as a bonus, it gave her the satisfaction of knowing her work might one day translate into useful medical applications. Flagellated bacteria include many of the infectious microbes that pose a threat to human health, including *E. coli*, *Salmonella,* and the bacterium that causes cholera. And understanding how these microbes get around could inspire new approaches to fighting them.

"How do you make something not infectious anymore?" asks Nirody. "Take away its ability to move."

She also views her work on microscopic motors as potentially useful for the development of tiny robots, or nanobots. If you want to design nanobots, it makes sense to draw inspiration from systems that nature has used again and again and again, says Nirody. Evolution is a brilliant engineer, and she doesn't secure patents.

Complementing Nirody's infectious obsession with hairless organisms is a similarly infectious futuristic imagination. The field of robotics has made extraordinary technological strides in recent years, but when it comes to literal strides, she says, robots are currently quite primitive.

"Robots only learned to convincingly walk about a year ago, and they're pretty limited in terms of where they can go. But *these guys*," she fawns, pointing at a water bear on her computer screen, "these guys walk in all sorts of environments."

As she verbally pivots from microanimals to nanobots and back again, it's difficult to decipher where Nirody's professional interests end and her personal obsessions begin. And that, according to Nirody, is exactly how it should be. She pursued mechanics because it granted her the freedom to enjoy a curiosity-driven career; and she accepted the fellowship at Rockefeller for the same reason.

A standard postdoctoral position requires committing to a lab and a research program. It entails burying one's head in a very specific project for four years or more; and, for biologists, it usually entails commitment to a single model organism. While this kind of program works well for a lot of scientists, to Nirody it sounded terrible.

As a fellow in physics and biology, she has access to the university's resources and researchers, but she works largely on her own and has the freedom to pursue multiple projects and as many organisms as she wants. She has access to mentors and advisers when she needs them, but nobody is looking over her shoulder or telling her what to do. Within less than three years, she's been able to continue her research on flagellated swimming, launch an investigation into water bears, and finish up a study exploring how geckos traipse across the surface of water.

Concurrent with her position at Rockefeller, Nirody also landed a fellowship at Oxford University's physics department. So she is now bouncing between continents and research subjects; and, true to form, she ably transitions across these landscapes.

"I imagine I'll answer a lot of different kinds of questions in my career in science," she says. One question she'll never get to the bottom of: Where did those snakes go? ◎

PHYSICS IS THE

They've done their chemistry and genetics.

Now scientists are ready to explore the mechanics of being alive.

By Alexander Gelfand

NEW BIOLOGY

Amy E. Shyer is watching a movie on her laptop.

It's a stop-motion clip her lab has created of cells on the move. And it reveals a fundamental truth about why cells do what they do.

Shyer's film shows what happens when skin cells, extracted from chicken embryos, are spread across a membrane that has just the right degree of rigidity. Frame by frame, the cells jostle and nudge one another until they begin to form small clumps. In living birds, these clumps would eventually become follicles, which would in turn sprout feathers.

Conventional wisdom says that the subtle dance these skin cells perform must be choreographed by genes buried deep within their nuclei. Those genes, so the story goes, express protein molecules that signal the cells to arrange themselves in patterns, migrating to form bits of tissue.

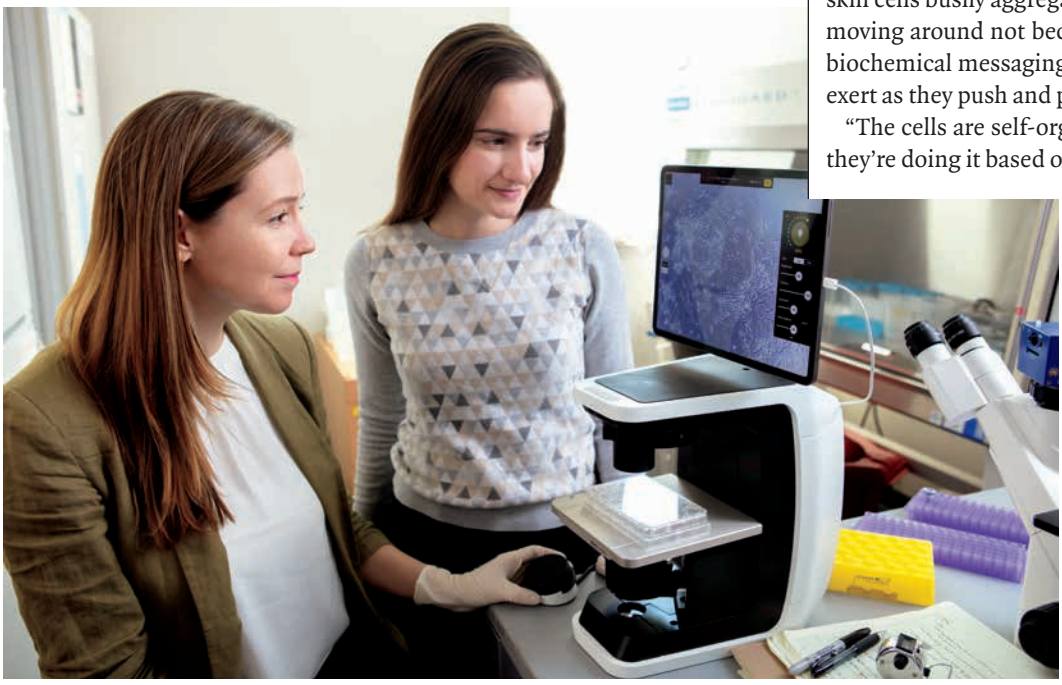
This model of morphogenesis, the process by which an organ takes shape, has been reinforced by decades of research that puts DNA at the center of all biological processes, from the healthy evolution of cells and tissues to the development of diseases like cancer and Alzheimer's. As a result, says A. James Hudspeth, head of the Laboratory of Sensory Neuroscience, "biology has been a monoculture for the last two or three decades," with scientists focused on using the tools of molecular biology to harvest the answers buried in our DNA.

That approach yields a theory of life that is simple and organized—DNA tells our cells what to do, and they do it—but that doesn't tell the full story. A growing number of researchers are finding that cells are capable of responding to more than just their own DNA, and that genomics and biochemistry can't explain everything.

Shyer and Hudspeth are interested in biomechanics: the same principles of force and motion, first established by Galileo and Newton, that allow engineers to build bridges and launch satellites. What they are finding is that the forces that act on cells, exerted by their neighbors and by the surfaces they live on—even the movements those cells make as they squirm, crawl, and otherwise go about their business—can be as essential to their functioning as genes and proteins, and may sometimes in fact trigger changes in gene expression and biochemistry.

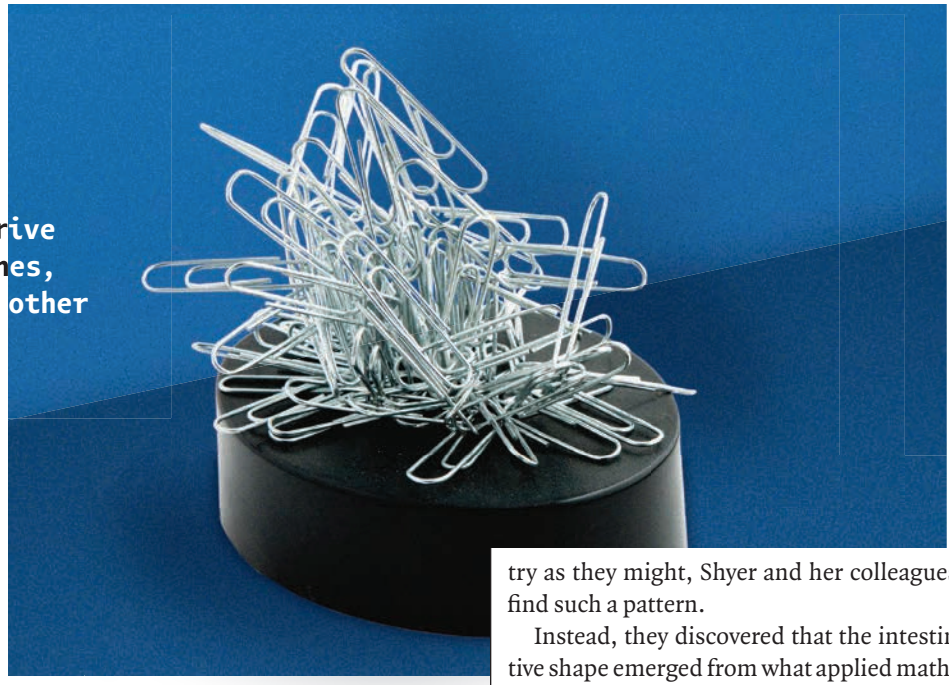
The results can be surprising, even counterintuitive. Shyer's research, for instance, indicates that the skin cells busily aggregating under her microscope are moving around not because of cues they receive from biochemical messaging, but only from the forces they exert as they push and pull themselves into formation.

"The cells are self-organizing," explains Shyer, "and they're doing it based on physical interactions."



Shyer (left) with graduate student Emily Atlas at a microscope they use to study chicken embryos.

MATTHEW SEPTIMUS



Mechanical events can sometimes drive molecular ones, and not the other way around.

