ISSUE 11
WINTER 2025

Seek

THE ROCKEFELLER UNIVERSITY

Balancing act

Reining in runaway inflammation

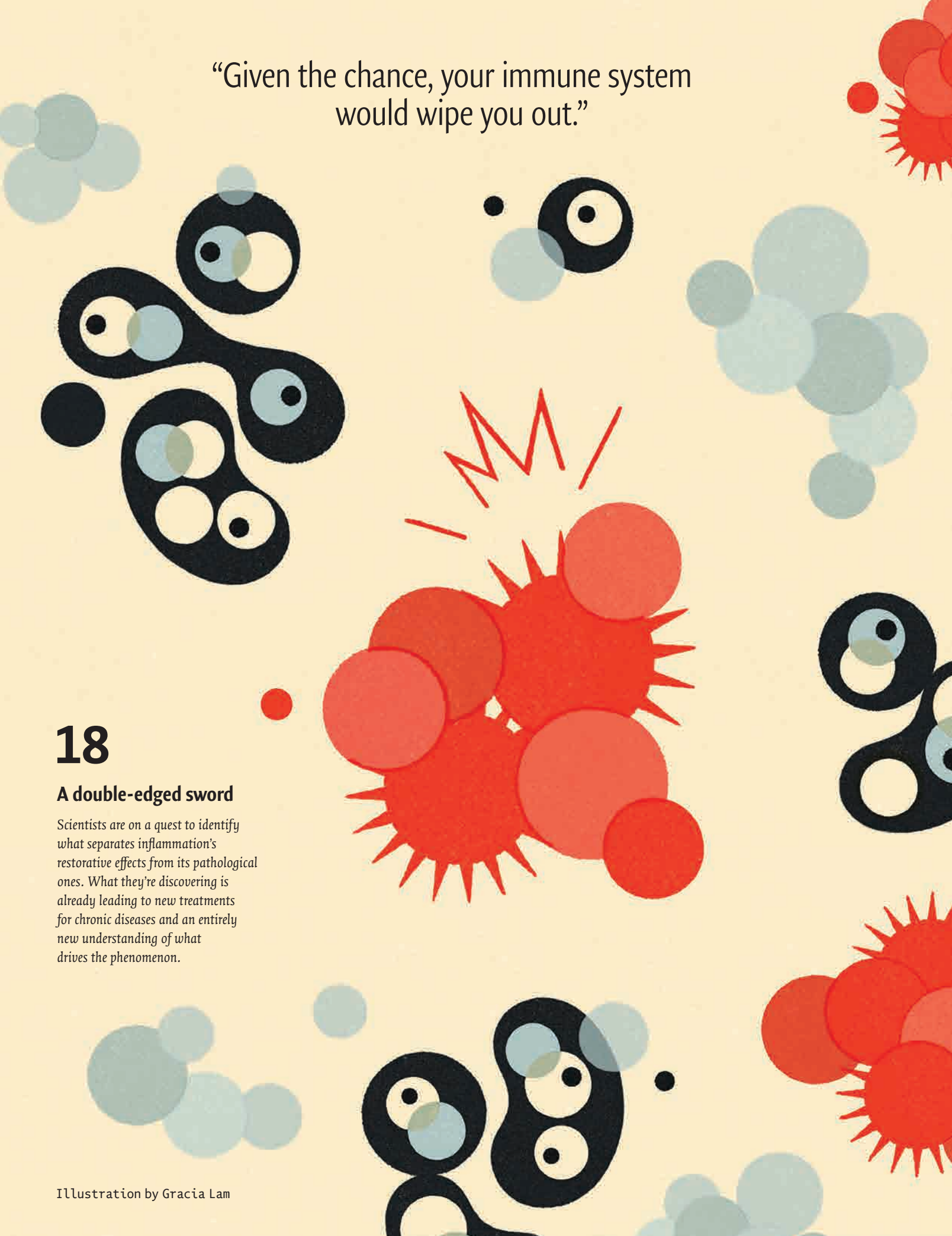
ALSO

RNA is changing everything

Getting from bench to bedside

The science of aging enters a new age

"Given the chance, your immune system would wipe you out."

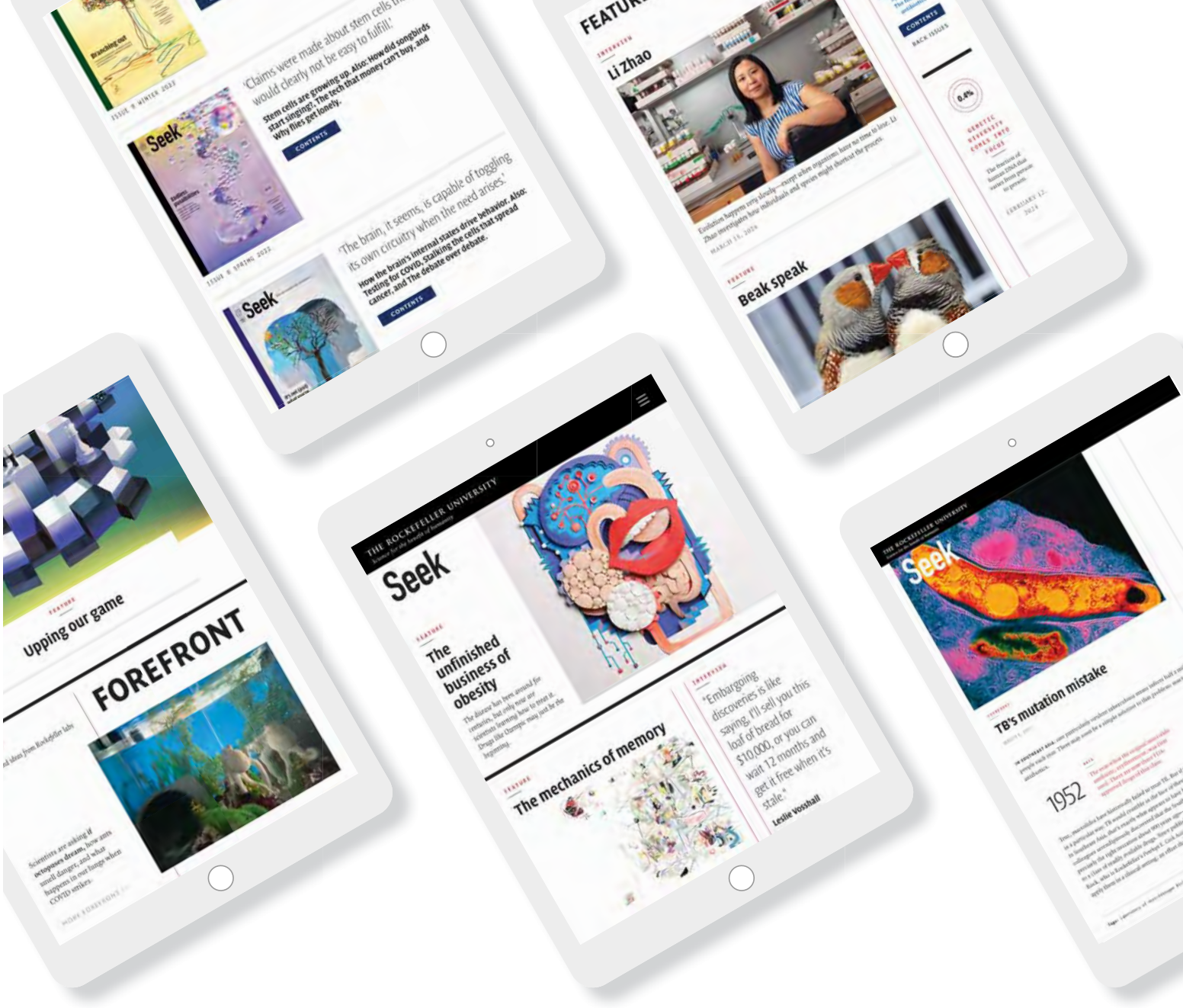


18

A double-edged sword

Scientists are on a quest to identify what separates inflammation's restorative effects from its pathological ones. What they're discovering is already leading to new treatments for chronic diseases and an entirely new understanding of what drives the phenomenon.

Illustration by Gracia Lam



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CONTENTS

ISSUE 11 WINTER 2025

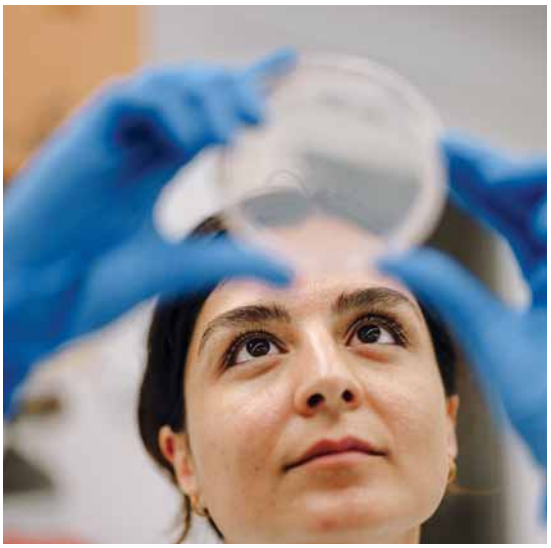
"I knew what my future was—to find this messenger RNA in our cells."

Illustration by Aleksandar Savić

38

In it together

In Sanford M. Simon's lab, patients and scientists work side by side to investigate a rare cancer. Their collaboration is resulting in a host of significant discoveries.



46

The path to commercialization

Over the past decade, academic labs have generated an increasing number of the new drugs coming to market. What does it take to turn a promising insight into a medical breakthrough?

ROSHNI KHATRI; CHRIS TAGGART; ROSHNI KHATRI; BRIAN STAUFFER

It was the scientific equivalent of finding a needle in a haystack.

PAGE 26

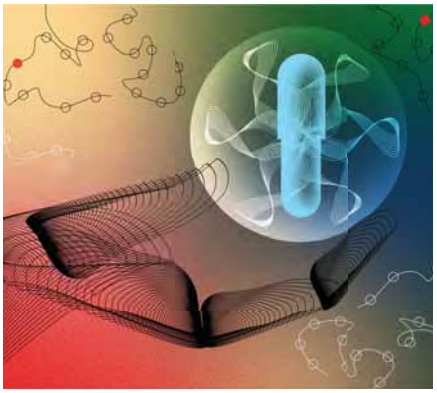
14

Q&A

Single-cell sequencing is transforming how scientists think about disease. Junyue Cao is transforming the science of single-cell sequencing.

6

How does addiction rewire the brain? What's the connection between breast cancer and sensory neurons? ***Can we trust AI to guide drug discovery?***



ON THE BACK COVER

The Rockefeller University by Nick Lu

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Seek is the research magazine of The Rockefeller University.

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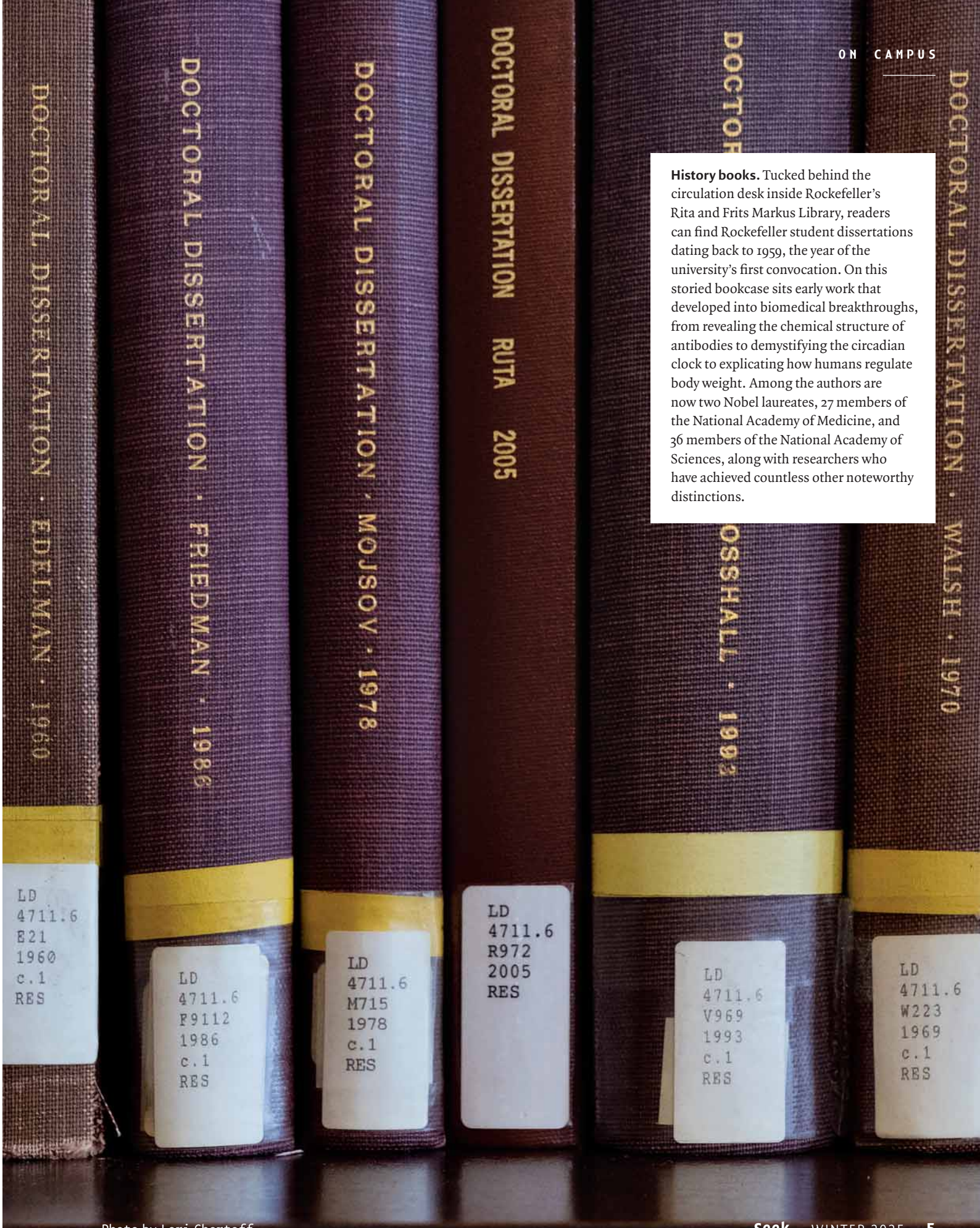
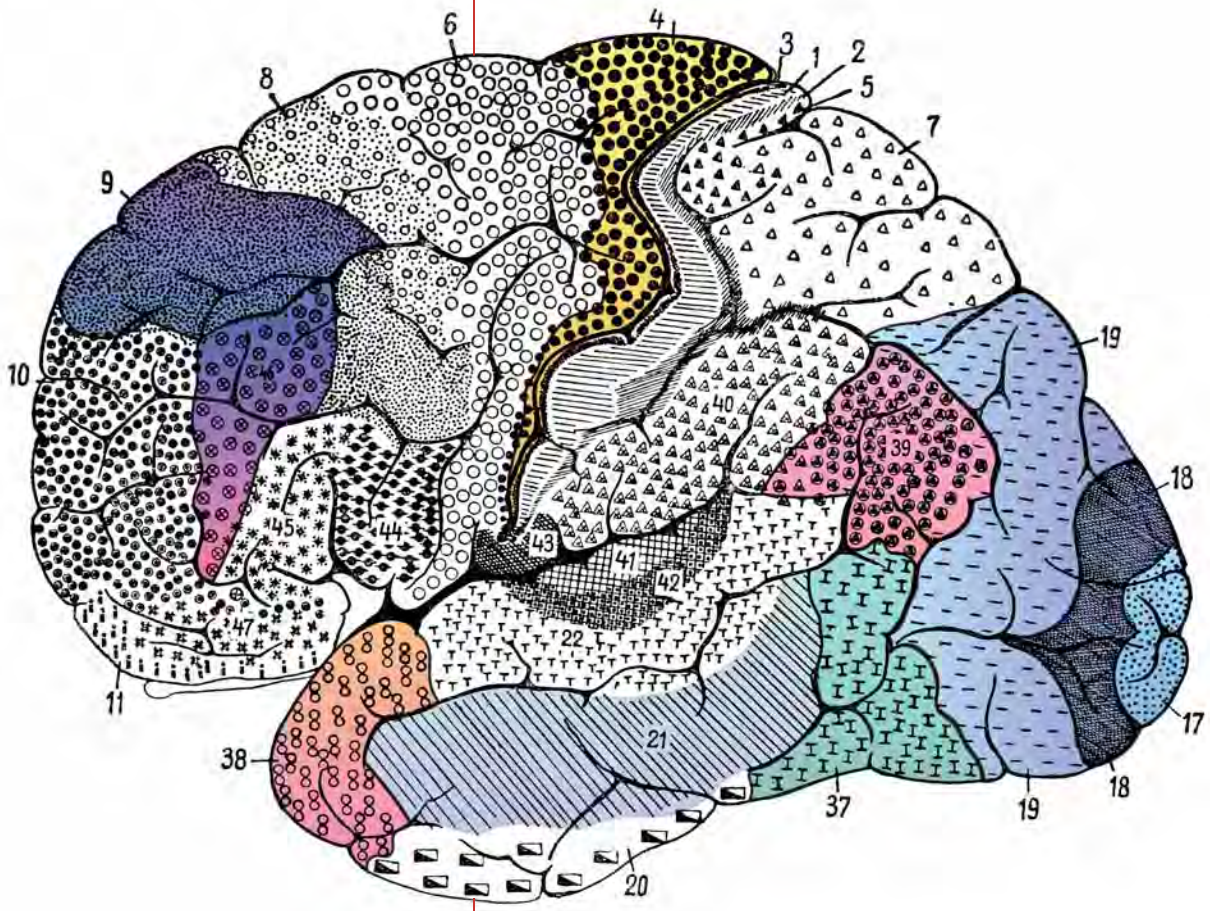