More broadly, her findings suggest that purely mechanical processes—ones that emerge from the physical interactions of moving cells as they exert force and respond to it—are just as central to morphogenesis as genes and the biochemical signals they regulate. They may even, in some cases, trigger the genetic and biochemical processes that have occupied center stage for so long.

This mechanically oriented perspective is gaining currency across the biological sciences. Researchers are now exploring the biomechanics of phenomena ranging from hearing to DNA replication, often using technologies of their own invention. In so doing, they hope to illuminate the fundamental mechanisms that drive both normal and abnormal development, understand how diseases originate, and even create new opportunities for treatment and prevention.

8,325

The average number of feathers on a Plymouth Rock chicken.

Shyer, who is head of the Laboratory of Morphogenesis, first became interested in biomechanics as a graduate student at Harvard, where she worked to understand how the intestine develops its signature array of loops and coils.

According to the central dogma of her field, that configuration ought to have originated in a special pattern of gene expression—a chain reaction in which the activation of one gene after another produces a series of molecular events that mold the developing tissue. But try as they might, Shyer and her colleagues could not find such a pattern.

Instead, they discovered that the intestine's distinctive shape emerged from what applied mathematicians and civil engineers call a "buckling problem": the same phenomenon that causes the columns in a building to bend and warp under stress.

For Shyer, the realization that an entirely mechanical process could determine the form of a biological organ was an epiphany. She set about trying to find other examples and chose, as her model, avian skin. Chick embryos are easy to work with—they are a staple in developmental biology—and the follicles they develop closely resemble the ones from which human hair grows.

Previously, scientists hypothesized that the clumping behavior shown in Shyer's stop-motion movie was driven by a unique gene expression pattern that caused cells to congregate around polka-dot concentrations of proteins. One particular protein, beta-catenin—which, among other things, helps cells adhere to one another—was thought to coordinate the entire process.

Recently, however, Shyer and her colleague, senior staff scientist Alan Rodrigues, showed that avian skin cells need no such master regulator to begin rearranging themselves. When she removed beta-catenin from the picture, the cells still happily formed little clumps, so long as the membrane they rested on was, like the bed in the story of Goldilocks and the Three Bears, neither too hard nor too soft.

Further experiments revealed that, once this clustering of cells was under way, it caused beta-catenin to accumulate in the cells' nuclei, presumably triggering the gene-expression changes required for follicle formation to proceed. These findings added considerably to our understanding of skin development, advancing a narrative in which beta-catenin, though still important, was no longer the all-powerful biochemical puppet master. They also illustrated how mechanical events can sometimes drive molecular ones, and not the other way around.

Shyer and Rodrigues suspect that in nature, embryonic follicle development probably involves a continuous give-and-take between mechanical and molecular processes, with changes on one side triggering responses on the other. Elucidating the precise sequence of mechanical and molecular steps in that feedback loop should help researchers understand human skin morphogenesis and enable them to grow more realistic skin tissue in the lab for research purposes.

In addition, their work may spur the development of powerful tools for studying and treating disease. Shyer's recent discoveries, for example, could lead to improvements in organoids, small lab-grown simulacra of human organs such as brains and livers that hold great potential for biomedical research and regenerative medicine. These ersatz mini-organs might one day allow researchers to more effectively study the development of diseases and to test new drugs more realistically than can be done with rats and mice.

There could be other payoffs as well. Shyer's lab is currently investigating the mechanical underpinnings of tumor formation in hopes of developing novel strategies for treating cancer—strategies that look beyond the bewildering assortment of genetic errors that can cause cells to turn cancerous and instead address the mechanical processes by which tumors grow and evolve.

"Cancer is fundamentally a physical problem, and it's related to how cells and tissues behave," Shyer explains. As a result, drugs that target the molecular mistakes that generate cancer cells could be even more effective if they were combined with treatments that addressed the physical events involved in tumor development.

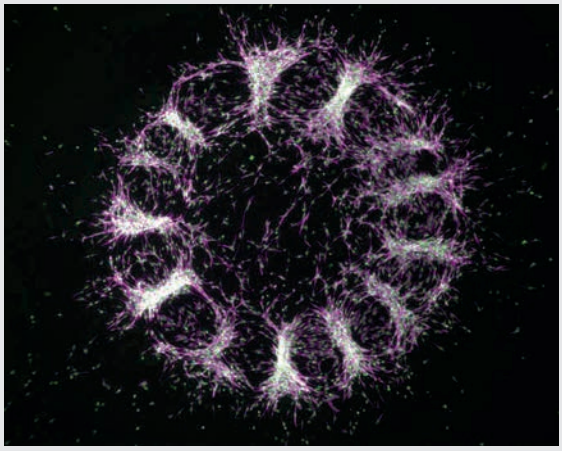
"Mechanics can't just be a side dish to the way we think about biology and development," she says. "Its power lies in how we can connect it to what we know about how genes are expressed and regulated."

SHYER'S FINDINGS RAISE an important question: If mechanical forces can induce cells to change behavior, how do cells detect these forces in the first place? In other words, how does a cell "feel" when it's being nudged by a neighbor, or whether the surface it's resting on is squishy or stiff?

Gregory M. Alushin, head of the Laboratory of Structural Biophysics and Mechanobiology, is attempting to solve these mysteries with a

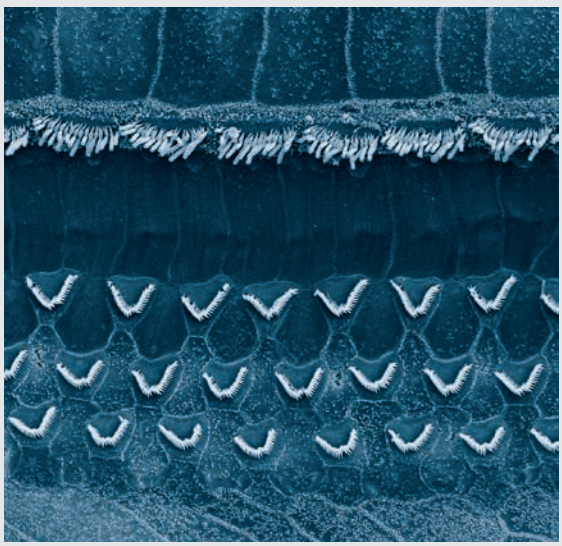
Mechanics in pictures

Self-organization



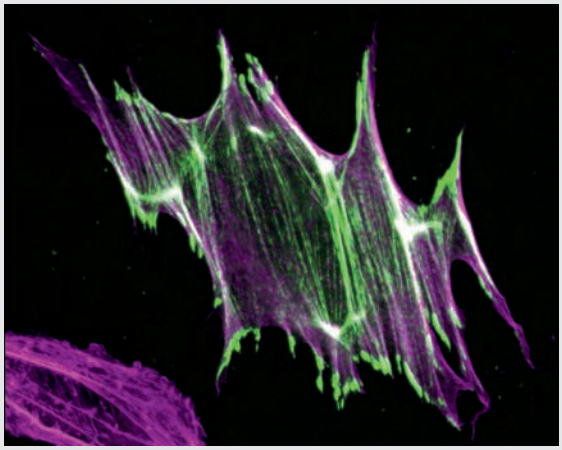
Amy E. Shyer's lab has found that embryonic skin cells communicate via mechanical cues and work together to create circular patterns that will eventually become follicles. Originally thought to be directed by chemical signals, Shyer's research shows that it's actually physics doing much of the work.

Hearing



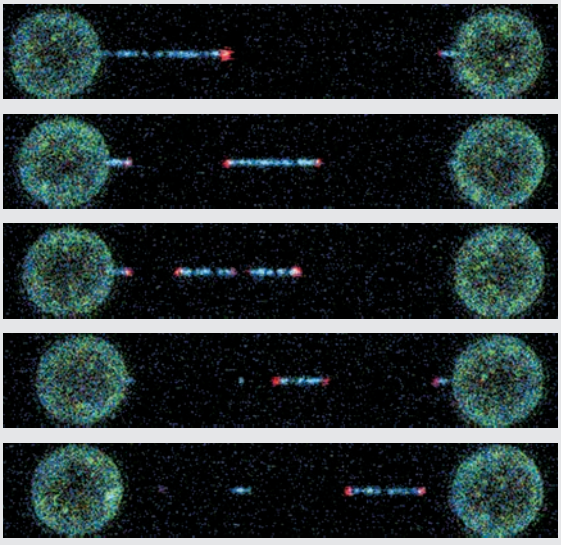
Hair cells of the inner ear come equipped with either a straight or a V-shaped bundle of stereocilia. The lab of A. James Hudspeth is developing methods to examine the mechanical work produced as the stereocilia rock back and forth—a movement key to the translation of sound-induced physical vibrations into neural signals.

Cell shape



A cell's actin filaments allow it to sense when it's being stretched. When they snap, molecular signals are generated, and, if needed, motor proteins are activated to help the cell retain its structure. In Gregory M. Alushin's lab, they call it the actin apocalypse.

DNA repair



To understand what happens when DNA breaks, Shixin Liu uses tiny glass beads that can be captured in a laser beam. He binds the ends of a DNA strand to the beads and then separates the lasers until the double helix comes apart. The experiments enable him to see how DNA repair processes unfold.

combination of approaches, including a cutting-edge form of electron microscopy.

Alushin studies mechanosensation, the process in which cells use their internal cytoskeleton to detect the forces they experience.

When a cell finds itself on a rigid surface, or when it comes into contact with another cell, its cytoskeleton is deformed. This communicates important information to the cell ("Warning: stiff floor ahead"; "Ugh, it's getting crowded"), triggering a cascade of biochemical signals and initiating an appropriate response.

In many cases, the response is movement. The cell's motor proteins—specialized molecules that can produce mechanical force and move under their own power—tug on bits of the cytoskeleton, altering its shape, shifting its balance, and setting the cell in motion. Ultimately, the cell begins to migrate.

Cell migration happens during healthy tissue development as well as in some diseases, including cancer. The more rigid a breast cancer tumor becomes, for example, the more likely the cells composing it are to migrate—which, in turn, increases the likelihood that the cancer will spread to other organs and decreases the patient's likelihood of survival. Understanding the mechanical processes involved, and the biochemical signals they elicit, could conceivably lead to new drugs for fighting cancer and spurring tissue regeneration.

But scientists don't yet understand exactly how changes in the cytoskeleton allow the cell to sense that it is being subjected to mechanical force. Nor have they identified the various molecular actors involved in converting, or transducing, mechanical signals into biochemical ones. They also have yet to determine exactly how a cell goes from experiencing a tug or a push to ramping up the production of a protein or crawling in a particular direction.

"We're focused on where molecules go and how they physically transform in response to mechanical forces," Alushin says. "That transformation could be at the level of 'turn left while you're moving' or at the level of 'let's change the expression of this or that gene.' You need to understand those signals at the molecular level in order to design drugs that can interfere with them."

Alushin is trying to achieve that by studying filaments made of the protein actin—thin threads that make up a major component of the cytoskeleton. He uses modified motor proteins to stretch these filaments to the point where they begin to rupture. He then takes high-resolution pictures of the filaments using

7 nm

The length of a typical actin filament.

cryo-electron microscopy—a technique that involves flash-freezing samples with liquid ethane, bombarding them with beams of electrons—and analyzing the resulting images using powerful software algorithms.

In so doing, Alushin has identified lesions on the filaments that he believes attract specific molecules—including a protein, FHL, that binds to actin in response to force. That last discovery promises to be highly significant because FHL molecules also happen to regulate gene expression.

Previous research has shown that FHL shuttles into the nucleus when cells are exposed to soft environments, and it shuttles out when they are in stiff ones, toggling gene expression on and off in response to differences in force. As in the case of Shyer's findings in avian skin cells, this appeared to be an abject lesson in how mechanics can influence biochemistry; but the mechanism driving that process remained unknown.

Alushin therefore engineered FHL, coupling it to fluorescent green protein so that he could track it using fluorescence microscopy. He then placed cells containing this modified FHL in a cell-stretching machine—a device resembling a wine fridge that stretches cells out like microscopic prisoners on a high-tech version of the medieval rack. (More precisely, the machine stretches the flexible silicone-based chambers in which the cells are deposited; but since the cells adhere to the surface of the chambers, they get stretched too.)

The resulting images clearly showed that FHL responded directly to force, coating a cell's actin filaments or accumulating in its nuclei depending on whether it had been stretched. Alushin suspects that FHL binds specifically to the lesions he previously identified on purified actin filaments, and he plans to test that hypothesis by using cryo-EM to image the two *in flagrante delicto* both inside and outside cells.

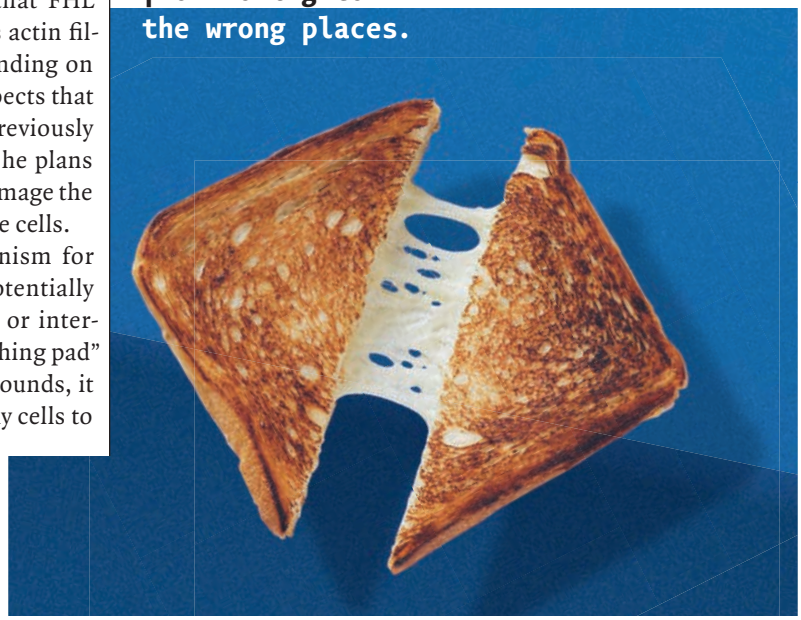
"That would reveal the physical mechanism for this actin-recognition ability and could potentially help others design molecules to promote or interfere with it," he says—establishing a "launching pad" for drugs of various kinds. With such compounds, it might become possible to encourage healthy cells to grow and move to the right places, for instance, or stop diseased cells from proliferating and moving to the wrong ones.

Alushin's cryo-EM setup can't yet provide quite the level of detail he requires. But he is already upgrading it—adopting new hardware for imaging entire slices of cells, for example, and developing new methods for boosting the resolution of his images—to push the quality of his data to the point where he can determine precisely how FHL binds actin, and how mechanosensation occurs in real life.

"I think you're going to see more and more of this," Hudspeth says of such technical innovations. "People will be asking mechanical questions and answering them with novel apparatus, because all of this is uncharted territory."

FOR MORE THAN four decades, Hudspeth, the *F.M. Kirby Professor,* has investigated the physiological basis of hearing—and he has the props to prove it. His office is littered with homemade devices for demonstrating how hair cells, the primary auditory receptors in our ears, transduce mechanical sound waves into electrical signals that can be interpreted by the brain.

With new compounds, it might become possible to stop diseased cells from moving to the wrong places.



"You're going to see more and more people asking mechanical questions and answering them with novel apparatus. All of this is uncharted territory."

"At a cellular level, this is the most complicated biological machine there is," he says, grabbing one device after another to illustrate his point.

A metal sculpture in the corner depicts a hair bundle: a densely packed bunch of actin-filled fibers called stereocilia that extend from the surface of every hair cell. A hinged contraption represents a mechanically gated ion channel that opens and closes as the stereocilia sway back and forth in response to physical vibrations, generating electrical currents. And an exercise band stands in for the protein filaments called tip links that extend from the stereocilia to the ion channels, sliding them open as the stereocilia bend away from the channels and closing them as they do the opposite.

Hudspeth and his team believe that these tip links are a crucial component in the hearing system's internal amplifier: a physical mechanism that boosts incoming auditory signals like a built-in hearing aid. When functioning properly, this amplifier allows us to hear the proverbial pin drop. But when it is damaged or degraded by injury, illness, or age, hearing loss ensues. Divining its secrets is therefore vital to helping the hundreds of millions of people who suffer from hearing problems.

For decades, scientists have suspected that a so-called gating spring endowed with elastic properties must be involved in opening and closing the ion channels located at the base of the stereocilia. Elasticity is key, since if the gating spring were too stiff—more like a pencil than a rubber band, for instance—our hearing system would lack its extraordinary sensitivity. Tip links have long been thought to serve as gating springs, but that theory has not been without controversy, in part because tip links are composed of relatively stiff proteins called cadherins that some argue are not suitable for the job.

Recently, however, Hudspeth and his team proved that this stiffness might not be a problem after all.

Doing so required another piece of cutting-edge technology: so-called optical tweezers, which use tightly focused laser light to trap and manipulate individual molecules. More specifically, it required an extraordinarily precise set of optical tweezers custom-built by postdoctoral associate Tobias Bartsch.

"There's probably no more sensitive microscope on the planet," Hudspeth says of the device, an unruly looking assemblage of cables, mirrors, and mysterious black boxes that lives in the basement of the Bronk building, isolated from stray vibrations that might throw off its exquisitely accurate readings.

Hudsepth and Erzberger scan tanks of zebra fish, which they use to study how organisms detect vibration.

MARIO MORGADO

For their experiments, Hudspeth and Bartsch tethered each end of a string-like cadherin molecule to two tiny beads, one fixed, the other mobile. The researchers then used Bartsch's optical tweezers to move the mobile bead by irradiating it with a laser, stretching the cadherin out with various amounts of force and measuring just how far and how fast it was able to extend. Those measurements, which were accurate to a single nanometer, or one billionth of a meter, proved the protein possesses mechanical properties compatible with the idea that tip links function as gating springs.

Now the team is trying to determine whether tip links are physically capable of transmitting mechanical force between stereocilia and ion channels fast enough for hearing—no mean feat given that humans can hear sounds at frequencies of up to 20,000 cycles per second, requiring response times as small as nanoseconds.

At the same time, the researchers are using their optical tweezers in conjunction with genomic methods to explore the mechanical consequences of the roughly 150 genetic mutations that affect tip link proteins. Though often extremely subtle, those mutations are nonetheless associated with a variety of developmental abnormalities, including deafness.