History books. Tucked behind the circulation desk inside Rockefeller's Rita and Frits Markus Library, readers can find Rockefeller student dissertations dating back to 1959, the year of the university's first convocation. On this storied bookcase sits early work that developed into biomedical breakthroughs, from revealing the chemical structure of antibodies to demystifying the circadian clock to explicating how humans regulate body weight. Among the authors are now two Nobel laureates, 27 members of the National Academy of Medicine, and 36 members of the National Academy of Sciences, along with researchers who have achieved countless other noteworthy distinctions.

Photo by Lori Chertoff

Reported by Lori Chertoff, Mindy Farabee, Joshua A. Krisch, and Jen Pinkowski.

FOREFRONT



LABORATORY OF MOLECULAR BIOLOGY

NEURODEGENERATION

The brain cells most vulnerable to Huntington's

SCIENTISTS KNOW A good deal about Huntington's disease, an inherited neurodegenerative disorder that slowly robs patients of their physical and mental health.

They know, for example, that it is caused by mutations to a particular gene; that these mutations involve the excessive repetition of tiny stretches of DNA bases known as CAG repeats; and that these repeats corrupt the proteins that the gene produces, ultimately causing neurons in certain parts of the brain to die.

But they have not yet learned enough about the molecular mechanisms underlying this process to have developed drugs that can stop or reverse the disease.

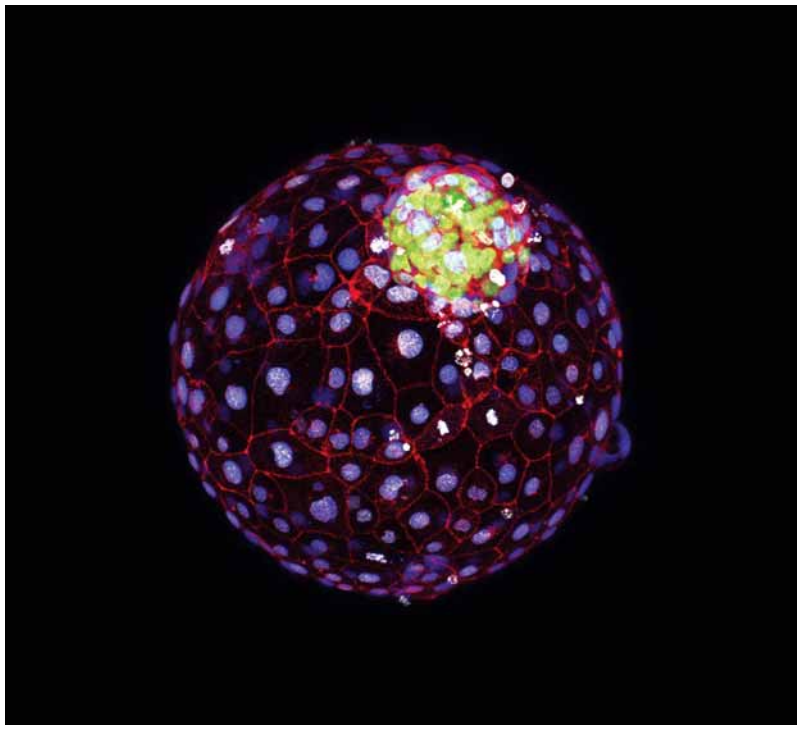
Hence the excitement when researchers in Nathaniel Heintz's Laboratory of Molecular Biology recently teased out some hitherto unknown nuances of those mechanisms, providing potential targets for therapeutic interventions.

Using cutting-edge molecular profiling techniques, the scientists discovered that CAG repeats are unstable—and therefore likely to produce more toxic proteins—in only certain types of brain cells. They also found that other cell types proved surprisingly resilient to the repeats.

In separate but complementary studies from Heintz's lab, Kert Mätlik, a research associate, and Christina Pressl, an instructor in clinical investigation, examined the brain cells of people who had died from Huntington's. The scientists focused on two brain regions that are profoundly affected by the disease: the striatum and the cortex.

SUPER MODELS

First glimpses of the human form



MERE WEEKS INTO human embryonic development, an indistinct ball of cells called a blastocyst rearranges itself into an orderly three-layered structure—a process called gastrulation that sets up the eventual emergence of the human form.

Understanding the molecular underpinnings of this pivotal event could help scientists prevent miscarriages and head off a host of serious disorders. But gastrulation has long been a black box. "It is the first moment that separates our heads from our behinds, and yet we had never seen ourselves at that stage," says Ali H. Brivanlou, the *Robert and Harriet Heilbrunn Professor*.

That changed this year when Brivanlou and his Laboratory of Synthetic Embryology created a new platform for studying human gastrulation through the use of blastoids—models of blastocysts developed from stem cells that can be cloned, manipulated, and programmed in the lab. Crucially, the platform allows blastoids to attach to plastic surfaces, much as real blastocysts attach to the uterus.

Thanks to this innovation, the team was able to directly observe key moments in process, including the emergence of molecular markers for two crucial structures in embryonic development: the so-called primitive streak, which marks the beginning of gastrulation; and the mesoderm, which gives rise to muscles, bones, and the circulatory system.

The future applications are many, says first author Riccardo De Santis, a research associate in Brivanlou's lab: "A better understanding of gastrulation impacts everything from survival of the fetus to autism to neurodegeneration." ◎

LABORATORY OF SYNTHETIC EMBRYOLOGY

1998

DATA

Year the first human stem cell line was created.

In the striatum, Mätlik found that CAG repeats were particularly unstable in medium spiny neurons, the cells most likely to be lost during the progression of Huntington's. Moreover, in their nuclei these neurons contained high levels of a protein complex called MutSβ that is known to promote expansion of CAG repeats in experimental models.

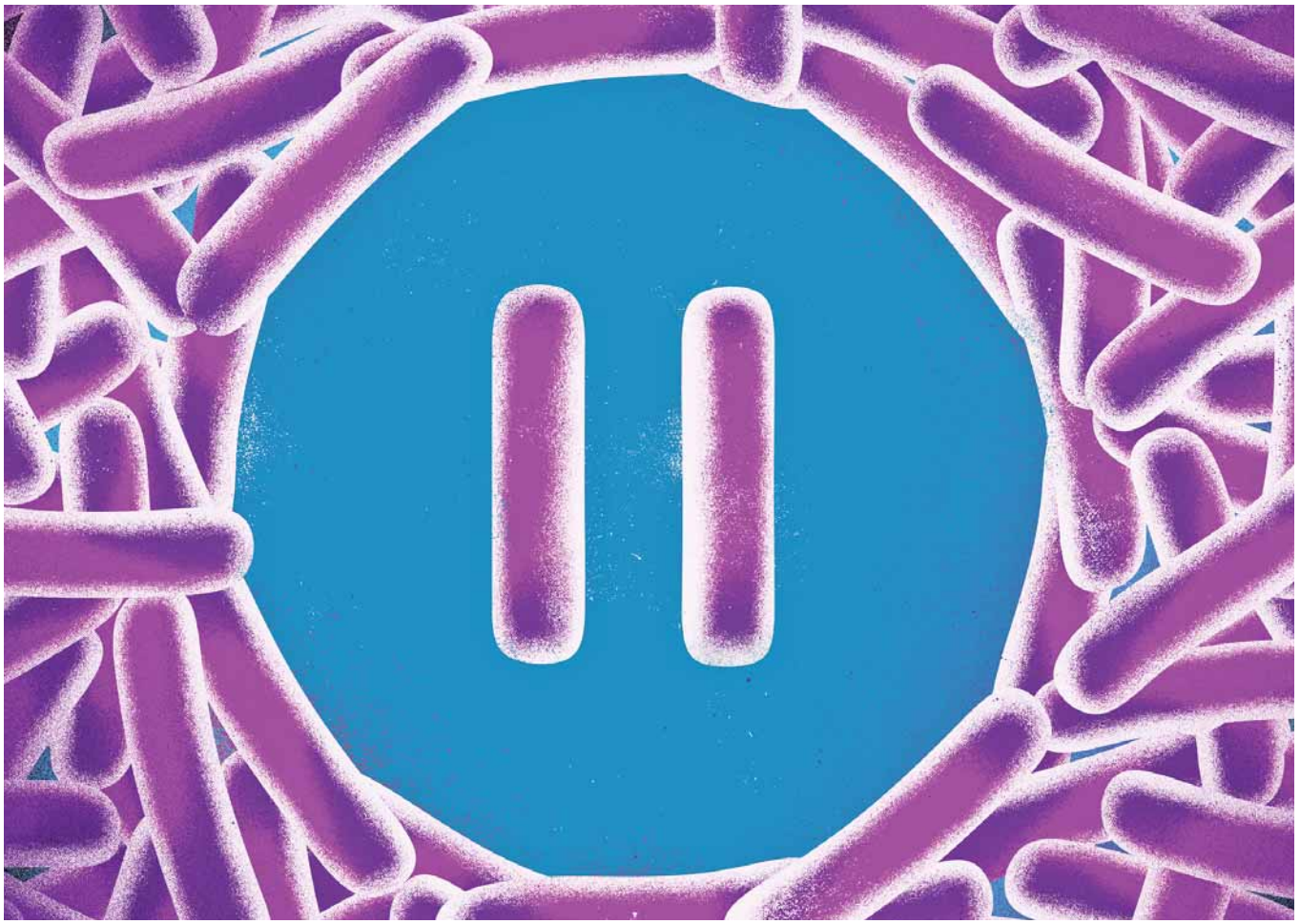
Meanwhile, Pressl discovered that although different types of pyramidal neurons found in the deep layers of the cortex had very long CAG repeats, only one population was more likely to die. The discovery "puts another cell type on the map for increased vulnerability to the disease," she says.

Her study also provided evidence that the susceptible neurons in the cortex project slender fibers called axons into the striatum, where Mätlik's medium spiny neurons reside; communication between the two brain regions is already known to falter in Huntington's. As such, the team's combined findings suggest that the vulnerable cells in both areas may be connected. "When it comes to Huntington's, the entire neural network breaks down at some point," Pressl says.

Heintz, the *James and Marilyn Simons Professor*, hopes to build on these studies to answer more questions about the disease.

"Is there a specific length of repeats at which the cells become dysfunctional? At what CAG repeat length do the cells die, and does it differ depending on the cell type?" he asks.

"We need to understand these things in order to develop new treatments for this devastating disease." ◎



BACTERIAL TRICKS

Taking a strategic pause

MYCOBACTERIUM TUBERCULOSIS (Mtb) is a wily foe, adept at bobbing and weaving around the immune system and antibiotics alike, and sometimes lying dormant for years.

"It's a very smart bacterium, with a lot of tricks," says Shixin Liu, head of the Laboratory of Nanoscale Biophysics and Biochemistry.

Liu has pulled the curtain back on one such trick, working with Jeremy M. Rock and *Corinne P. Greenberg Women & Science Professor* Elizabeth Campbell, who heads the Laboratory of Molecular Pathogenesis. Together, they found that Mtb can control its gene expression by pausing transcription, or the process by which DNA is copied to RNA. Taking transcriptional "breathers" may give the bacterium a chance to adapt to changing conditions, such as a different environment or the presence of antibiotics.