And in much the same way that Amy Shyer examines how the interplay between mechanical and biochemical events causes skin cells to form follicles, postdoctoral fellow Anna Erzberger, in Hudspeth's lab, is investigating the combination of molecular and mechanical factors that drive the development of sensory organs in zebra fish.

"We all agree that biochemistry is only half of the story, and the other half is mechanics," Erzberger says.

85 db

The point at which a sound may start causing permanent hearing damage. (Calm conversations are around 60 decibels.)

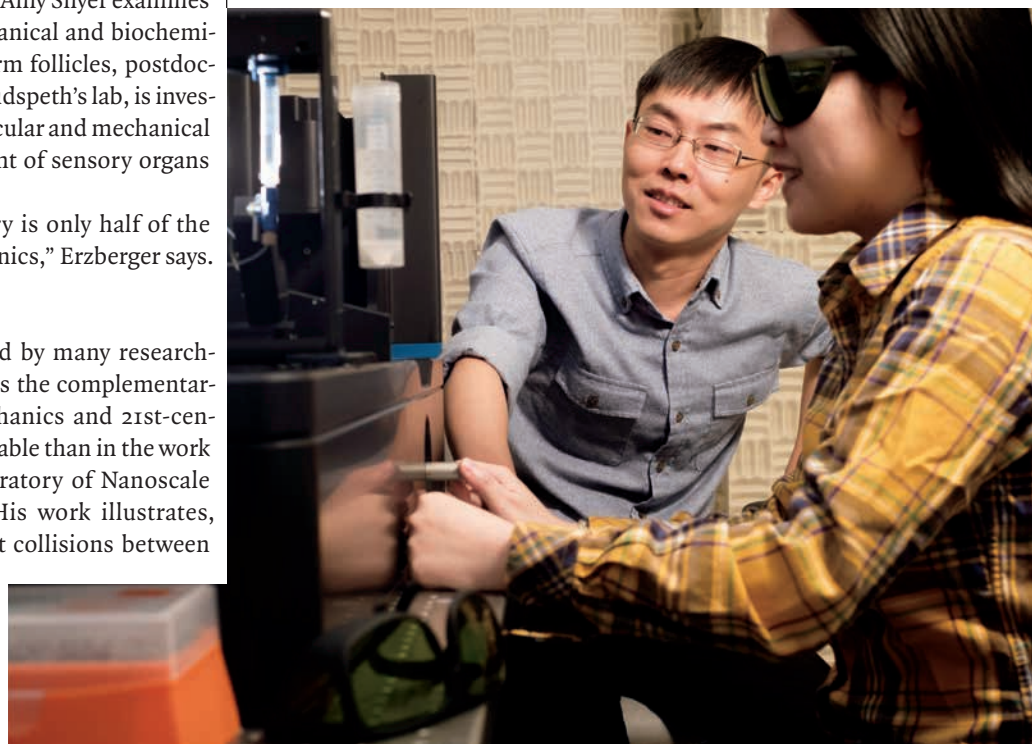
That sentiment is shared by many researchers. But perhaps nowhere is the complementarity between classical mechanics and 21st-century molecular biology more palpable than in the work of Shixin Liu, head of the Laboratory of Nanoscale Biophysics and Biochemistry. His work illustrates, among other things, how violent collisions between molecules play an important role in ensuring healthy gene expression.

Liu investigates molecular machines: specialized protein complexes that convert chemical energy into mechanical work. Measured in nanometers, these minuscule workhorses do much of the heavy lifting inside our bodies. The motor proteins that Alushin uses in his research, for example, belong to a class of molecular machines that contract our muscles, transport chemical cargo, and enable the skin cells that Shyer studies to crawl about.

"They're not that different from real-world machines," says Liu, who compares them to car engines, albeit ones that burn high-energy biological molecules rather than gasoline.

Liu is particularly interested in the molecular machines that power gene expression and regulation. These complex tasks require close coordination among several different molecular machines, including DNA and RNA polymerases, which replicate DNA and help manufacture RNA, respectively.

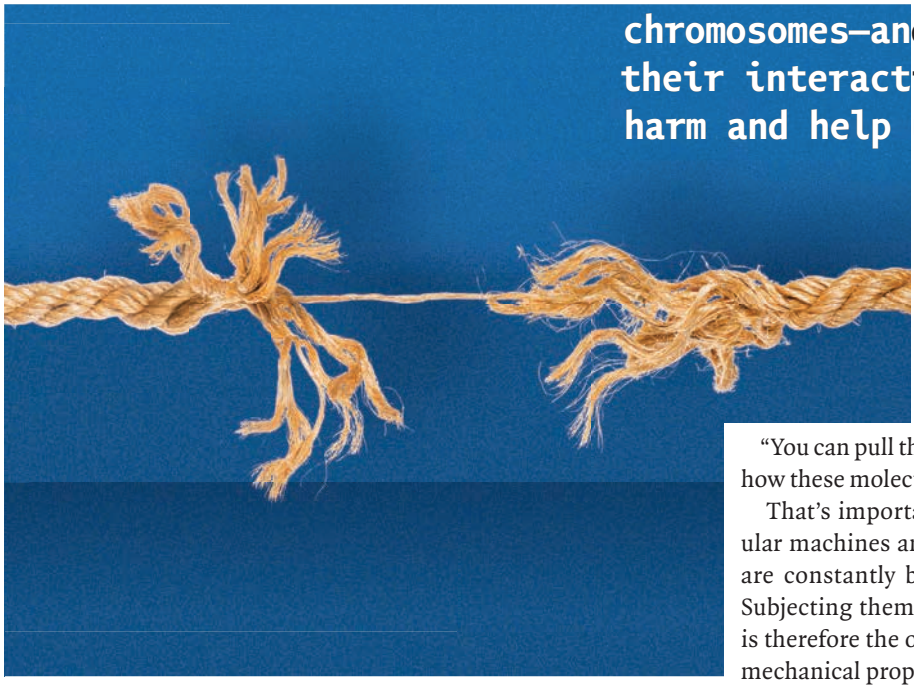
Scientists do not yet fully understand the mechanics, much less the consequences, of what happens



Liu (left) with postdoc Sai Li. The instrument they use to manipulate DNA is housed in a basement room with vibration-dampening walls.

MARIO MORGADO

You can paint incredibly detailed pictures of how these machines operate on chromosomes—and see how their interactions can both harm and help us.



when these molecular machines come into physical contact with one another, with our DNA, and with the chromosomes inside which that DNA is stored—in part because those interactions are so subtle that, until recently, scientists had no way of directly visualizing and recording them. Yet such information could prove invaluable.

"These machines are implicated in disease: cancer, neurodegenerative diseases, and many others," Liu says. Consequently, understanding how they both enable and disrupt normal gene expression could lead to all manner of novel drugs and therapies.

To that end, Liu has built a unique experimental platform for analyzing the intricate ballet these machines perform together.

On the one hand, he uses high-resolution fluorescence microscopy to create movies of molecular machines as they bind to DNA and do their work. By tagging a machine such as DNA helicase with a fluorescent marker, for instance, he can watch as it alights on a piece of DNA, unwinds the double helix so that DNA polymerase can read it, and flits off again. By tagging different bits of the machine with different colors, he can deduce the conformation of the protein. By tagging two different machines with differently colored probes, he can see how they interact.

On the other hand, he employs optical tweezers like the ones Bartsch uses to poke and prod molecular machines in ways that reveal their underlying mechanics.

"You can pull them, you can twist them—you can see how these molecules respond to force," Liu says.

That's important, he explains, because the molecular machines and genetic materials inside our cells are constantly buffeted by forces of various kinds. Subjecting them to comparable treatment in the lab is therefore the only way to get a realistic idea of their mechanical properties.

By combining these two streams of data with next-generation genomic techniques, Liu can paint incredibly detailed pictures of how molecular machines operate on chromosomes—and how their mechanical interactions can both harm and help us.

In the crowded environment of the cell, for example, DNA and RNA polymerase sometimes collide like runaway locomotives on the same track, causing genetic mutations that can lead to cancer.

In a recent study, however, Liu and his colleagues were able to demonstrate that at least some head-on collisions between RNA polymerases may actually serve a useful purpose; namely, preventing the molecular machines from reading too far into a genetic sequence.

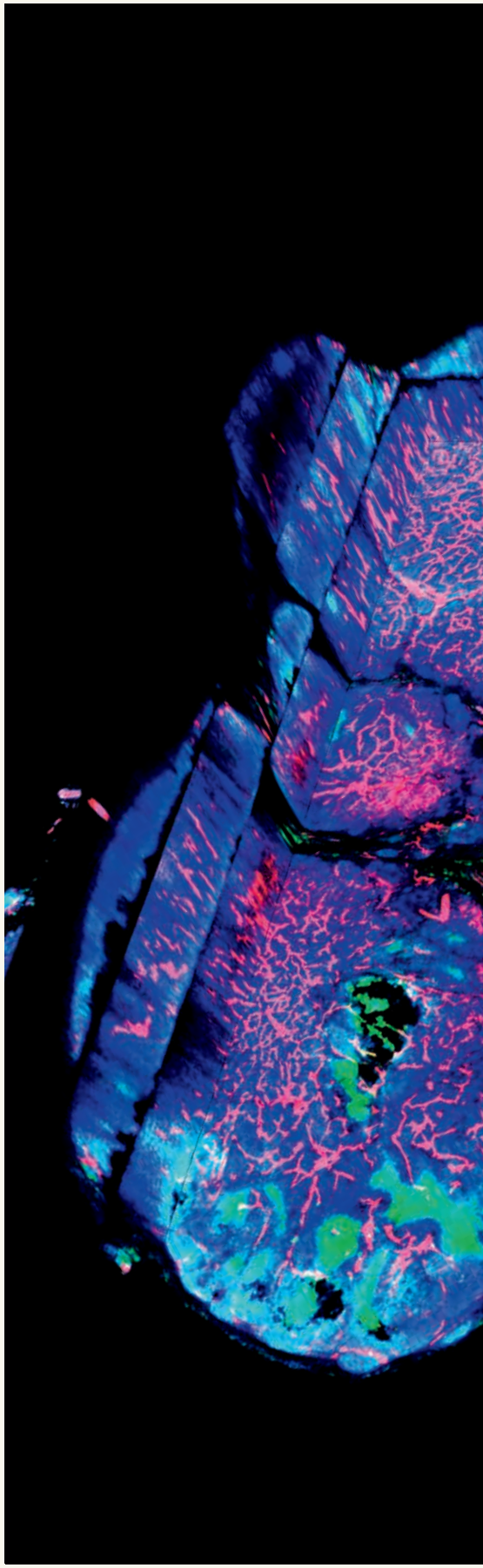
"You want the gene to be stopped precisely at a well-defined position," he says. Sometimes the stopping mechanism appears to involve a nanoscale pileup, and to flesh out precisely how this works Liu plans to observe such molecular train derailments in action.

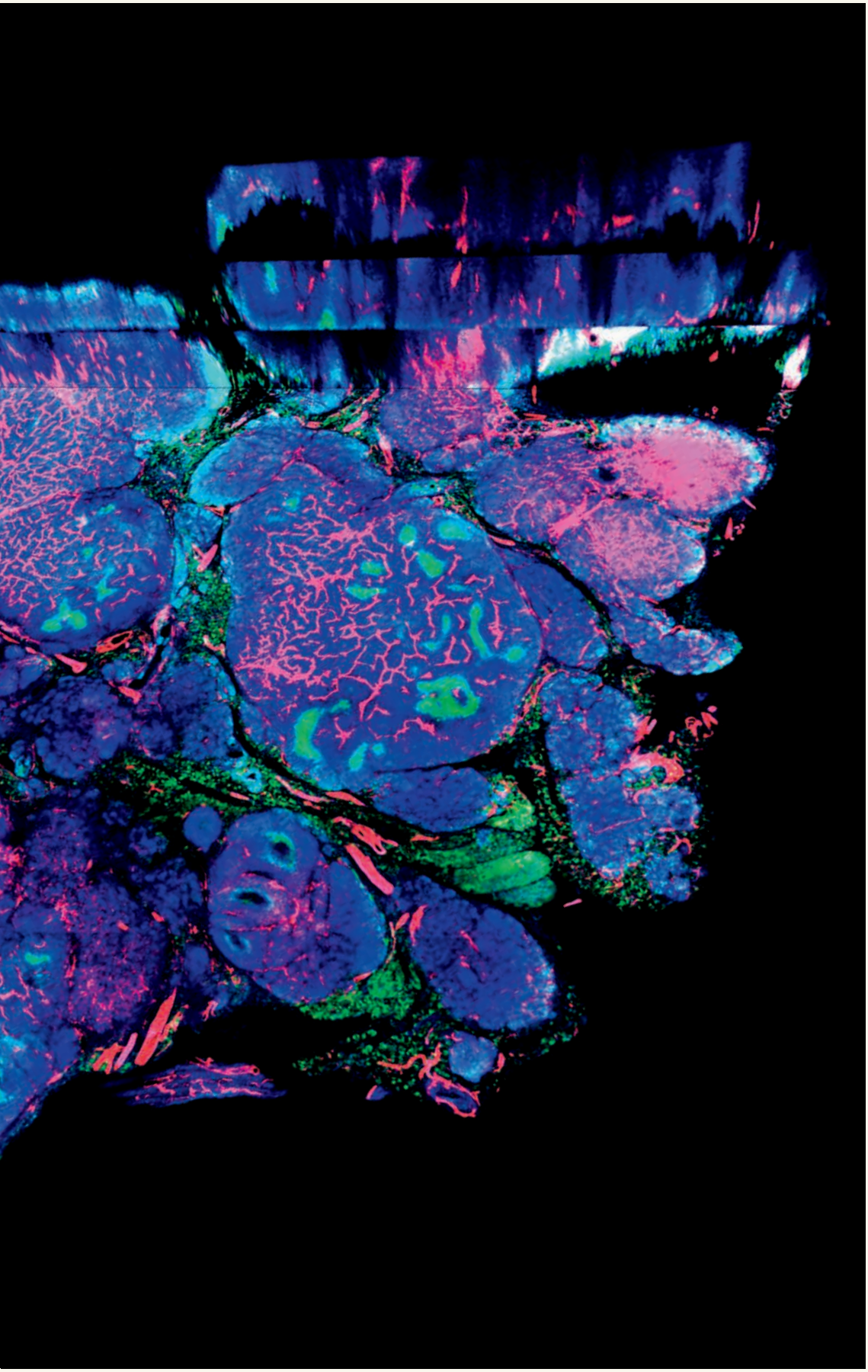
Given the differences in scale and purpose, Liu's molecular movies may seem but distant relatives of Shyer's cellular slide shows, just as Alushin's cell-stretching actin experiments may seem worlds away from Hudspeth's optical tweezer tests.

Uniting all these projects, however, is a conviction that there is much to be learned from the physical interactions of biological components that cannot be gleaned by any other means—and that what has been discovered so far represents only the tip of the iceberg.

"The role of mechanics in biology," says Hudspeth, "has been greatly underestimated." ◎

CANCER'S BIG APPETITE





All living things must eat, and cancer cells are no exception. A fresh look at cellular nutrition is yielding new ideas for shrinking tumors.

BY DAVID NOONAN

A tumor, having outgrown its surrounding blood vessels, thrives despite being starved of oxygen and nutrients.

First we figure out what cancer cells need that other cells don't. Then we devise a way to deprive them of it.

THERE'S NO SHORTAGE of ways to kill a cancer cell. Cut it out, poison it, blast it with radiation, shower it with killer immune cells—they all get the job done. But there *is* a shortage of *good* ways to kill cancer cells. One that knocks out all the bad cells in one swipe, leaving the good ones unscathed, and that doesn't allow the disease to return. We have yet to find that perfect treatment, whether it's one miracle drug or several therapies cleverly combined. Until we do, cancer will continue to kill, and the medicine that stops it will continue to hurt.

For Kivanç Birsoy, the ideal cancer treatment doesn't kill cancer cells with violent attacks at all. He wants to simply stop feeding them and let them die.

Birsoy, the *Chapman Perelman Assistant Professor*, has taken this simple premise—that cancer cells need nutrients to survive—and built a sophisticated research program around it. His work is driven by a vision of the future where patients survive as their tumors, starved of the nutrients they depend on to grow, wither away. The key to defeating cancer cells, he says, is to understand their metabolism.

LIKE MANY GOOD IDEAS, Birsoy's is not new. The study of cellular metabolism began almost a century ago and has long been perceived as settled science. The textbooks have been written, the Nobels awarded, and the world has moved on to sexier subjects.

But the scientists who pioneered the field, who asked the important questions and wrote those textbooks, were limited by their experimental tools, Birsoy explains as he sits in his office in Rockefeller's newest research building. "With the tools we have now, genetic tools, I can go back and ask those questions again," he says, "and get more sophisticated answers."

When it comes to metabolism, cancer cells are remarkably adaptable. They have several tricks they can employ to maintain their growth, even in the face of inhospitable conditions that would leave other cells lifeless.

For one, they can tweak their own metabolic processes, a lethal power that is unique in human biology—heart cells can't do it, brain cells can't do it. Deprived of sufficient blood flow due to a heart attack or stroke, those normal tissues die. But cancer cells are somehow able to hunker down and pull through, and, having survived these hostile conditions, they go on to thrive and multiply.

Still, there are some nutrients even cancer cells can't live without, which is why they have a second trick up their sleeve: the ability to import what they need from the environment instead of producing it themselves. And it is here that Birsoy sees an opportunity. Working with cells derived from lung, breast, blood, and other types of cancer, his plan is to figure out what cancer cells need that other cells don't, and then devise a way to deprive them of it.

PREVIOUS SPREAD: SCIENCE PHOTO LIBRARY

FRANK VERONSKY

Birsoy's vision: a nonviolent attack on cancer that causes little collateral damage.

Cancer cells grow fast. In fact, their ability to grow and divide rapidly, and outpace the cells of healthy tissue, is exactly what makes them so deadly. But fast can mean sloppy. Although cancerous tissue can create its own blood vessels, for instance, the new supply is often not enough to meet the cells' demand. Despite their varied diet, they find themselves facing a scarcity of the oxygen and nutrients they need to survive.