13 MILLION

DATA

Number of people living with inactive TB in the U.S., according to CDC estimates.

Previously, bacteria weren't thought to prominently use such strategic pausing to regulate their gene expression, which is common in more complex organisms. "The findings were so unexpected that I initially didn't believe them," says Rock, the *Penrhyn E. Cook Associate Professor* and head of the Laboratory of Host-Pathogen Biology.

Their startling discovery came via new technology: SEnd-seq, a high-resolution RNA sequencing tool developed by Liu and Xiangwu Ju, a senior research associate in the Liu lab, which the team used to analyze Mtb's RNA transcripts at an unprecedented level of detail.

The researchers suspect that homing in on the pausing mechanism could provide a particularly fruitful avenue for identifying new drug targets against their cunning bacterial adversary.

"We can use this information to think about how we might inhibit its life cycle," Liu says. ◎

Illustration by Sebastian Thibault

METASTASIS

Sensory nerves help cancer spread

CANCER HAS AN unsettling ability to circumvent our natural defenses, growing and metastasizing from one place to another despite the body's best efforts to contain it. Now, Rockefeller researchers have shown how the disease appears to be co-opting the nervous system to extend its reach.

Previous studies had shown that cancer and the nervous system often pair up in a malignant pas de deux known as the "neurocancer axis," with tumor cells recruiting nerves to their primary site and the nervous system kickstarting tumor growth in turn.

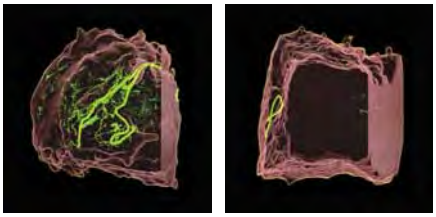
But researchers in Sohail Tavazoie's Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology have learned that nerves don't just foster tumor growth, they also drive metastasis, which is the main cause of death in most cancers. "This is an exciting discovery—no one has seen peripheral nerves release a signal to enhance metastasis before," explains Veena Padmanaban, a postdoctoral fellow in the Tavazoie lab and lead author of the study exploring the relationship between sensory nerves and breast cancer.

Tavazoie's team used mouse models to compare innervation between highly metastatic and less metastatic tumors and found that sensory nerves were spurring breast cancer metastasis. When they analyzed publicly available data, they discovered a similar trend among human breast cancer patients. But the implications of their work could be even broader: The group found that nerve-tumor interactions also activated genes in nearby cells through a process known as RNA signaling.

While the ramifications of that aren't yet clear, "it was unexpected and may have relevance that extends beyond cancer," Tavazoie, *Leon Hess Professor*, explains.

In the meantime, the team managed to impede the growth and metastasis of multiple models of breast cancer when they treated mice with aprepitant, an FDA-approved anti-nausea medication already commonly prescribed for chemotherapy patients.

"Because aprepitant is already approved and safe, oncologists may consider clinical trials to test the impact of this medication on cancer progression in patients with breast cancer," Tavazoie says. ◎



The tumor on the right with few nerves remains localized; the one on the left with many more has spread.

LABORATORY OF SYSTEMS CANCER BIOLOGY; LORI CHERTOFF

INTERACTOMES

Getting the message

DESPITE RECENT EFFORTS to catalog all the different cell types in our bodies, the great mystery of how those cells work together to form tissues and organs remains unsolved. A comprehensive map detailing how cells communicate and collaborate would revolutionize basic biology. But no such "interactome" is possible without a method of reliably tracking millions of intercellular interactions.

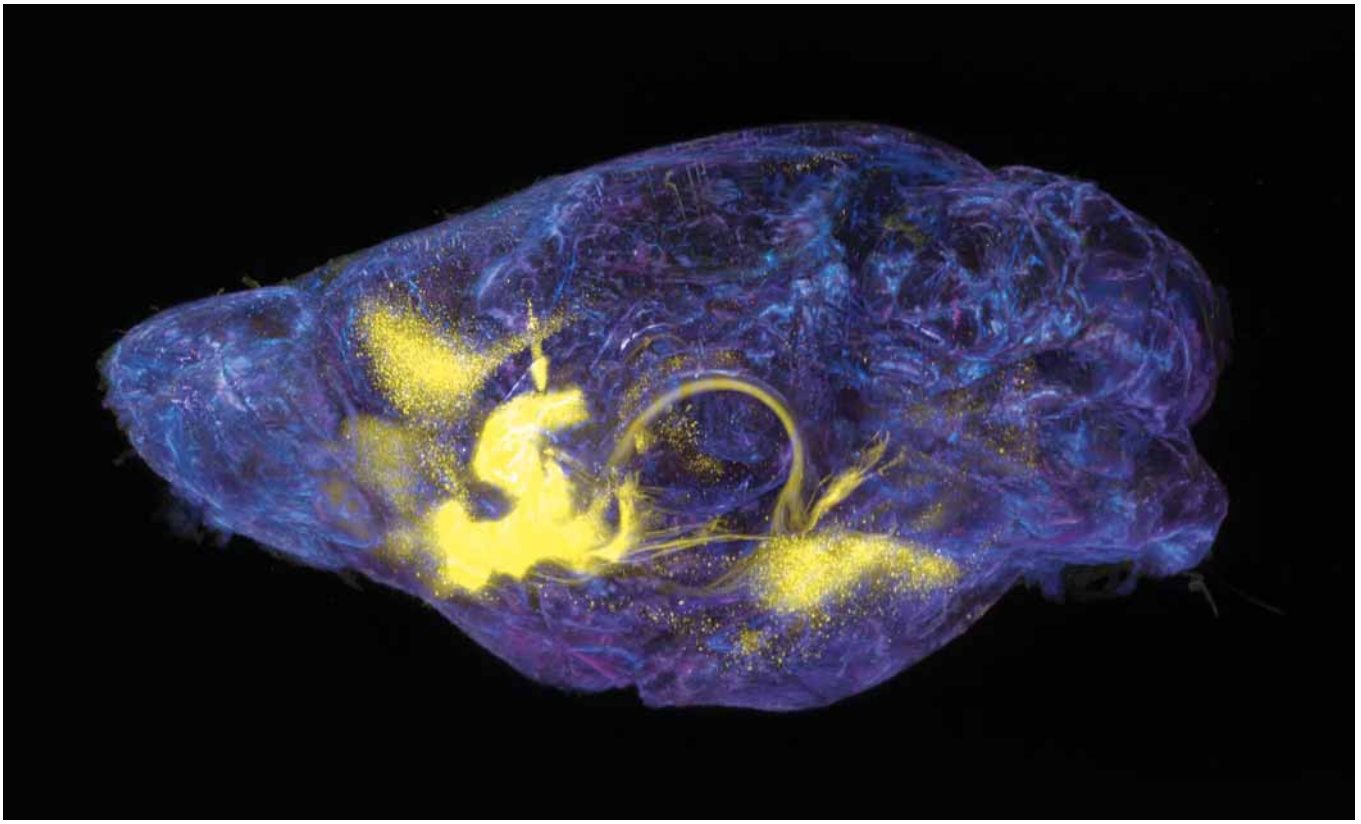
Gabriel D. Victora's Laboratory of Lymphocyte Dynamics developed a limited version of such a method several years ago.

"With uLIPSTIC we can ask how cells work together, how they communicate, and what messages they transfer."

The team named its approach LIPSTIC because it involves labeling cellular structures that touch when two cells make fleeting, "kiss-and-run" contact before parting ways. In essence, it allows researchers to track physical cell-to-cell interactions by causing any cell that "kisses" another to leave behind a biochemical mark like a lipstick trace, which can later be analyzed in the lab. The platform was initially designed only to record a specific type of interaction between immune cells, but, when other researchers got wind of LIPSTIC, they began clamoring for a universal version.

Hence the new and improved tool, which allows scientists to theoretically smear LIPSTIC on any kind of cell and track its physical interactions with other cells. *Laurie and Peter Grauer Professor* Victora and his team hope to use uLIPSTIC to better understand how cells unite into tissue at the molecular level, and they envision it serving as a central tool for building a comprehensive cell-to-cell interactome.

"With uLIPSTIC we can ask how cells work together, how they communicate, and what messages they transfer," Victora says. "That's where biology resides." ◎



"What we hadn't been able to understand is how repeated exposure to drugs alters the function of these neurons."

NEURAL CIRCUITS

Rewiring the brain for addiction

SCIENTISTS HAVE LONG understood that addictive drugs like cocaine and morphine hijack the brain's internal reward system, causing us to crave them while simultaneously disrupting our natural urges to eat and drink. Yet exactly how these drugs rewire our brains hasn't been understood.

A collaboration between scientists at Rockefeller and Mount Sinai recently shed considerable light on the situation by identifying a common reward pathway in a brain region involved in pleasure, motivation, and decision-making. Known as the nucleus accumbens (NAc), this region works closely with dopamine and serotonin, which modulate mood and reinforce behaviors that feel good, such as eating a meal, socializing—or using drugs.

"What we hadn't been able to understand is how repeated exposure to drugs alters the function of these neurons, resulting in escalated drug-seeking behaviors and a shift away from normal drives such as eating and drinking," says Bowen Tan, lead author on the paper and a graduate student in the Laboratory of Molecular Genetics headed by Jeffrey M. Friedman.

To capture what's really happening inside the brain when it's exposed to both drugs and natural rewards, *Marilyn M. Simpson Professor* Friedman and his team turned to advanced brain imaging techniques developed in the Laboratory of Neurotechnology and Biophysics, headed by Alipasha Vaziri, who worked with them to track the neural activity of mice in real time. Coupling those high-tech imaging methods with cutting-edge molecular and genomic techniques, the researchers identified for the first time how drug addiction warps natural urges by commandeering a molecular pathway that plays a crucial role in neural plasticity, the process that neurons use to reinforce learning and memory.

A gene called *Rheb* is at the center of this pathway. When drugs like cocaine activate brain cells expressing *Rheb*, this stimulates a pathway that appears to alter how neurons process stimuli from food and water. This may explain why mice and humans who are addicted to these substances escalate drug use and show decreased needs for natural rewards like food and water.

The team's findings provide new insights about the different effects of natural rewards and addictive drugs, potentially paving the way for new approaches that more directly address how addiction subverts expected behavior.

LABORATORY OF MOLECULAR GENETICS

THE CEREBELLUM

How a key gene contributes to autism

AUTISM SPECTRUM DISORDER (ASD) has a strong genetic component. But sorting out how the scores of genes that have been linked to the developmental disorder actually contribute to it has been difficult. Recent research by Mary E. Hatten is bringing some much-needed clarity to the situation.

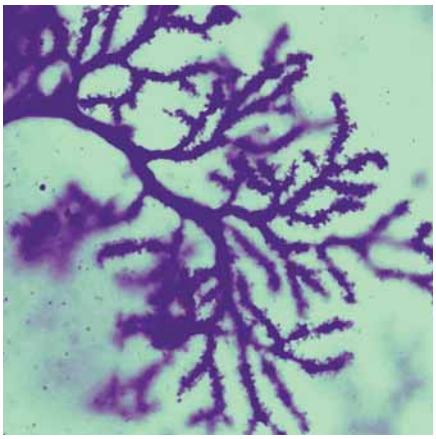
In 2018, Hatten and her colleagues in the Laboratory of Developmental Neurobiology discovered how defects in the protein produced by a gene called *ASTN2* disrupted circuitry in the cerebellum of children with ASD and other neurodevelopmental conditions. This year, Hatten's lab found that knocking out the same gene in mice led to several hallmark ASD behaviors, as well as to physiological changes in the brain.

Mice that lacked *ASTN2* vocalized and socialized less but were more hyperactive and repetitive in their behavior than their wild-type nestmates. When briefly isolated, for example, knockout pups were less likely to call out for their mothers and used simpler vocalizations.

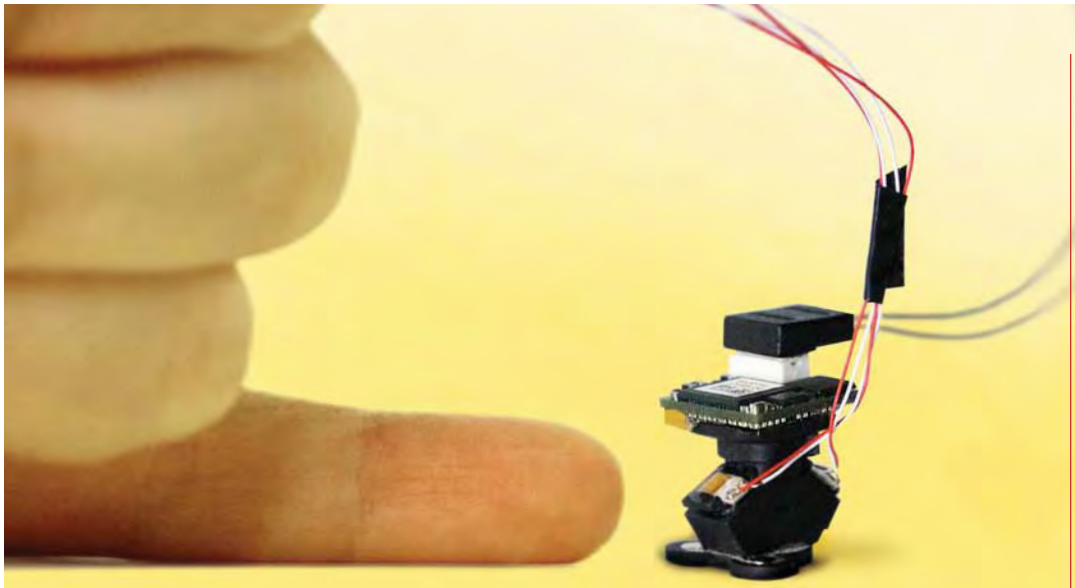
Similar communication and behavior issues are common in people with ASD, says first author Michalina Hanzel: "Some autistic people don't understand metaphor, while others echo language they've overheard, and still others do not speak at all."

The physiological changes centered around abnormalities in brain cells that are located in specific parts of the cerebellum.

"The differences are quite subtle, but they are clearly affecting how the mice are behaving," says Hatten, the *Frederick P. Rose Professor*. "The changes are probably altering the communication between the cerebellum and the rest of the brain."



In addition to providing crucial insight into the genetic causes of ASD, the team's findings add to the growing body of evidence that the cerebellum—the oldest cortical structure in the brain—is important not just for motor control but also for language, cognition, and social behavior. "It's a big finding in the field of neuroscience," Hatten says.