In an experiment, Birsoy subjected 28 cancer cells lines derived from patients to low oxygen conditions. None of them were able to synthesize an amino acid called aspartate, which they require to grow. But six of the 28 overcame this hindrance by altering their metabolism and ingesting aspartate from their surroundings. And having successfully outsourced aspartate production to their neighbors, these cells continued to grow, divide, and proliferate. Like most of Birsoy's work, the study was done in vivo, using tumor tissue grafted onto mice, a method that provides a more complete picture of biological events than experiments conducted in cell culture.

The findings excite Birsoy for two reasons. First, they provide clear-cut evidence supporting the general hypothesis that cancer cells are able to alter their metabolism to get the nutrients they need to grow. And second, they show the importance of aspartate in particular; tumors can't grow in low oxygen settings without aspartate, which makes limiting its availability a potentially viable cancer therapy.

Such a treatment, he believes, would target cancer cells without affecting nearby healthy tissue.

Sixty-six years ago, a series of studies began that led to a similar discovery. Researchers working with guinea pig serum found that cells with a particular form of cancer, acute lymphoblastic leukemia, are unable to produce an amino acid called asparagine. It's similar to the situation with aspartate, with a key difference: The inability to produce asparagine was due to a rare internal anomaly, not an external factor like oxygen level.

"There is a small fraction of cancers that cannot make certain metabolites or nutrients that all other cells are able to make," Birsoy explains. "So they naturally become dependent on taking it from the outside." Since the 1960s, oncologists have exploited

"Because these pathways were in biochemistry textbooks, there was supposedly nothing left to learn about them."

the leukemia cells' asparagine dependency by treating patients with a drug called L-asparaginase, which depletes all the asparagine in their blood. As a result, the survival rate for acute lymphoblastic leukemia, which typically strikes children between ages 2 and 10, has reached nearly 90 percent.

Birsoy wondered whether there were other blood cancers with the same kind of rare defect—cells that were unable to make necessary nutrients and that could therefore be targeted by depleting that nutrient. Soon, his group found a rare cancer called ALK+ anaplastic large-cell lymphoma whose cells can't synthesize cholesterol, an essential building block for membranes. "If you deplete cholesterol from the environment," says Birsoy, "these cells die, even though normal cells don't care." It was the first such discovery since 1953.

With the advantage of tools that earlier researchers could not have imagined, including a CRISPR-based genetic screen that targeted 200 enzymes involved in the metabolism of the ALK+ lymphoma cells, Birsoy quickly honed in on the culprit. (Among other things, CRISPR, a gene-editing system, makes it possible to deactivate a specific gene in a cell in order to determine what the gene does and whether the cell can survive without it.)

In this case, when the gene for a specific receptor, LDLR, was knocked out by the CRISPR screen, the cells died because they could not import cholesterol from the extracellular environment. That makes the LDLR pathway what Birsoy calls a targetable liability, one that could be exploited by devising a treatment to prevent the lymphoma cells from taking up cholesterol.

The decades-long gap between the asparagine and cholesterol discoveries, Birsoy says, wasn't for a lack of trying. Postwar scientists in fact spent a great deal of effort hunting for additional metabolic dependencies, but they were held back by the limitations of their methods and technology. Then, in the 1980s, the search for cancer genes took center stage and fundamental metabolism research went out of style.

"I think people thought they knew everything about it and that it's boring," Birsoy says. "Because these pathways were in biochemistry textbooks, there was supposedly nothing left to learn about them."

Now, cellular metabolism is attracting a new generation of scientists who are using 21st-century tools to revivify the field. Birsoy, a native of Turkey, is a Rockefeller alumnus who did his graduate work in Jeffrey M. Friedman's lab, where his focus was obesity. As a postdoc at the Whitehead Institute, his interest shifted to cancer. In order to study the metabolism of tumor cells, he began to design new tools, including an instrument for mimicking the nutrient-deprived environment within tumors.

Five ways to kill a tumor

1 POISON IT

A.k.a: chemotherapy
Used since: 1942

Kills or slows the growth of quickly dividing cells, including cancer cells, but tends to cause unwanted side effects by also harming normal cells.

2 ZAP IT

A.k.a: radiation
Used since: 1895

Uses high doses of ionizing radiation to destroy DNA, especially in quickly dividing cells. Like chemotherapy, it comes with the risk of damaging healthy cells.

3 TAKE IT OUT

A.k.a: surgery
Used since: at least 1600 BC

Shrinks or gets rid of tumors confined to one area by using scalpels, lasers, liquid nitrogen, electrical currents, or robots. It's not always an option and may not by itself prevent the cancer from returning.

4 FLAG IT

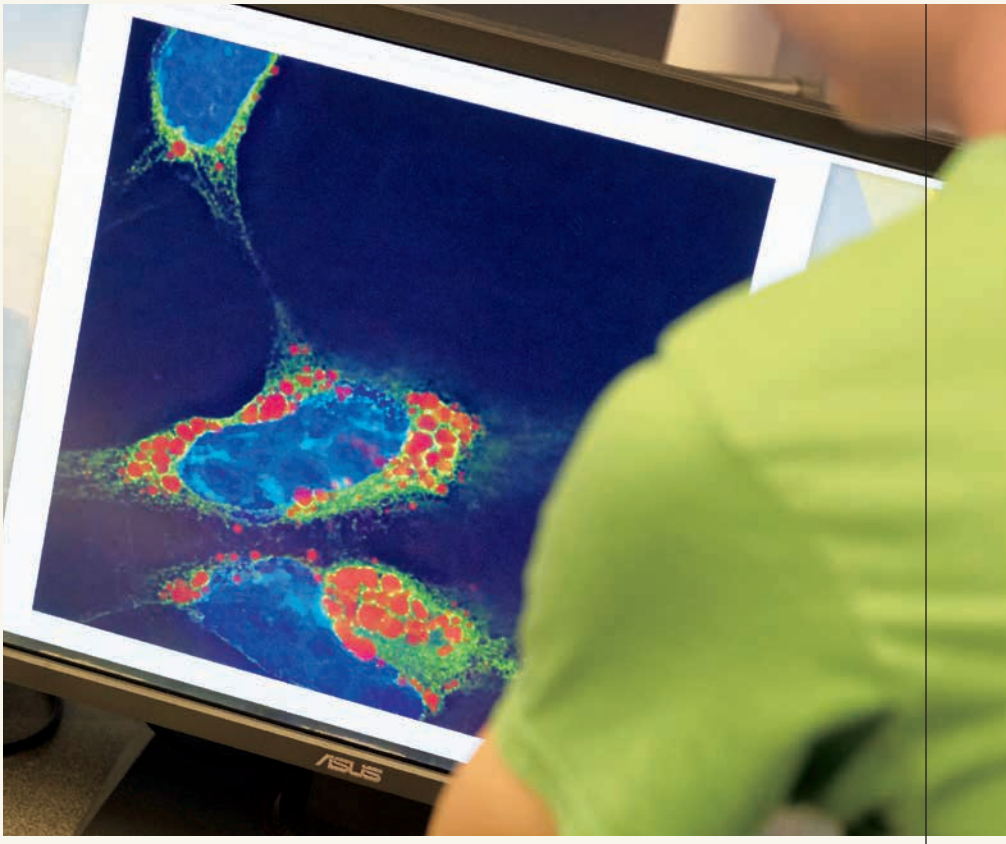
A.k.a: immunotherapy
Used since: 1891

Improves the odds that the body's immune cells will eliminate tumors, for instance with drugs that prevent cancer cells from tricking them. It's effective in some patients but doesn't work for many people.

5 STARVE IT

A.k.a: targeted metabolic therapy
Used since: still in development

Scientists want to develop new drugs that block a cancer cell's access to the nutrients they need to grow. They hope this will provide another asset in the cancer-fighting tool kit, potentially in combination with others.



MARIO MORGADO

THERE ARE MANY good reasons to learn more about cellular metabolism. For Birsoy, a major one is finding new ways to curb cancer, but he has other applications in mind as well. Every cell in the body converts nutrients into energy, and the recipes they use are diverse. If Birsoy's work can uncover new details into the workings of, say, fat cells or pancreatic cells, it could lead to a new framework for understanding obesity or diabetes.

Of particular interest to Birsoy are mitochondrial disorders. When he talks about them, you can hear the mix of fascination, frustration, and resolve that drives so much of his work.

"With mitochondrial disorders," he says, "as with other inborn errors, we know what the problem is, we know the genetics. But we don't know how to connect the two."

In some cases, mitochondrial disease makes people deaf; in others it causes seizures; and in still others the result is neuropathy or muscular atrophy. And despite decades of research, Birsoy says, scientists still have no clue why dysfunctions of mitochondria, the cellular organelles that process nutrients into energy, cause these disorders. All we know is that somehow a metabolic process has gone awry.

Birsoy's work has shown that mitochondria play an important role in synthesizing aspartate, the same amino acid that cancer cells sometimes steal from their neighbors. When those mitochondria are dysfunctional, he says, their aspartate levels are low—and supplying the cells with aspartate restores their function. Birsoy suspects that aspartate depletion might be a root cause of the mitochondrial disease, and that supplementing aspartate might be an effective treatment strategy. But it's a theory that remains to be tested.