LABORATORY OF DEVELOPMENTAL NEUROBIOLOGY; LORI CHERTOFF

BIG IDEAS

Tiny and mighty

IT'S HARD TO study how brain activity correlates with behavior when the animals being studied aren't behaving freely. This poses a unique challenge for neuroscientists, since tracking activity across the brain of a moving, active subject is no mean feat.

The solution is generally a head-mounted microscope that mammals wear like a hat. But mice, the go-to model organisms for understanding the brain at work, cannot carry anything heavier than a penny. And microscopes that small can only capture what's going on in a tiny portion of the brain.

"Those microscopes typically support rather small imaging fields of view," says Alipasha Vaziri, head of the Laboratory of Neurotechnology and Biophysics, who decided to tackle this issue from a unique angle.

Using conventional methods to increase the field of view had required a frustrating trade-off: Either reduce resolution to widen the field of view or maintain single-cell level resolution by adding more complex and multi-element lenses, which also adds an unwieldy amount of weight.

Vaziri circumvented the problem by going back to the drawing board and coming up with a radical solution: What if the lenses weren't actually necessary? If an optical system can faithfully encode 3D points from a sample to 2D points on a camera, that's sufficient, since that process can be computationally reversed. That is, the optical system does not necessarily need to be image-forming, per se. The result is an innovative, essentially lensless, microscope that's light enough for a mouse to wear on the go, yet packs a field of view wide enough to get the job done (pictured here, not actual size).

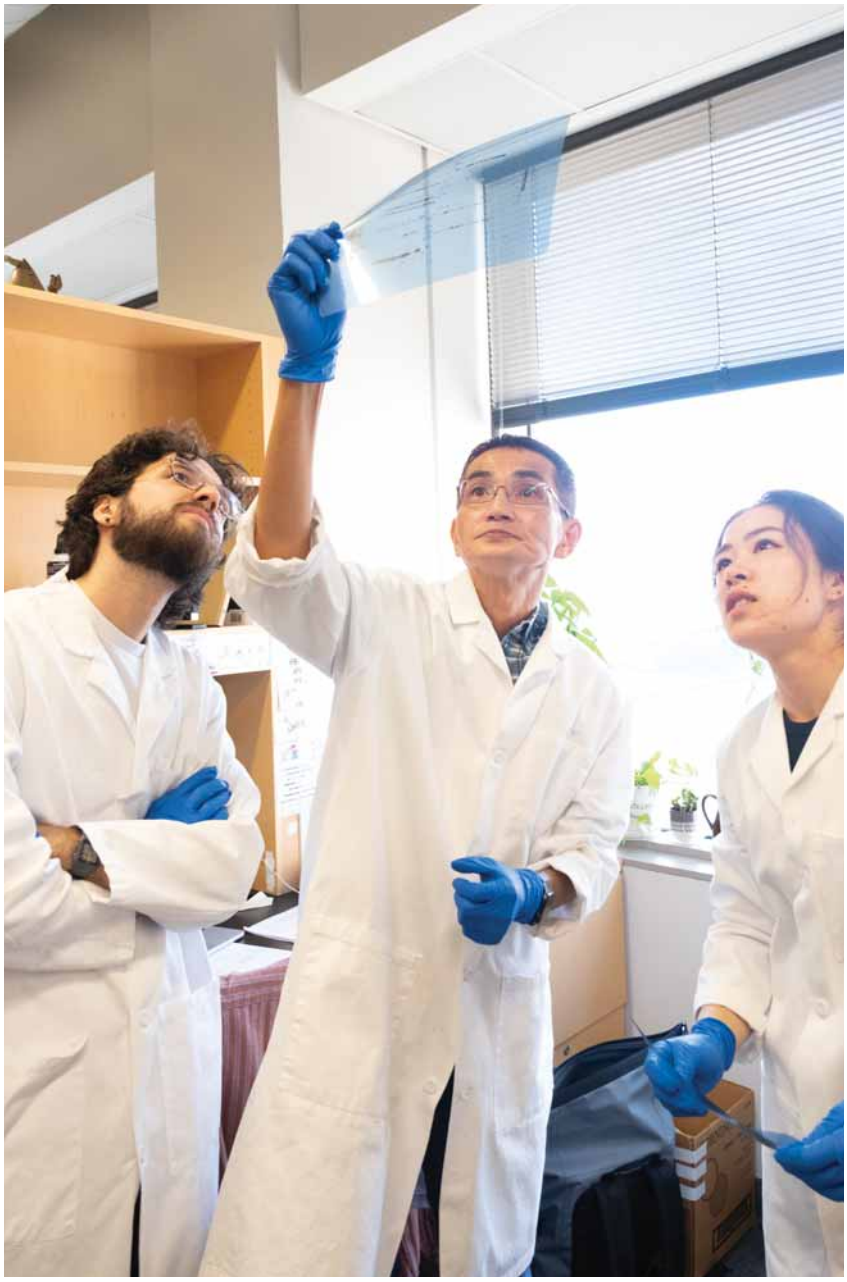
"This tech could advance our understanding of how brain-wide distributed neuroactivity relates to naturalistic behavior," Vaziri says.

MAINTENANCE DEPT

Rewriting the textbooks on telomeres

LIKE HABITABLE PLANETS orbiting distant stars, the chromosomes that contain our DNA are subject to a Goldilocks principle. Telomeres, the protective caps found at chromosome ends, must be kept at just the right length: too short, and dangerously accelerated aging ensues; too long, and they predispose their owners to cancer. Precise regulation is paramount, and Titia de Lange's Laboratory of Cell Biology and Genetics is cracking the code on how three specific enzymes keep telomeres in check.

Among their many findings, de Lange's team discovered that two of these enzymes work in concert to ensure proper telomere maintenance. The telomerase enzyme helps prevent telomeres from growing shorter with each round of DNA replication. But every DNA double helix has two strands that must be copied, and telomerase is capable of handling only one of them. In a recent study, *Leon Hess Professor* de Lange and her team demonstrated that a second enzyme—known as the CST–Polα-primase complex—is responsible for managing the other strand. They further determined how that enzyme complex is recruited and regulated.



"Telomerase should only be acting at the natural ends of healthy chromosomes. When it goes to work anywhere else, very bad things happen."

In addition to fundamentally changing our understanding of telomere biology, these insights could lead to potential treatments for individuals who suffer from telomere disorders such as Coats plus syndrome, a devastating multi-organ disease characterized by abnormalities in the eyes, brain, bones, and GI tract.

Meanwhile, related work from de Lange's lab elucidated a key mechanism for preventing telomerase from accidentally preserving damaged DNA. The main actor turned out to be the enzyme ATR kinase, which stops telomerase from adding telomeres to the ends of broken bits of DNA rather than to the ends of intact chromosomes, where they belong. In light of many studies suggesting that telomerase runs amok in tumors, de Lange is now exploring whether glitches in this self-protective process may help maintain the altered chromosomes that promote cancer progression.

"Telomerase should only be acting at the natural ends of healthy chromosomes," de Lange says. "When it goes to work anywhere else, very bad things happen."

LORI CHERTOFF

Passing the test

DEEP-LEARNING ALGORITHMS CAN unpack the unique 3D structures of a protein in less than an hour—a task that used to take scientists a year. But do these models have the same ability to guide drug discovery as experimental structures do?

If so, the implications for medicine would be immense: Once the molecular nuances of a protein's structure have been identified, researchers could begin targeting it with drugs to correct dysfunctions, combat infections, and improve health.

Research by Jiankun Lyu indicates that at least one such algorithm, Google DeepMind's AlphaFold2, is up to the job. Lyu's lab used sophisticated molecular docking (or virtual screening) software to sift through billions of chemical compounds—searching for potential drugs by matching them against protein structures—and found that for the two drugs they tested, AF2's predicted structures are just as capable of guiding virtual drug screening as are experimental structures. Based on those findings, Lyu says, the algorithm could potentially expedite some drug-discovery projects by as much as several years.

Future deep-learning algorithms will almost certainly be even more powerful. An exciting prospect, but Lyu advises an equal measure of caution: "A lot of AI is currently overpromised and under-delivered. If we don't tread carefully, AI in biomedicine will end up being just another hype."

Case in point: Google DeepMind recently released AlphaFold3, which Lyu describes as "a huge upgrade" over its predecessor. Unlike AlphaFold2, however, AlphaFold3 is a black box; the company has not released the underlying deep-learning model to researchers, which means that they can't properly test it.

"We would not have been able to run the current study on AlphaFold3," says Lyu, now head of the Evnin Family Laboratory of Computational Molecular Discovery. "And without that, we can't know whether the new model is better for drug discovery." ◎

50–70

DATA

Typical number of times a human cell can divide before its telomeres become too short to operate properly.

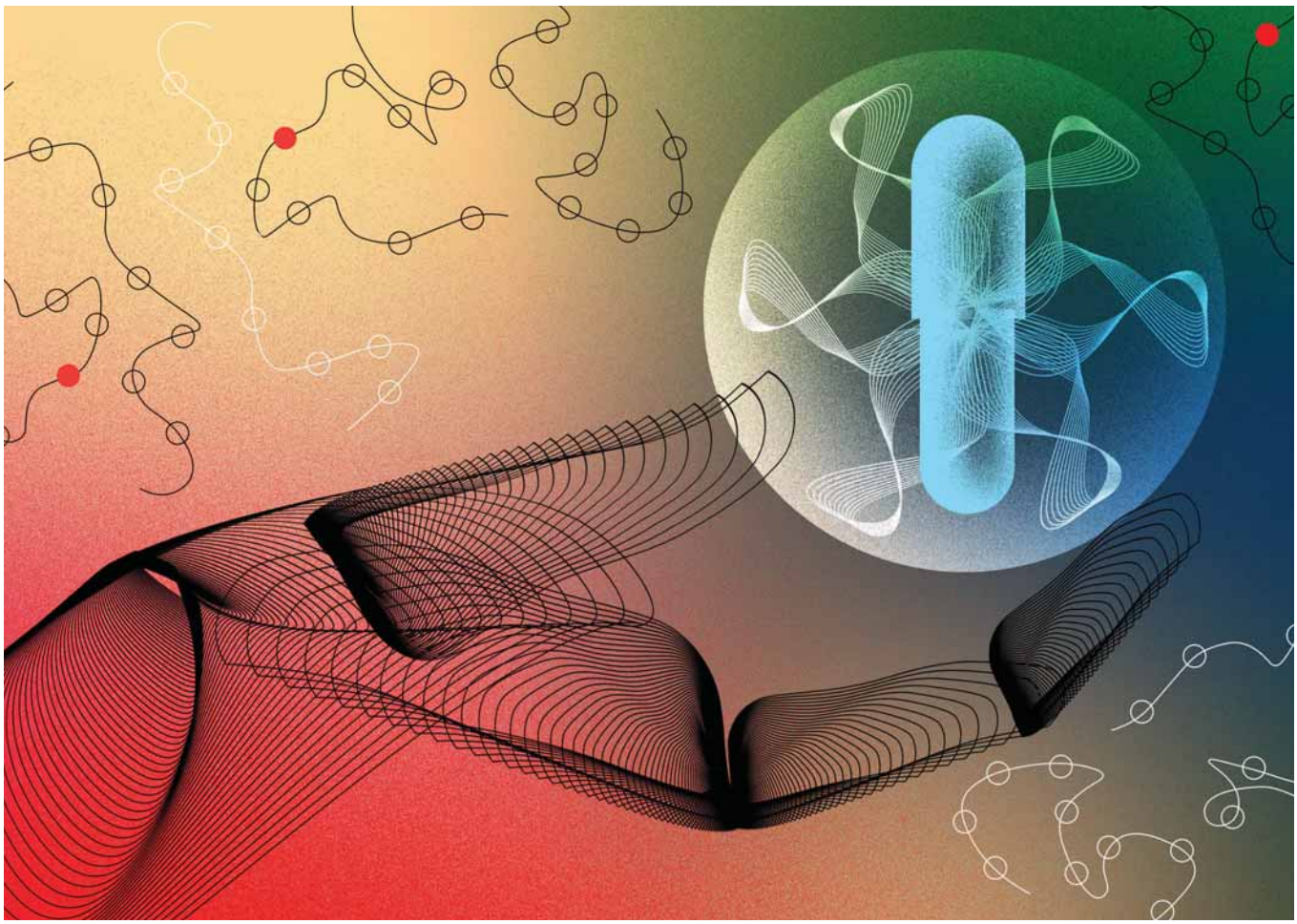
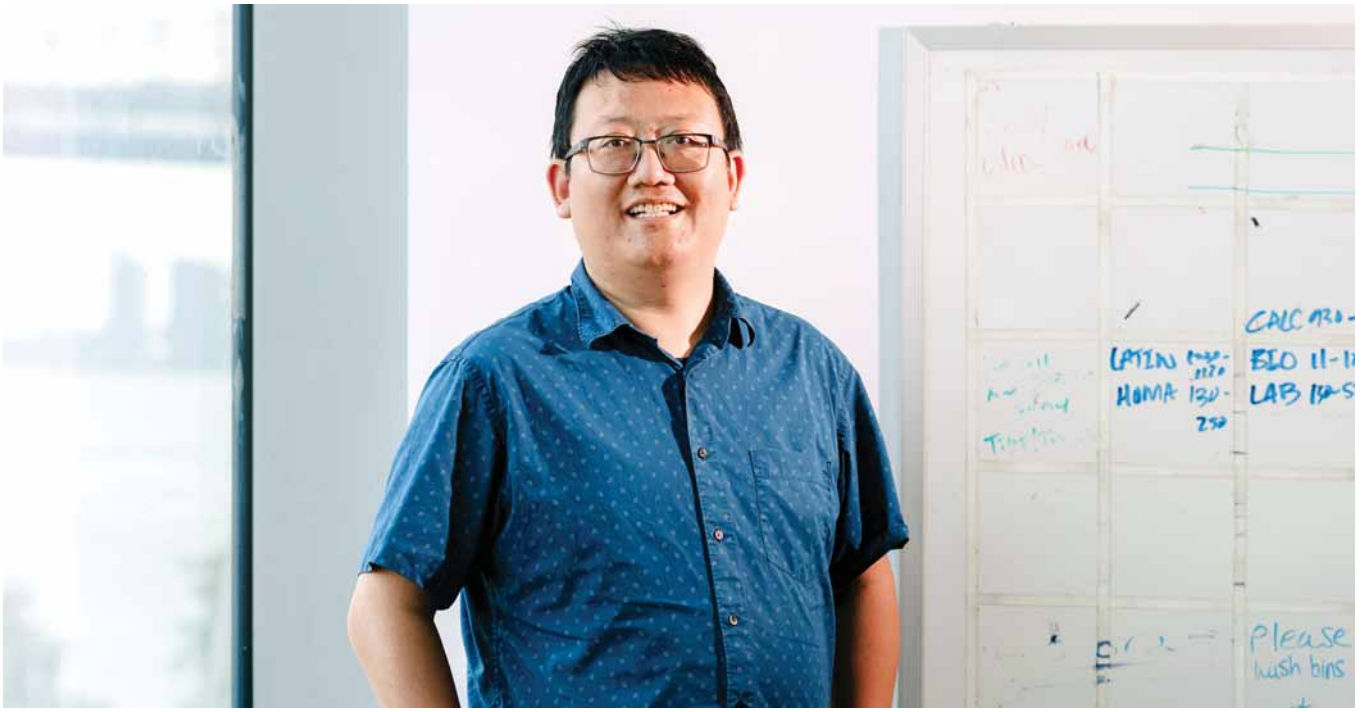


Illustration by Brian Stauffer

Q&A

What if aging isn't what we thought it was

With Junyue Cao



WHAT IF AGING weren't just the result of years of wear and tear on the body, as is commonly believed? What if it were, as Junyue Cao has come to see it, another stage of development—one that could be regulated by thwarting age-related changes on the molecular level?