As with cellular metabolism, our understanding of how mitochondria function got frozen at some point in the history of biological discovery, Birsoy says, and it hasn't been revisited. In some sense, we don't even know what mitochondria *are*. The initial idea was that they were a powerhouse organelle, but that's clearly not the full picture, and they probably do different things in different types of cells. "It's time to go back and figure out exactly what the function of mitochondria is in different cell types," Birsoy says. "In neurons, what's the function? In muscle, what's the function? And in cancer cells, what's the function?"

METABOLISM IS UNIVERSAL—every cell needs nutrients to survive. And although Birsoy's work has enormous potential, there's also a mountain of his predecessors' aging experiments to revisit.

"The way I look at this is, if you don't have a cure for something, that means you don't know enough about it," he says. "We treat cancer and people may live five weeks, five months, or five years longer with existing therapies. But too often the treatment fails and the patients die. And that means there is a lot more to discover."

Regardless of what the textbooks say.

Every aspect of who you are affects your health, from your genes to your income bracket; yet few bioscientists look beyond molecules and cells. Bruce McEwen says it's time we broaden our perspectives.

Biology could be so much more

By Eva Kiesler

If there's one thing all scientists should be able to agree on, it's that the world is incredibly complex. To even begin to make sense of it, you need to specialize—to dedicate yourself to untangling one aspect of reality without letting the rest distract you.

Whether you've chosen to study the function of an enzyme or the causes of a stock-market hiccup, specialization has long been the ticket to success in academia. It's how you obtain the training and knowledge needed to solve complicated problems, find a community of colleagues to work with, and keep yourself employed.

But at some point, all that hard-earned expertise can get in the way. After all, nature isn't neatly divided along disciplinary lines, so understanding it requires an integrated way of thinking. Put it this way: There's a lot you can't see when your eyes are glued to the microscope.

Illustration by Edmon de Haro

Neural plasticity goes both ways. The brain can change to make us sicker, but it can also change to make us healthier and more resilient.

It's a problem that Bruce S. McEwen often thinks about. A neuroendocrinology specialist and self-described nerd, he is wary of the fact that the more you become an expert on something, the more isolated you become. So throughout his career, McEwen has challenged himself and those who train in his lab to avoid forming silos, relate their work to other disciplines, and explore new ways of thinking.

It is not inconceivable that this mind-set is part of the lab's secret sauce. Not long after joining Rockefeller in the mid-1960s, McEwen began establishing himself as an international authority in research on stress, transforming our understanding of the brain—specifically by challenging conventional wisdom about how it communicates with the rest of the body. At that time, many scientists believed that the brain's architecture was incapable of changing with experience. In other words, the adult brain was considered neuroanatomically stable and fairly self-sufficient, a kind of CEO issuing instructions to subordinate body parts without receiving much feedback.

However, McEwen and his colleagues revealed that the brain-body connection is in fact reciprocal: Neural circuits deep inside the brain respond to various body commands mediated by stress hormones like cortisol, metabolic hormones like insulin, and sex hormones like estrogen, prompting lasting changes in the brain's basic structure and functioning.

The lab's continuing work on stress and its impact on the brain has implications for a wide range of conditions, including Alzheimer's, depression, PTSD, and normal aging. In a sense, it is furthering our understanding of how all aspects of the human experience, from cognition to constipation, hang together. And it is lending scientific clarity to holistic medicine—an ancient concept that until recently didn't get much attention from the medical establishment—and according to which health care professionals need to consider the emotional, environmental, social, and spiritual aspects of patients' lives, along with the physical and biochemical factors.

This is why McEwen, the *Alfred E. Mirsky Professor*, is now widening his lens beyond conventional biology questions to also work on sociopolitical ones—asking, for instance, why virtually all public-health problems in the United State disproportionally affect poor people, and why those born in poverty are predisposed to remaining poor.

We asked him to talk to us about what a broader understanding of human health and disease might look like.

Much of your work focuses on how life experiences reshape the brain, affecting our ability to cope with stress, for example. What do we know about the biology of this rewiring?

Much of our understanding has come from modern research on epigenetics, a field interested in the processes that cells rely on to activate the right genes at the right time.

While DNA is something we are born with, and although it gives us certain possibilities and limitations, it does not in and of itself account for the changes our bodies undergo in response to experiences of all kinds—including what we eat, where we live, how much we exercise, and whether we have experienced abuse or neglect during childhood. These changes are epigenetic in nature, and they begin in the womb, continuing throughout life until we die. My lab has found that epigenetic changes can literally reshape the nervous system. We first observed this in the brain's hippocampus, which regulates emotion and memory, and those findings opened the door to similar discoveries in other brain regions.

Only a few decades ago, scientists believed that an adult's brain doesn't change. The reasoning was that a sophisticated machine like the brain is not to be messed with and must therefore remain static once it has fully developed. So when it emerged that the adult brain can in fact be induced to grow new cells and neural connections—work pioneered by Rockefeller's Fernando Nottebohm and later built upon by scientists in my lab and elsewhere—it was a real paradigm shift.

Is the brain's malleability good news or bad news?

It is both. On the negative side, it's becoming increasingly clear that toxic stress can alter the brain in problematic ways. For example, children who grow up in chaotic households with abusive or neglecting parents are more likely to lose certain cognitive skills, and their overall brain development may be limited. These limitations may later be passed on from one generation to the next, interfering with people's capacity for proactive planning and their ability to self-regulate their thoughts and feelings. This will affect their performance in school and in society, and ultimately put them at risk of a host of diseases—not only obvious ones like anxiety, substance abuse, and depression, but also Alzheimer's, diabetes, cardiovascular disease, and others.

All of this suggests that for many diseases, a pill will not get us very far. To cure a disease, we will need to understand the biological and behavioral causes of that disease as well as the whole gamut of factors shaping people's lives.

On the bright side, neural plasticity goes both ways. If the brain can change to make us sicker, it can also change to make us healthier and more resilient. We are learning that the negative impact of toxic stress is treatable, especially early in life. In infants and young children experiencing adverse events, there are opportunities to reprogram the brain, for instance with interventions that promote nurturing family relationships and strong community support. In fact, studies have shown that

FRANK VERONSKY

the beneficial effects of such interventions can last for decades.

And this isn't only true for children: In almost every stage of life there are things we can do to improve our brain-body functions. We're not stuck the way we are.

Yet so much research, even in neuroscience, is focused on drug development. Is that a mistake?

There is an imbalance here, certainly. Consider that even the most successful drugs don't work for everyone. Take depression, for example: A pill like Prozac does not work in 60 to 70 percent of patients, including some with treatment resistance caused by early-childhood trauma. And even for people who respond to the drug, combining it with some form of concurrent behavioral therapy is important.

Efforts are under way to develop new drugs that will work for more people, but in the meantime, how do we help the nonresponders?

Drugs have come to occupy so much of our mental space. We constantly see ads for new drugs, and they can steer us away from doing the hard work: making lifestyle changes that have been shown to promote good health.

It's unequivocal that many conditions can be alleviated or prevented by what I call top-down treatments: doing things like getting more sleep, eating healthier, increasing one's physical activity, alleviating loneliness, establishing a positive social network, and learning to self-regulate the nervous system through mindfulness training. It's ultimately up to us to take control of our bodies and our lives—possibly with the help of pharmacologic agents, which sometimes can increase our ability to make these lifestyle changes.

Is the common denominator of these top-down treatments that they help reduce stress?

Well, it depends on what you mean by stress. I think it's helpful to think beyond this word, which has acquired many different meanings—people talk about good stress versus bad stress, for example. My colleagues and I coined a concept called allostatic load to describe how experiences of all kinds, and the conditions under which we live, affect the brain and the body.

The organism has several systems in place—including the neuroendocrine, metabolic, and immune systems—that normally help us adapt to new situations. It's when these systems become overused or dysfunctional that the mind and body begin to wear and tear.

How can scientists get better at seeing the big picture?

Just as scientists tend to create silos around our own academic fiefdoms, so do institutions and funding agencies define their priorities in the context of specific research areas. But in recent years, there has been a push from both government and private agencies to bring scientists together from diverse fields to tackle humanitarian problems on a national scale. For example, I'm a member of the National Scientific Council on the Developing Child, which brings together biomedical and social-science experts. Our goal is to provide the scientific foundation needed to develop sensible policies that we hope will help make people's lives better.

It's hard to overstate the importance of having access to this kind of convergent-science teamwork. I'm lucky to have a collaboration with my brother, Craig A. McEwen, a sociology professor at Bowdoin College specializing in law and mediation. Craig is very active in his community. He's an advocate of prison reform and also works to help those with limited resources. He has taught me a lot about the practical aspects of improving the lives of Americans struggling with poverty, hunger, or homelessness, and that has influenced how I frame questions as a neuroscientist.

So can we solve medical problems by addressing socioeconomic issues? What would that look like?

It is certainly a daunting task, but we can no longer ignore the fact that these issues go hand in hand. They won't be solved by scientists alone but will require all of us to engage as citizens and voters. We won't see significant improvements in public health unless we deal with economic segregation, for example. The fact that the nation's poor keep getting poorer and sicker isn't only a social-justice problem; it is also a huge economic burden on our country that negatively impacts everyone's welfare. Addressing it must be a bipartisan priority.