Should that become possible, it will be thanks largely to single-cell sequencing, a breakthrough technology that is transforming how scientists like Cao think about disease. When the technology came online in 2010, it offered researchers the ability to explore, for the first time, a handful of cells simultaneously. Each was a world unto itself, with its own dynamic ecosystem and distinct purpose in the body. The potential to explore the connection between cellular and biological health seemed infinite—as long as the technology could catch up with scientists' ambitions for it.

As a Ph.D. student studying embryonic development at the University of Washington in 2015, Cao was perhaps one of the most ambitious. By then, single-cell sequencing could analyze several thousand cells at once. But Cao wanted millions. After all, the human body alone holds some 37 trillion cells, and not a single one is exempt from the effects of time. When he shared his goal with his colleagues, they gently told him that the idea was absurd.

Cao's tailored techniques illuminate how cells differentiate into distinct types and maintain their stability.

Today, less than a decade later, he can sequence 20 million cells simultaneously—a remarkable advancement that has led him to intriguing new ideas about aging and disease.

As Rockefeller's *Fisher Center Foundation Assistant Professor* and head of the Laboratory of Single-Cell Genomics and Population Dynamics, Cao uses his own tailored techniques—currently numbering eight—to study patterns of gene expression in single cells, illuminating how they differentiate into distinct types and maintain stability for as long as they can. In the process, he's revealed various cellular mechanisms behind aging and disease, both of which involve the destabilization of cell populations.

Diseases, it's now generally understood, don't affect tissues uniformly; certain cell types deteriorate before others. If we could target these cells with anti-aging interventions at specific stages of life, he suggests, we might be able to transform the treatment of related conditions—and perhaps defy aging itself.

How did your first major sequencing breakthrough come about?

In the first year and a half of my Ph.D., I tested about 200 different ways to increase the number of cells I could analyze at once, and nothing worked. I almost

ROSHNI KHATRI

gave up. People kept questioning whether my goal was realistic, and I was getting nowhere.

But on New Year's Day in 2017, I was in Florida with my family for the break, and I decided to analyze the data from my latest experiment on roundworm cells. I tested a bunch of enzymes to see which might be compatible with our platform. One called SuperScript IV had just become available. When I looked at the data, I was amazed. The enzyme was the key to making our technique work. I immediately emailed my Ph.D. mentor, Jay Shendure, and we were both so excited. For the first time, we had results as accurate as those produced by commercially available platforms, but we had the ability to profile many more cells.

Over the next year, I further improved the technique by testing hundreds of reactions. By the time I graduated, I was able to profile a million cells at a time.

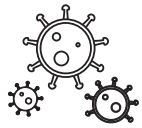
What can your different methods now accomplish?
Among other things, we can track newborn cells throughout their lifetimes, identify thousands of new and rare cell types, pinpoint which cell numbers plummet during aging and which increase, and show how the same types of cells located in different organs behave in vastly different ways. Each technique is like opening a window that allows us to see unexpected things, and that lets us ask new questions.

When you joined Rockefeller, you switched to investigating the aging process. What have you learned in the last four years?
One thing we didn't expect to discover is that, across cell types, there's an enormous amount of variation in how they respond to aging and diseases such as Alzheimer's. Some populations remain stable, but others drastically change, either in gene expression or in the size of the population. For example, we've seen that alterations in immune cells are really common, and that the changes differ from organ to organ. The immune system is almost certainly a key regulatory force in aging.

Each technique allows us to see unexpected things, and that lets us ask new questions.

So far, we've found more than 3,000 unique cellular states and 200 subtypes that undergo significant age-associated depletion or expansion. Within that, there is so much diversity between organs, ages, and sexes. For instance, female mice are more enriched with B-cell subtypes that are associated with autoimmune diseases, and that's noteworthy because we know women have higher rates of autoimmune conditions.

Has your research made you rethink what's happening to our bodies as they get older?
It has. Aging is generally seen as a steady accumulation of damage moving in a linear progression—the wear-and-tear theory. But our research implies that it's more like a stage of development, where cell types greatly change in distinct time windows. For example, we've seen that some cell populations, such as stem cells in the brain and progenitor cells in muscles, are depleted in mouse middle age, which is about 40 in human years. But others expand in later stages of life. This correlates with some human studies that have found accelerated cell changes around age 40.



DATA

Studies suggest adults tend to become happier as they age, reporting greater life satisfaction in their 80s than in their 20s.

The idea of aging as a developmental stage seems like a new paradigm.
It is quite different from the current model, and yet it's consistent with previous studies finding that successfully introducing anti-aging interventions is highly time-window specific. It may be that we need to intervene before critical cell types—stem cells or other progenitor cells, for example—disappear entirely.

There was a paper published in *Science* in 2022 that looked at whether the diabetes drug metformin—which has shown promise for treating various age-related ailments—could slow aging in mice at middle and very late stages. It turns out it's effective only if administered during the middle stage.

We've also seen that there is some overlap of different types of cells changing in the same phase of life. Maybe they're all regulated by a shared mechanism. If that's true, perhaps we could target the mechanism itself.

If interventions are successful only at certain stages, does that mean ill-timed ones could have negative effects?
Potentially. For example, the population of inflammation cells just explodes later in life. So if someone receives a treatment that increases the proliferation of inflammatory aging cells, that could be harmful.

It's also important to note that pinpointing which cell type changes occur at what stages can shorten the time needed to determine if a therapy works. If we know what types we're targeting, we can quickly see if they aren't being rescued in the target time window. That may also expedite identification of therapeutic targets. If some therapies are in the wrong time window, you could eliminate them right off the bat.

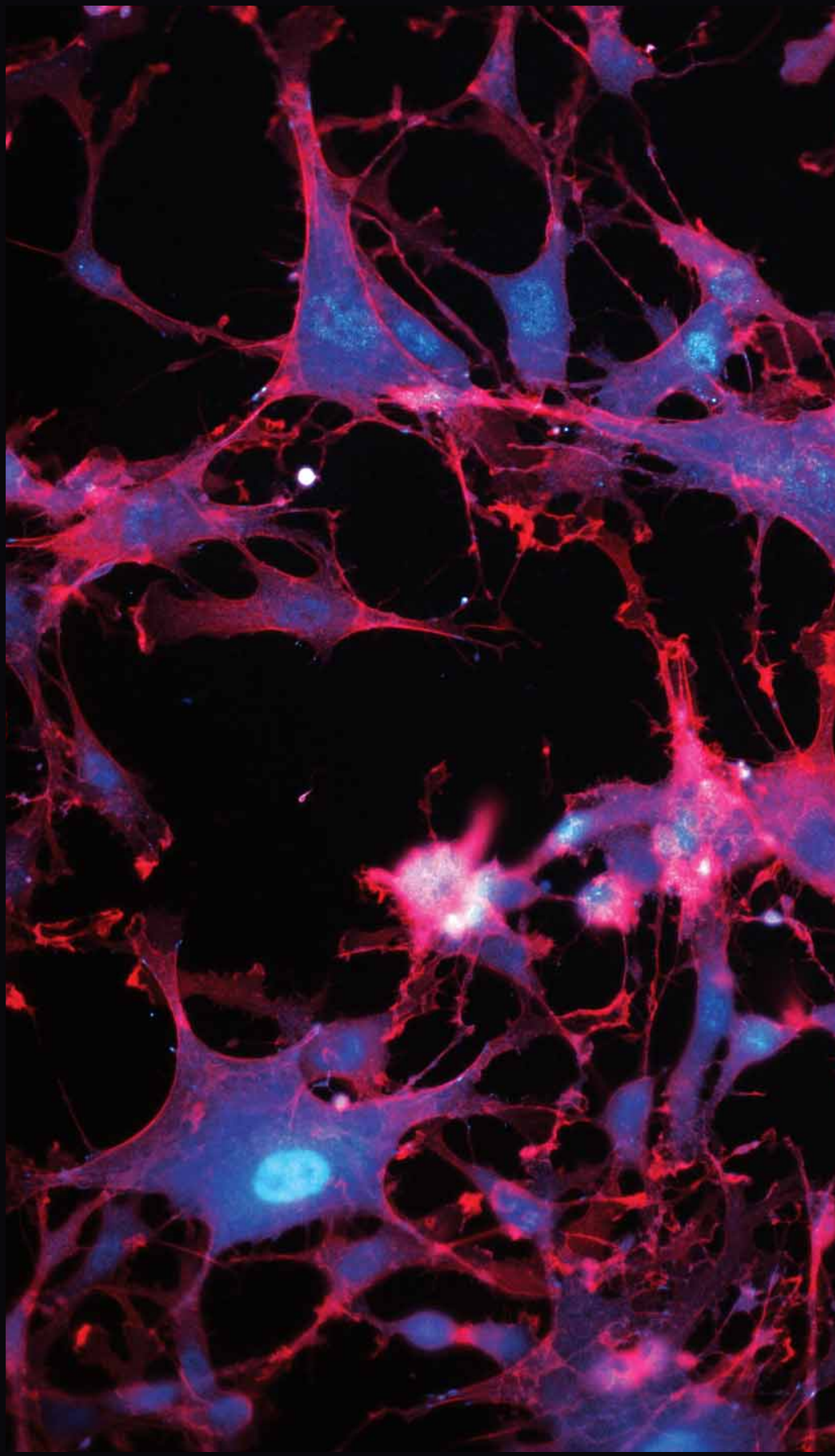
Is it possible that in the future, we'll be able to dramatically alter how we age?
Thirty years ago, the idea that we could direct a cell to differentiate into almost any type desired would have sounded crazy. Now we can easily direct pluripotent cells to do just that. So if we do come to understand the cellular regulatory network—how different cells interact with each other during different stages to maintain the functions of the entire organism—in theory, we could engineer the human system to go beyond its current limitations. ◎

Cellular sensation

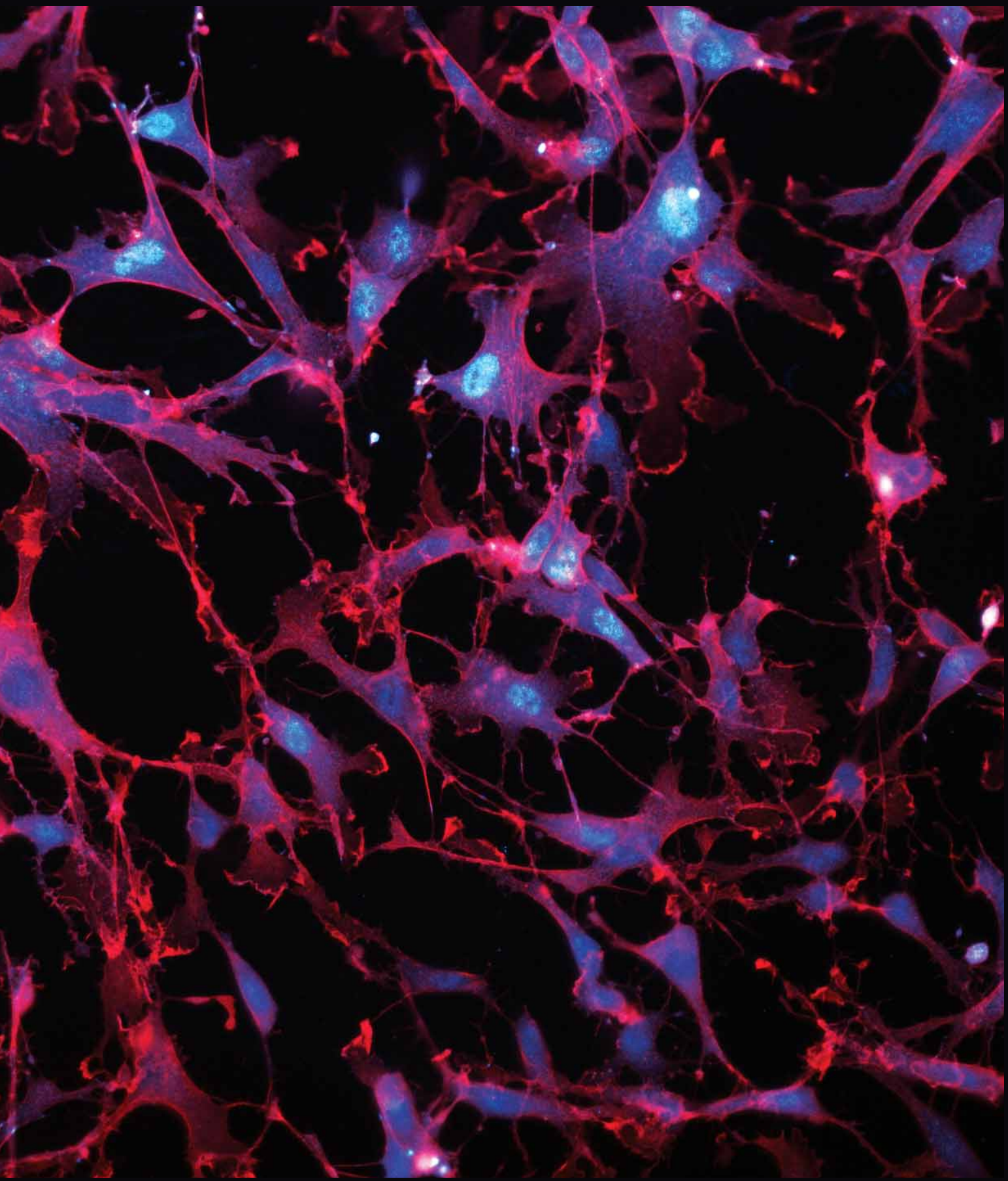
ANY NEW YORKER jostling onto the subway during the morning rush doesn't need eyes to know the train is crowded. Likewise, those riding home later at night can sense the relative quiet. So too does every cell in the body detect its environs and respond appropriately through a technique scientists call mechanosensation.

Whether a cell's habitat is soft and spacious, or hard and crowded, has a powerful effect on gene expression, spurring different cellular actions. To get that information, eukaryotic cells (the type humans are made of) send out feelers connecting the nucleus to the cell's microenvironment, via a network of specialized proteins.

Donovan Phua, a graduate student in Gregory M. Alushin's Laboratory of Structural Biophysics and Mechanobiology, wants to know exactly what those sensors (like FLH2, seen here in cyan) are up to inside the nucleus, the headquarters for genes. Understanding that helps explain how mechanical forces act on normal cells—as well as the bad behavior of diseased ones, which create tumors by growing uncontrollably despite dense surroundings. Phua hopes that this work could inform efforts toward new cancer therapies that teach rogue cells their proper place. ◎



LABORATORY OF STRUCTURAL BIOPHYSICS AND MECHANOBIOLOGY

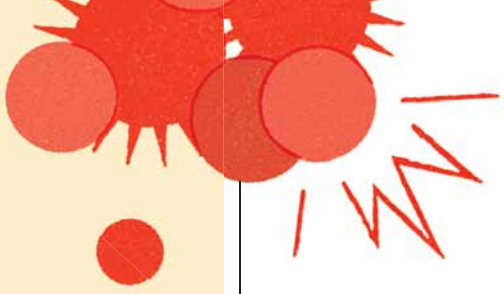


Inflammation is both our body's best natural defense and the underlying cause of many serious, chronic illnesses. How do you treat a dangerous condition that's also a fundamental biological process?

Walking the line

By Alexander Gelfand

Illustration by Gracia Lam



When Rockefeller immunologist Jeffrey V. Ravetch asks his students to describe the function of the system he's studied for the better part of four decades, he typically gets a variety of answers. But his own is always the same.

"Its primary function is not to kill you," Ravetch says. "Because given the chance your immune system will wipe you out."

At first, Ravetch says, students may need a moment to take that in: It can feel counterintuitive to reframe the body's tools for warding off infections and recovering from injuries as simultaneously life-threatening. But that duality is exactly the point.

Ravetch, the *Theresa and Eugene M. Lang Professor*, has spent his career probing the mercurial properties of antibodies and demonstrating how the subtlest molecular tweaks to this or that receptor can result in dangerously different outcomes. Antibodies are famously the means by which we neutralize an invading virus or shut down a burgeoning cancer. Yet they can also be pathogenic in and of themselves, spontaneously triggering a runaway inflammatory process that scientists now know can lead to enormous harm.

"How," Ravetch asks, "does one molecule accomplish all these diverse functions?"

The answer lies at the heart of one of the biggest questions currently vexing medicine: how to rein in uncontrolled inflammation.

In recent years, our body's natural defense system has been implicated in a growing list of serious and chronic conditions, from food allergies and colorectal cancer to obesity and autoimmune disease. Driving conditions from asthma to lupus and increasing the risk of everything from Alzheimer's to heart disease, inflammation has even been linked to the degenerative effects of aging.

As awareness of these health impacts spreads, an entire anti-inflammatory industry has sprung up, with advocates touting cold plunges, special diets, and

Nearly 25 years ago, scientists came upon a conundrum that neatly encapsulated the fickle quality of antibodies.

other lifestyle changes meant to calm the system. Some of these trendy life hacks may turn out to be truly beneficial; the science is still out. But without understanding the basic biological mechanisms that drive inflammation and its effects, trying to manage the phenomenon by jumping into a tub of ice water or eating a bucket of blueberries is like throwing darts at a board. And none of the trends addresses the fundamental quandary of how we should treat a dangerous condition that is also an essential biological process.

This is where researchers like Ravetch and Rockefeller colleague Elaine Fuchs, who focuses on the biology of skin stem cells, come in. Their labs are a part of a larger effort to identify what separates the restorative effects of inflammation from its pathological ones, and how the line between the two can become blurred or even erased entirely. What they are learning is just how complex inflammation truly is, and how many different systems intersect to produce and regulate it. All of which, they say, boils down to one central problem:

"A little bit of inflammation is a good thing," says Fuchs. "But how do you control it?"

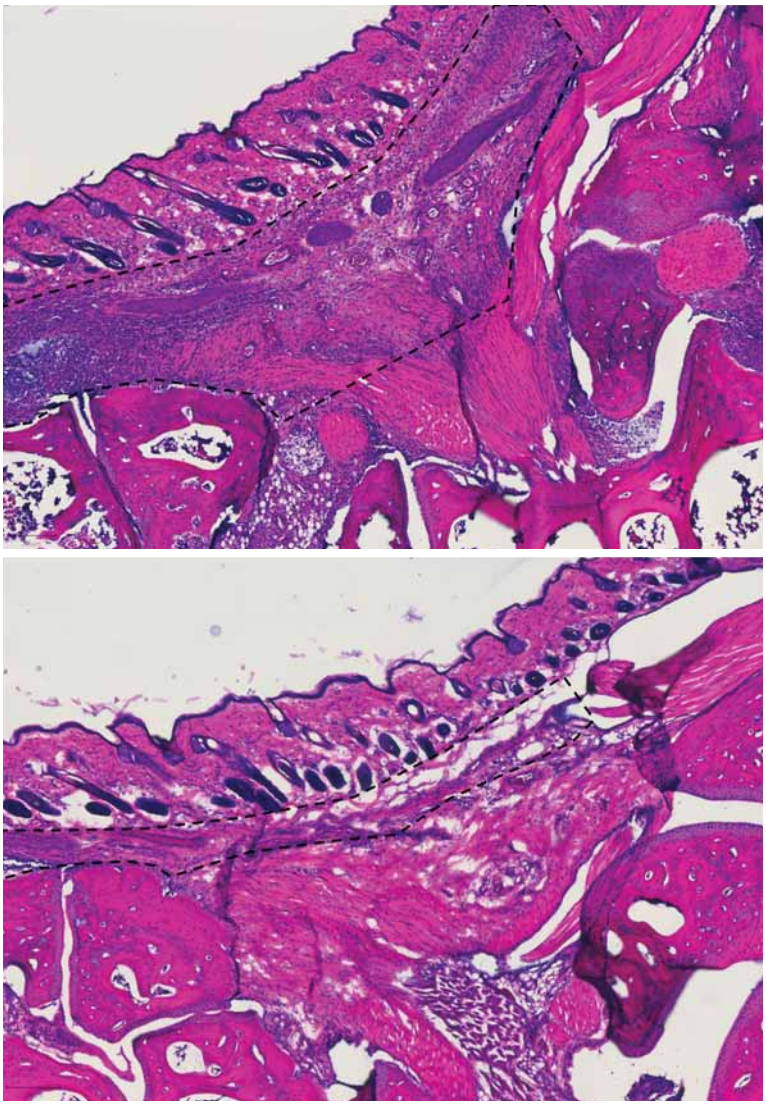
Doctors still learn the signs and symptoms of inflammation by reciting a Latin phrase invented by the Roman scholar Celsus 2,000 years ago: *calor, dolor, rubor, tumor*—heat, pain, redness, swelling. (The term itself comes from *inflammare*, to set on fire.) By the 18th century, scientists had begun to relate those overt characteristics to the microscopic processes (increased blood flow, fluid buildup, a rush of white blood cells) that the body relies upon to defend and repair itself. But while it was understood that inflammation represented one of our best tools for survival, the question of how it fought infection, killed dysfunctional cells, and repaired damaged tissues remained largely unanswered.

Centuries later scientists are still teasing out inflammation's causes and effects. But one thing has become increasingly clear: Its dark side emerges when protective mechanisms run amok, failing to shut down when they should (e.g., chronic inflammation) or attacking healthy tissues when they shouldn't (e.g., autoimmune disease).

Nearly 25 years ago, scientists came upon a conundrum that neatly encapsulated this fickle quality. As antibody therapies first entered clinical use, doctors began to notice something odd: Giving people with compromised immune systems infusions of these drugs helped them mount the inflammatory responses necessary to fight infection. But administering larger doses of the same antibodies *suppressed* inflammation in other patients with autoimmune disease.

Ravetch, who heads the Leonard Wagner Laboratory of Molecular Genetics and Immunology, was uniquely equipped to explain this apparent paradox. Long fascinated by how antibodies trigger inflammation to eliminate threats and suppress it once they've passed, he has focused on a component of their structure known as the Fc region, or "the Fc." Most immune cells have receptors that either activate or inhibit inflammation by binding to the Fc, and Ravetch has both explored and exploited the region's pro-inflammatory and anti-inflammatory capabilities in many contexts, and for many purposes.

In this case, Ravetch discovered that the seemingly contradictory effects of low versus high doses of antibodies were in fact caused by chemical changes to the Fc. Some changes ratcheted up inflammation, while others tamped it down. But since the anti-inflammatory changes were rarer, their effects become pronounced only at high dosages. Ravetch and his colleagues subsequently figured out how to engineer these anti-inflammatory effects to create more



Images from Ravetch's lab show inflammation of an ankle joint before (above) and after (below) treatment developed by the researchers.

Jeffrey V. Ravetch

effective autoimmune therapies, the first of which is now entering clinical trials. Standard antibody therapeutics, which are used to treat a variety of serious inflammatory autoimmune disorders affecting the heart, blood vessels, and nervous system, must be made from the pooled blood of thousands of donors and given in large volumes to patients over the course of several days, making these treatments hard to come by and difficult to administer. Because the drug developed from Ravetch's lab is 10 times more potent than current treatments for rare but potentially disabling conditions like Guillain-Barré syndrome and Kawasaki disease, however, it could solve both problems.

Ravetch's team has also tinkered with the Fc to increase the efficacy of therapeutic antibodies used to treat cancers of the blood, breast, and colon. The use of such drugs, known as immunotherapy, has revolutionized cancer care in recent years; augmenting their inflammatory power has made them even more effective. "About a dozen antibodies have been re-engineered based on this understanding that Fc modifications can enhance their pro-inflammatory properties," he says.

Ravetch is also leveraging the Fc to identify people who are at high risk of experiencing severe infectious disease, the most harmful effects of which are often caused by rampant inflammation. Dengue, or "break-bone" fever, is a good example of this. In most people, the viral illness is painful but not life-threatening. In some, however, the body's inflammatory response is so extreme it can prove deadly. Why? The difference, Ravetch discovered, boils down to a pro-inflammatory modification they carry in this region.

This finding allowed Ravetch to develop an antibody that can screen for patients who are at risk of developing severe dengue—and may even be able to prevent it. Another illness whose worst effects are caused by runaway inflammation? COVID-19. Ravetch hopes to employ the same method to screen for—and develop strategies to protect—high-risk patients.

Elaine Fuchs

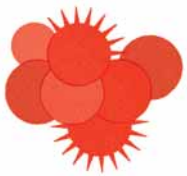
OUR SKIN BEARS the brunt of what the world throws at us, from scratches and scrapes to allergens and ultraviolet radiation. Elaine Fuchs had long been fascinated by the biology of the organ's underlying stem cells, and by how they generate new tissue and repair wounds. Her lab has produced a long string of insights at the intersection of genes, aging, and cancer.

About a decade ago, however, Fuchs's curiosity about stem cells led her in an unexpected direction. It started with another widely observed phenomenon that had never been adequately explained: Why is it that inflammation will often strike a particular location on the skin (an angry red spot on the arm, a scaly patch on the upper thigh) in response to a specific stimulus like a wound or allergy; resolve completely once the stimulus disappears; then reappear in exactly the same location years later in response to an entirely different stimulus? And why is the second response often stronger than the first?

To investigate, Fuchs, who is the *Rebecca C. Lancefield Professor* and heads the Robin Chemers Neustein Laboratory of Mammalian Cell Biology and Development, met with her team and developed an experiment that involved applying a chemical irritant to one side of a mouse's back. After the resulting inflammation died down, a mild wound was administered to the same spot, as well as to the side that had not been irritated. Remarkably, the spot that had previously been inflamed healed faster than the one that had not—even though the new irritant was different from the original source of inflammation.

Intrigued, Fuchs set out to identify which biological actors were hastening the healing process—and discovered a mechanism that changed how scientists think about inflammation in general.

Many researchers had believed the likeliest culprits behind this inflammatory memory were immune cells, which have long been known to store details of past encounters with pathogens—a phenomenon also known as trained immunity.



READY TO RESPOND

During an initial inflammatory episode, regions of stem cell DNA containing "response genes" turn on, allowing the cells to enter repair mode.

Much to the surprise of the scientific community, Fuchs found that long-lived epidermal stem cells sat in the driver's seat, retaining and recalling memories of inflammatory incidents without the help of immune cells. During the first inflammatory episode, inflammation response genes turned on, allowing the stem cells to enter repair mode. But while most shut back down after the initial inflammation had resolved, some DNA "inflammation sensors" associated with these response genes remained active for up to six months in mice—or approximately five to six years in human terms. The next time these educated stem cells faced an inflammatory stimulus, they were ready to respond more quickly and robustly, even when the new stimulus differed from the old one.

This dynamic helps explain the skin's ability to quickly jump-start a reaction to stressors it has never experienced before. It also helps explain why local sensitivity to an inflammatory response can linger long after the stimulus that provoked it has vanished. "While lifesaving for wound healing, this can lead to chronic inflammatory disorders," Fuchs explains. As a result of Fuchs's work, researchers are now pursuing the role that this previously unknown mechanism may play in other tissues where chronic inflammatory conditions can occur.

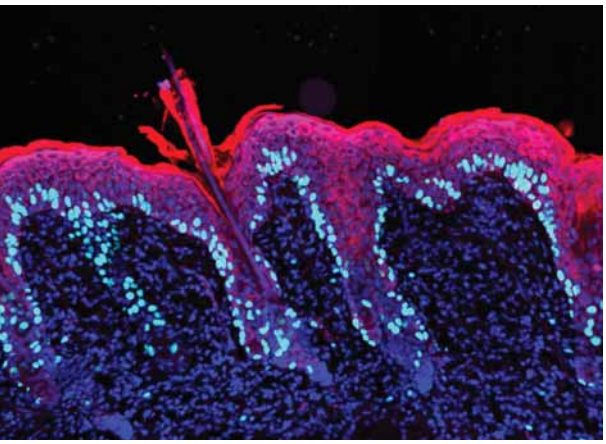
Fuchs herself is looking at how she can leverage her discovery to address a whole host of disorders, from skin conditions such as psoriasis and atopic dermatitis to inflammatory bowel disease.