Fortunately, there are examples of successful policy changes that our nation can learn from. In some Scandinavian countries, for example, prison reform that involves helping convicts heal and behaviorally retrain has helped reduce incarceration rates and improve prisoners' health outcomes. Now, you might argue that the United States faces a very different set of challenges that comes with being a big and highly diverse nation, and that's true. So we must find our own way to implement social change. We may have to do it more gradually—in a state-by-state fashion rather than at the federal level, for example. But whatever it takes, we have to get it done. ◎

SCIENCE GADGET

Yeast bioreactor

SEBASTIAN KLINGE needs a lot of yeast.

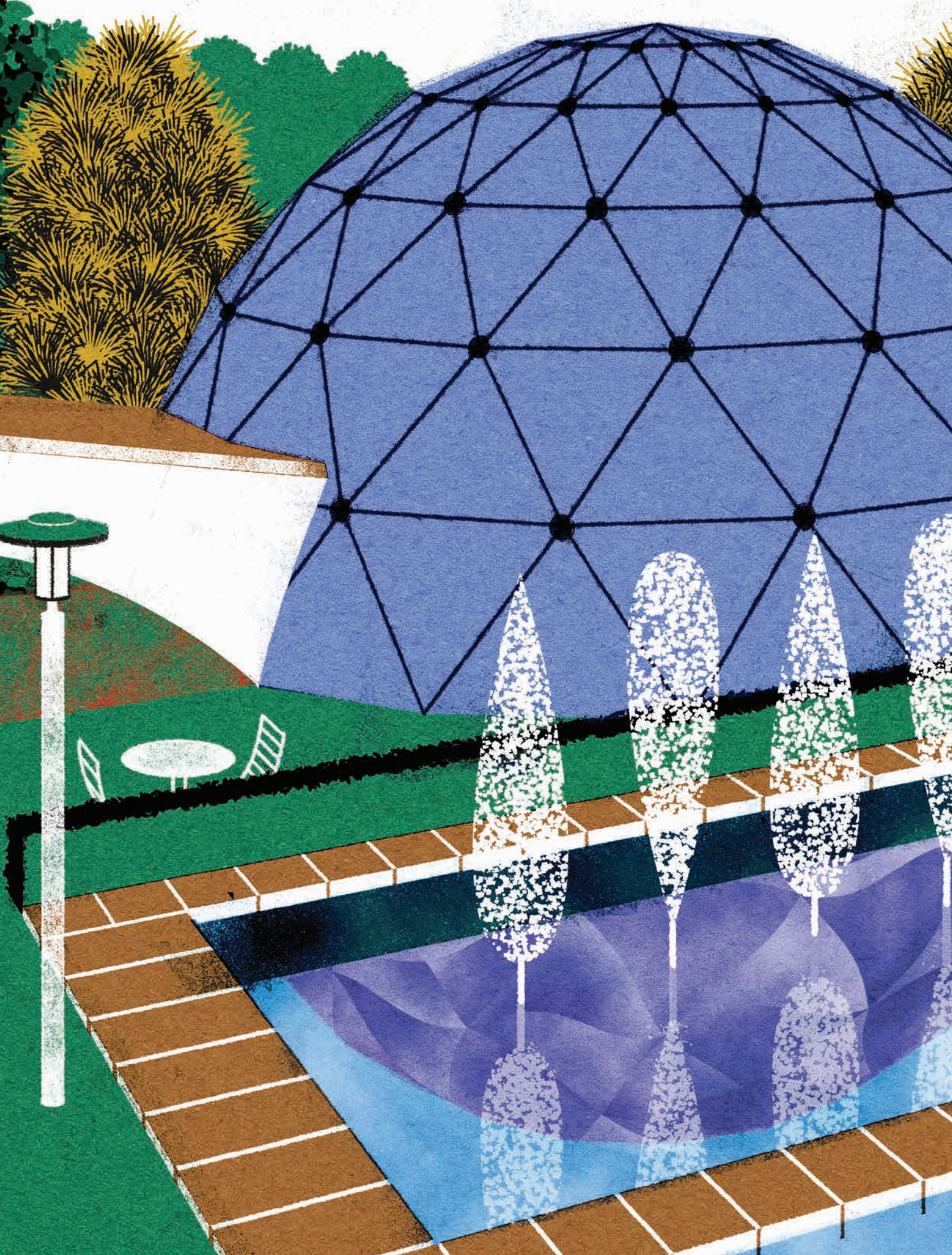
Saccharomyces cerevisiae has long been a favorite model organism for cell biologists—it grows quickly and is easy to manipulate. But while many biologists get by with a smear or two, Klinge produces dozens of liters of yeast at a time. With that quantity, a flask won't do.

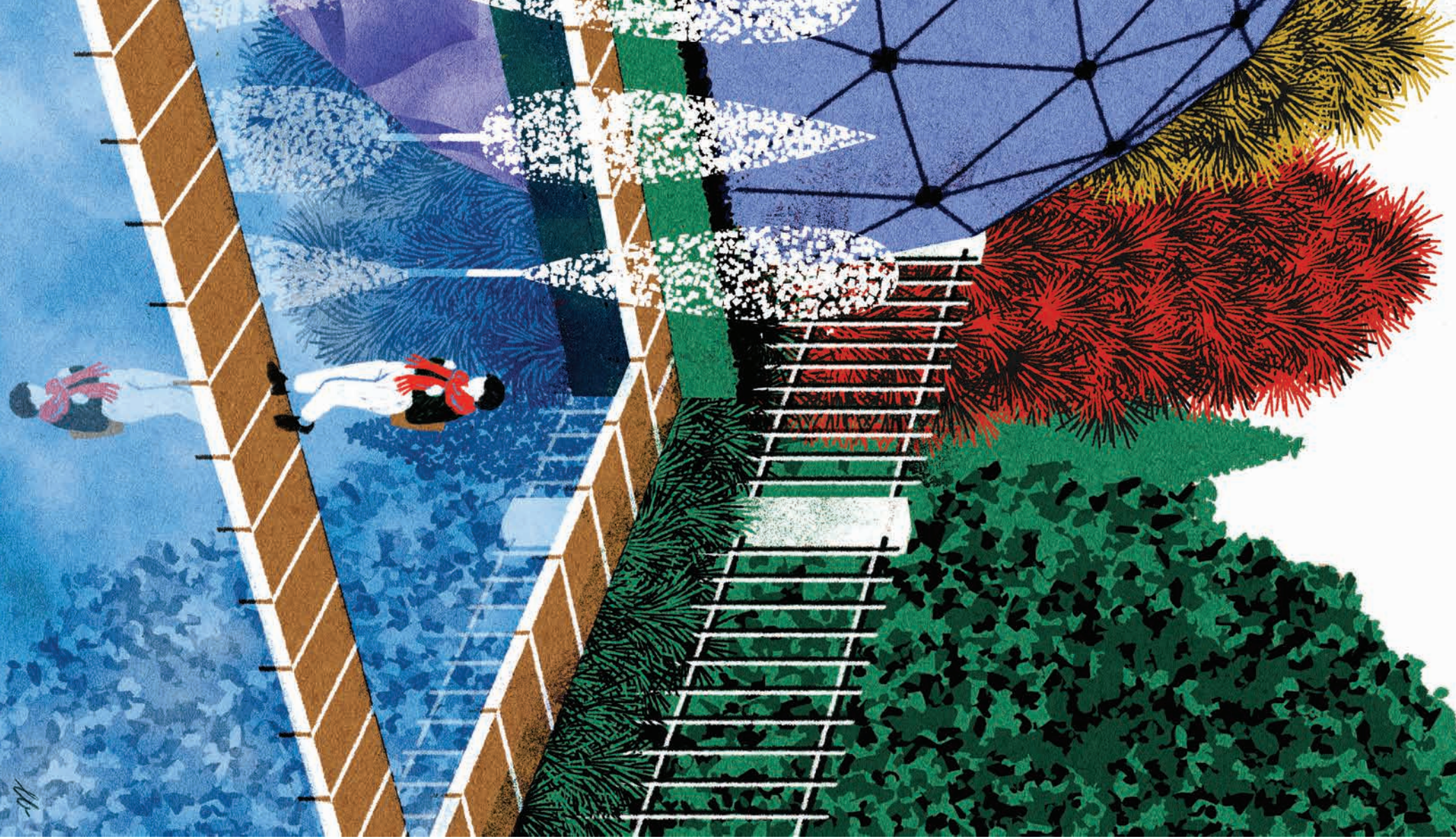
Klinge is interested in the complexes that help piece together ribosomes, molecular machines that, among other useful things, manufacture the proteins that make life possible. But the molecules he's after are both rare and fleeting; the more yeast he has, the more likely he is to find what he's looking for.

Custom-made by a Swiss company and housed in a dedicated room just off the lab, Klinge's bioreactor is able to grow yeast by the barrel. Similar to the equipment that microbreweries use—but carefully calibrated for precision—its tank holds up to 50 liters, and it supplies heat, air, and a precisely controlled flow of growth chemicals to optimize production.

After brewing for 72 hours, a batch of Klinge's concoction can contain up to 700 billion cells. Each may have as many as 200,000 ribosomes—pretty good odds for catching their assembly in action.

Photograph by Matthew Septimus





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