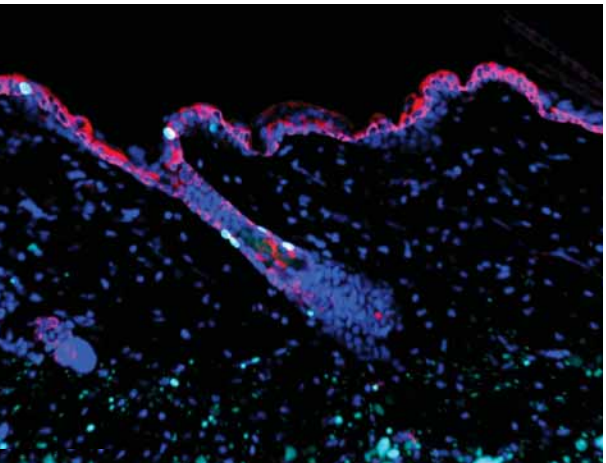
Her team is also exploring the relationship between inflammation and cancer—in particular, squamous cell carcinomas, which affect not only skin but also the head, neck, lungs, esophagus, and cervix, making them one of the most common and life-threatening forms of cancer worldwide.

The skin is remarkably adept at clearing cancer cells, in large part thanks to interactions between skin stem

cells and the immune system. Yet once a tumor has formed, inflammation can actually feed the malignancy by promoting cell proliferation, a process that is largely driven by disordered communication between cancerous stem cells and their environment. Determining how and why that switch occurs could lead to novel therapies not just for skin cancer but also for tumors that form in other parts of the body that aren't nearly as adept at dealing with the disease.

"Once we figure out why skin stem cells are so good at responding to insult and communicating with the immune system, we hope to be able to control the response in chronic inflammatory disorders—and also teach other parts of the body how to better respond in potentially cancerous situations," Fuchs says.





Images from Fuchs's lab show inflamed skin (above) and skin that has undergone inflammatory resolution (below).

Daniel Mucida

IN SCIENTIST DANIEL MUCIDA'S research, balance is everything.

Mucida studies intestinal tissue, which has become the subject of intense scrutiny in recent years.

For one thing, the gut is extraordinarily complex, comprising multiple layers of tissue and more neurons than are found anywhere outside of the brain, to which it is directly connected.

For another, it plays an essential role in maintaining our overall health. Indeed, if the skin is the primary barrier between our bodies and the outside world, the gut is the principal portal between the two: a place where everything we swallow—food and drink, toxins and parasites—eventually winds up.

This constant influx of foreign material, coupled with the presence of our own gut microbiota—the collection of (mostly) helpful microbes that have colonized it—means that the gut is in a constant state of inflammation: The epithelial tissue that lines the intestines, and the immune cells that patrol it, are forever sorting friend from foe, generating protective responses against dangerous invaders while tolerating everything else. When that system goes out of whack, however, uncontrolled inflammation can lead to painful and potentially deadly conditions like colitis, food allergies, and cancer.

Mucida, who heads the Laboratory of Mucosal Immunology, is working with his team to understand how the gut strikes this exquisite balance between tolerance and resistance at a cellular and molecular level, and what happens when that balance breaks down.

Mucida and his colleagues are investigating, among other things, T cells, a diverse group of immune cells that recognize a huge range of antigens, kill infected and cancerous cells, and coordinate the activities of other immune cells. Under normal conditions, T cells are exceptionally good at distinguishing harmless residents and interlopers from dangerous ones, and they play an important role in detecting nutrients, sensing infections, and preventing allergic reactions.

Albana Kodra, postdoc, and former Mucida lab colleague Bernardo Reis utilizing specialized equipment to prepare delicate intestinal samples for analysis.

CHRIS TAGGART

"But they can also go crazy and cause disease," says Angelina Bilate, a research associate in the Mucida lab. One such example is celiac disease, an autoimmune disorder in which T cells react to gluten by attacking the small intestine.

By studying the antigens that T cells recognize and the receptors they use to do so, Bilate aims to describe the whole spectrum of inflammatory responses that a typical individual's gut can mount. That, in turn, should allow her to determine how that spectrum changes with illness, as otherwise tightly regulated responses go unchecked.

In a similar vein, graduate student Marwa Saad is exploring how immune cells monitor the gut, and how they communicate with epithelial cells to coordinate that surveillance. Most recently, she has been using cancer as a model to understand how the immune system perceives and responds to insults to the gut, and how communication between immune and epithelial cells can be disrupted.

Under healthy circumstances, immune cells zip from epithelial cell to epithelial cell in a pattern called "flossing." With each pass the immune cells scan the epithelial cells and receive information about pathogens in the gut. When tumors form, however, the immune cells can no longer "see" the epithelial cells properly, and communication breaks down. Figuring out how that happens—and how to restore proper perception and communication—could lead to new therapies for colorectal cancer and other illnesses.

Psoriasis is an inflammatory skin disease that affects between two and three percent of the global population. It most often presents as itchy, scaly lesions called plaques that are both uncomfortable and unsightly. But it can also prompt a massive inflammatory response, sending patients rushing to the ICU. In very rare cases, it can kill a person.

When dermatologist James G. Krueger began practicing medicine in the 1980s, the drugs used to treat its most dangerous forms were blunt instruments that suppressed the entire immune system—the medical equivalent of throwing the baby out with the bathwater.

Krueger was intent on finding safer and more effective therapies for the disease. In the 1990s, he and his colleagues conducted experiments that indicated psoriasis was most likely caused by abnormal activity among T cells. In the case of psoriasis, they appeared to be generating inflammation in response not to some foreign pathogen but to a substance that the skin itself generated, making psoriasis an autoimmune disease as well as an inflammatory one.

Unfortunately, there were no trustworthy animal models for psoriasis that Krueger could use to identify specific inflammatory pathways and test potential treatments. He realized, however, that drug companies had already developed a number of molecules that targeted various pathways by blocking inflammatory signaling molecules called cytokines. So, he and his team came up with a creative approach to trace back the root cause of the disease.

They began a series of meticulously conducted small clinical trials at The Rockefeller University Hospital, where Krueger is now senior attending physician, giving psoriasis patients existing drugs that blocked different cytokines and carefully analyzing the results back in the lab. This allowed them to simultaneously identify the pathways underlying the disease and effective treatments for it.

James G. Krueger

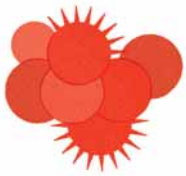
It was the scientific equivalent of finding a needle in a haystack—and then deducing how the needle had found its way into the haystack in the first place.

Krueger's small trials eventually led to larger ones, which in turn led to FDA approval for a whole new class of psoriasis drugs that are safe and effective in approximately 90 percent of patients. As a result, says Krueger, who heads the Laboratory of Investigative Dermatology, psoriasis is now "the best-treated inflammatory or autoimmune disease, period."

What's more, psoriasis is only one of several T-cell-mediated inflammatory skin conditions that together affect 10 to 15 percent of adults worldwide—and Krueger's bed-to-bench-and-back approach can be applied to all of them. Atopic dermatitis, for example, affects as many as 20 percent of all infants; as was once the case with psoriasis, the only treatments for its most severe forms were themselves potentially dangerous. In recent years, however, researchers have identified safer and more effective therapies by adopting Krueger's method of probing the underlying mechanisms of the disease with cytokine-blocking drugs. And Krueger himself, the *D. Martin Carter Professor in Clinical Investigation*, is currently working to identify new, pathway-targeted treatments for an excruciatingly painful inflammatory skin condition called hidradenitis suppurativa.

But his work has implications far beyond the skin. A paper Krueger co-authored in 2021 showed that patients with psoriasis were 50 percent more likely to develop cardiovascular disease—a finding that indicates inflammatory skin diseases can be signifiers of other serious disorders, and not just ones that are commonly thought of as being inflammatory in nature, like arthritis and asthma. (Research by other scientists suggests that psoriasis patients are also more likely to develop dementia.) Sometimes, Krueger says, such comorbidities are due to shared genetic factors and common disease pathways. But they are also likely driven by something else—namely, the passage of cytokines from the skin into the bloodstream. "Every tissue in the body starts to be bathed in an inflammatory cytokine mix," he says.

The resulting constellation of inflammation-related health problems can reduce the lifespan of a psoriasis patient by five to 10 years—years the new drugs Krueger helped develop now promise to restore.



THE BEST-TREATED

Krueger's series of clinical trials eventually led to a new class of drugs that effectively treat psoriasis in about 90 percent of patients.

Such discoveries illustrate why it's hard to overstate how much harm inflammation can do when it gets out of hand, and how much good can be done by reining it in. And they represent just the beginning of what Rockefeller scientists hope to achieve.

Ravetch, for instance, recently showed that by modifying the Fc in an antibody-based cancer drug that had shown promise in mice but failed in humans, he could generate cancer-killing effects that were both powerful and long-lasting: Patients who received the Fc-enhanced drug in a clinical trial at The Rockefeller University Hospital not only saw their skin and metastatic breast cancer tumors melt away but also remained cancer-free for months afterward. Trials are now underway at other institutions to test this potentially revolutionary treatment on brain, bladder, and prostate cancer.

Fuchs, meanwhile, is exploring the role of inflammatory memory in chronic inflammation. She and her colleagues have already identified hundreds of skin stem cell genes that act as inflammation sensors after undergoing an inflammatory experience, just waiting for some fresh insult to occur so that they can leap into action. Under normal circumstances, once the inflammatory stimulus has subsided, everything goes back to normal. Now, however, she and her team are designing experiments to reveal what happens when that cycle of inflammation and relief repeats over and over again in an endless loop, battering the skin without mercy. "When you keep doing it, what will you get?" she asks. "Can the skin figure out what to do?"

On the gastrointestinal front, Mucida is investigating the inflammatory relationship between the

immune system and the nervous system—a particularly promising line of inquiry for gut researchers, since the organ is loaded with neurons that communicate directly with the brain and spinal cord. For instance, Albana Kodra, a postdoctoral associate in his lab, is looking at allergic reactions in mice to see if the nervous system can act as a reservoir of inflammatory memory. If so, identifying the biological mechanisms at work could lead to new treatments for food allergies in humans.

And Krueger, who has already helped deliver life-changing drugs to millions of patients, is now turning his attention to Lyme disease. While most people who acquire this tick-borne infection suffer nothing more than a distinctive skin rash and flu-like symptoms, a small subset goes on to develop chronic inflammatory conditions characterized by heart problems, nerve damage, and brain fog. A collaborative team of clinicians and scientists at other institutions has asked Krueger to help explain this phenomenon, and he hopes to discover why the inflammation associated with Lyme disease sometimes spreads beyond the skin—and whether such systemic inflammation can be treated with the same drugs that are used to combat inflammatory skin diseases.

Projects like these promise to solve some of the enduring mysteries of inflammation: Precisely which cellular and molecular actors control it, and what role does memory play? How does inflammation both contribute to cancer and protect us from it? And why does the immune system's ability to mount an inflammatory response against the right targets, or shut that response down at the right time, sometimes fail to such devastating effect?

Answering these questions will help scientists further understand and harness the power of inflammation—a power that can sometimes be tamed, but never overestimated.

"The body's defenses," Ravetch says, "must be respected at all times." ◎

How a skin rash can turn into heart disease

Patients with moderate to severe psoriasis are 50 percent more likely to develop cardiovascular diseases. But they may also have an elevated risk for a surprising number of other comorbidities. Research from Krueger and colleagues suggests that's because this skin condition triggers system-wide inflammation, the effects of which can take a decade or more to manifest. In the meantime, damage accumulates largely asymptomatically until it causes a dangerous health event, such as heart attack or stroke.

There are three main ways inflammation migrates from the skin into the body.

CYTOKINES

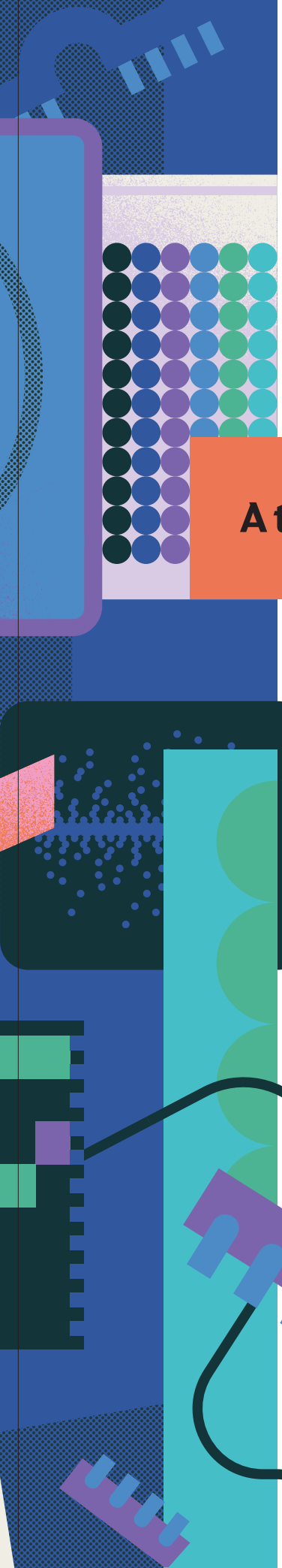
During psoriatic flare-ups, one to 10 percent of inflammatory products like cytokines can leak from the dermis into the bloodstream. That is enough to cause major impacts, percolating throughout tissues and organs and effecting biological functions in ways not fully understood.

DENDRITIC CELLS

These cells sense the presence of foreign antigens and carry them to lymph nodes, where they pass the message on to the immune system. From here, T cells reacting to the antigen kick off additional immune responses.

T CELLS

These cells, tailored to respond to the original autoimmune reaction, then continually recirculate between the skin, lymph nodes, and bloodstream.



A transformative moment for RNA

Once considered DNA's rote protein generator, RNA has fully emerged from the shadow of its more famous cousin. As researchers discovered its myriad types—small, long, noncoding, small interfering, piwi-interacting, micro, ribosomal, small nucleolar, and many others—they've also revealed how central RNA is to a range of biochemical tasks, from regulating gene expression to mobilizing other molecules into action. Far from a mere go-between for DNA and ribosomes, RNA actually possesses a diversity of form and versatility of function that is virtually unrivaled in biology.

From the outset, Rockefeller scientists have played a crucial role in transforming our understanding of RNA. Their foundational discoveries illustrate how cells use it to respond to environmental signals; pinpoint how its dysregulation leads to disease; underpin RNA-based therapeutics for formerly untreatable conditions; explicate its role in the quick-change evolution antibiotic-resistant bacteria are capable of; and help exploit RNA's complex architecture for drug potential, among other breakthroughs. Together, their work is demonstrating how RNA's impressive skills can be harnessed to fine-tune human health.

By Joshua A. Krisch and Jen Pinkowski

Illustration by Aleksandar Savić / Photography by Lori Chertoff

JAMES E. DARNELL JR.

When James Darnell graduated from medical school in the mid-1950s, no one knew how profoundly the science of RNA would revolutionize vaccine development and disease treatment—and even alter our understanding of heredity itself. But already the burgeoning field was raising huge questions, and Darnell saw a challenge.

Only a decade had passed since scientists had demonstrated that DNA was the principal vehicle of heredity, and none other than Francis Crick had just proposed that another nucleic acid was required to turn the information it contained into proteins. Researchers were racing to discover this missing link in protein synthesis in hopes of filling out the story of how genetic information is passed on.

"I knew what my future was—to find this messenger RNA in our cells," Darnell says. While working at the National Institutes of Health, Darnell helped develop a technique for extracting RNA from viruses to better understand how they hijack cells and force them to produce viral proteins. Less than a decade later, he used a version of this technique to investigate mRNA in animals, solidifying our understanding of RNA's central role in carrying genetic information and directing protein synthesis. "No one had ever successfully removed all of the RNA from an animal cell intact," Darnell says. "But I knew that I could do it."

Over his next five decades at Rockefeller, Darnell, today the *Vincent Astor Professor Emeritus*, conducted work on RNA and the expression of genes within the cell nucleus, a.k.a. nuclear transcription. This research built the backbone of modern molecular biology.

The Darnell lab focused on understanding how signals received at the cell surface affect nuclear transcription, in part by studying the proteins that relay those signals and initiate the process. By clarifying how these proteins affect gene activation, Darnell and his colleagues proved that they play a key role in regulating gene expression—and in controlling cell growth and immune responses, both of which become dysregulated in cancer. Darnell ultimately confirmed that aberrant activation of these proteins could lead to uncontrolled cell growth, a finding that spurred the development of novel drugs that are now in clinical trials for cancers such as leukemia.

These foundational insights led researchers to uncover the pivotal surface-to-nucleus "Jak-STAT" pathway—partially named for the STATs (or relay proteins) he first identified—which underlies numerous processes from inflammation to cell specialization and since has been implicated in disorders as varied as susceptibility to fungal infections and dwarfism.

Through his previous ingenious detection of the long RNAs that serve as precursors to mRNA, Darnell had paved the way for discovery of RNA splicing, filling a critical gap in our understanding of gene expression and providing the first full explanation of how cells translate genes. By explicating surface-to-nucleus signaling, Darnell showed how cells can use RNA to quickly respond to changing environmental signals.

The revolution was now well underway. –JK

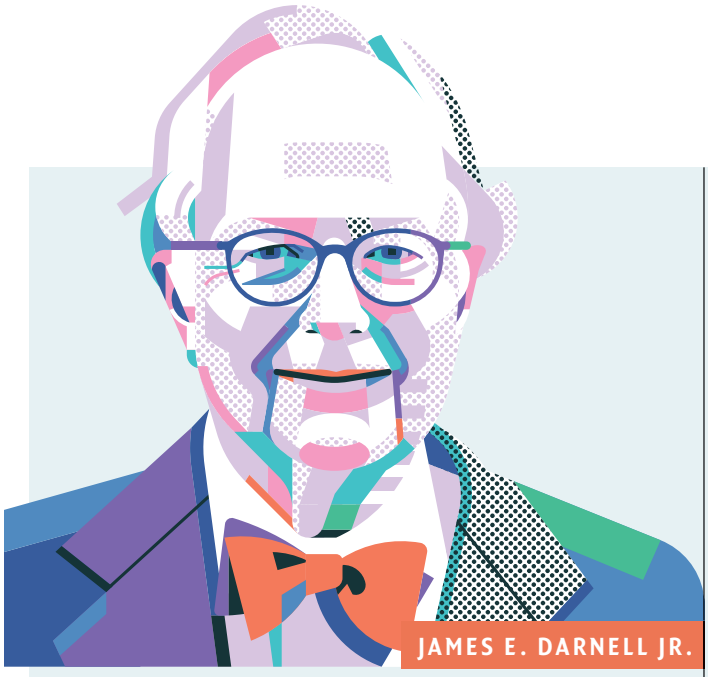
ROBERT G. ROEDER

As a boy, Robert Roeder enjoyed taking apart clocks and putting them back together to see how they worked. As a scientist, he became enamored of the idea of doing the same thing with cells.

Specifically, Roeder wanted to unpack the mechanisms that drive transcription in animal cells—in particular, RNA polymerase (RNAP), an enzyme that orchestrates the intricate process of gene activation and repression by binding and unwinding DNA.

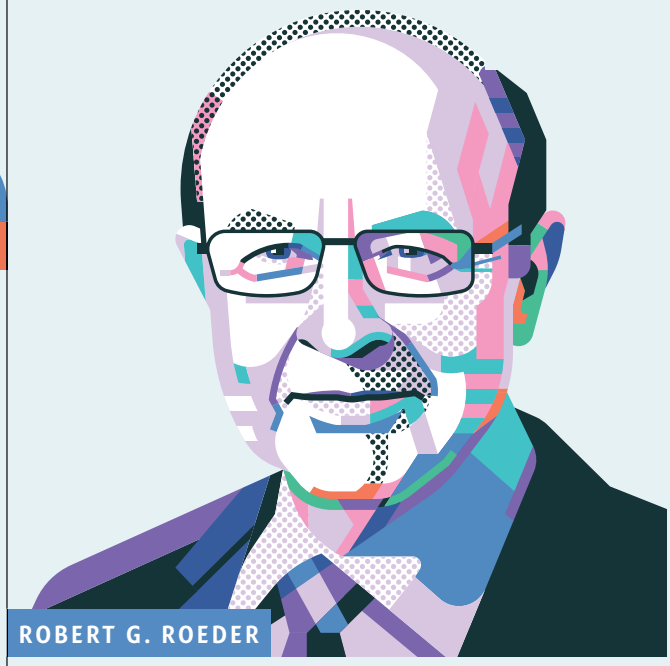
"I was fascinated by how RNAP initiates the decoding of each cell's DNA blueprint," he says. "Understanding how and when the cell reads DNA—I couldn't think of anything more essential to study."

While still a graduate student in the late 1960s, Roeder discovered that transcription in animal cells involves not just one RNAP but three, contributing fundamentally new insights into gene expression and paving the way for subsequent research into gene regulation and heredity itself. Building upon this work, Roeder was the first to elucidate the general functions and complex structures of the RNAP trio, known as RNAPs I, II, and III. He ultimately found that each of these three enzymes performs a distinct function in the synthesis of three major classes of RNA that are collectively necessary for protein production: RNAP I is central to ribosomal RNA, RNAP II to messenger RNA, and RNAP III to transfer RNA. He also discovered the first of some 1,600 gene-specific transcriptional activators responsible for regulating cell-specific gene expression programs in animal cells.



JAMES E. DARNELL JR.

"No one had ever successfully removed all of the RNA from an animal cell intact. But I knew that I could do it."



ROBERT G. ROEDER

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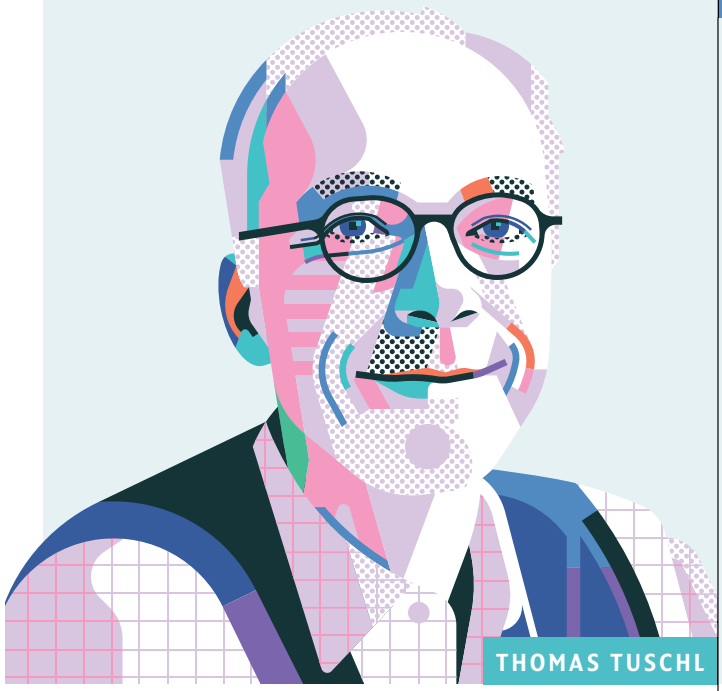


THOMAS TUSCHL

"Small RNAs play a complex role in maintaining genomic integrity and regulating gene expression."

A microtiter plate assay used by the Tuschl lab in drug screening to identify new antivirals.

At Rockefeller, Roeder, the head of the Laboratory of Biochemistry and Molecular Biology, determined that, in eukaryotes, each of these enzymes requires a distinct set of general accessory factors to kick off transcription, quite unlike their close cousins in bacteria. Notably, however, these general bits of cellular machinery are used differently by different cells, leading Roeder, who is also the *Arnold and Mabel Beckman Professor*, to suspect that RNAPs and accessory factors alone weren't enough. Deploying RNAPs for specific needs, he realized, must require not only gene-specific transcriptional activators but also a set of specialized coactivators.

He found this to be especially true of RNAP II, and he has applied this pivotal insight to the study of numerous biological processes. His work on fat cell development and differentiation, for instance, has shown how precise regulation of RNAP II is essential for maintaining metabolic balance and energy storage; he is also exploring how factors regulating RNAP II contribute to the process by which the body burns fat to generate heat. Both results offer new ways to think about managing obesity and metabolic disorders.

Roeder's research has also revealed that disruptions in RNAP II regulation may lie at the heart of immune disorders and blood cancers. "Understanding RNAP regulation is a powerful tool for addressing disease," Roeder says. –JK

THOMAS TUSCHL

When Thomas Tuschl began his career in the 1990s, the study of RNA was at a turning point.

Scientists were beginning to understand that RNA does more than just carry genetic instructions from DNA—it can also trigger and control reactions within cells. This discovery opened up new possibilities for using RNA in biotechnology and medicine. And one class of RNA, known as small RNA, showed unique potential. With it, scientists could start imagining a future in which precise RNA-based therapies lead to treatments for genetic disorders, cancer, and infections.

Of the many classes of genome-encoded RNAs, only small RNA is involved in turning genes on and off. Tuschl, who heads the Laboratory of RNA Molecular Biology, was instrumental in explaining how these regulatory RNAs work, and his insights have opened the door to RNA-based therapeutics for once-untreatable diseases by targeting the mechanisms that control gene expression.

Early on, for example, Tuschl proved that RNA interference (RNAi), the process by which small RNAs suppress gene expression, operates in mammalian cells, making years of laboratory research on other organisms suddenly relevant to humans. But his pioneering achievements haven't stopped there.

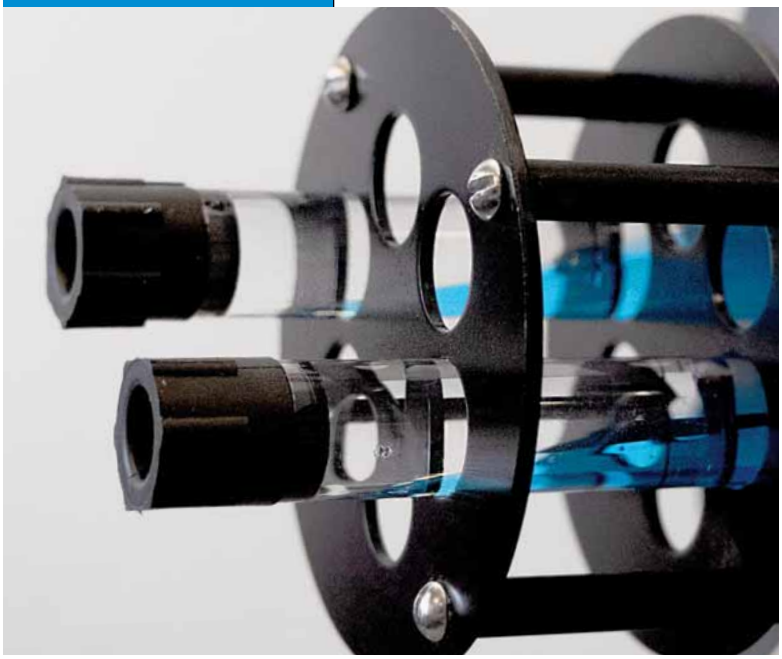
Tuschl was also the first to uncover the critical role of piwi-interacting RNAs (piRNAs) in preserving genome stability within the germ cells that give rise to sperm and eggs. He found that this type of small RNA acts as a kind of genomic guardian, silencing disruptive elements to ensure healthy germ cell development and

fertility. His work on microRNAs (miRNAs), meanwhile, revealed those molecules to be the master regulators of gene expression, binding to and destabilizing specific mRNA sequences to fine-tune gene activity.

Tuschl has channeled his numerous RNA-related discoveries into practical and life-saving applications. In addition to demonstrating that miRNA plays a central role in cancer, he has founded two pharmaceutical companies dedicated to developing drugs that modulate RNA to combat a range of genetic and autoimmune disorders, including lupus and Parkinson's disease.

"Small RNAs play a complex role in maintaining genomic integrity and regulating gene expression," says Tuschl, who is the *F. M. Al Akl, M.D. and Margaret Al Akl Professor*. "As a result, understanding them is crucial to developing certain new therapeutic strategies." –JK

Sucrose gradient mixer used as part of a method for confirming functional implications of Darnell's CLIP data.



ROBERT B. DARNELL

Robert Darnell never intended to join the family business.

Darnell's father and fellow Rockefeller researcher, James, helped launch the field; Robert had no intention of following in his footsteps. "When I got into science, the only thing I didn't want to work on was RNA," he says.

But when the younger Darnell dove into the study of neurodegeneration—presumably a safe distance from his father's legacy—"lo and behold, there it was." Through sheer serendipity, he discovered the proteins that regulate RNA metabolism in brain cells, illuminating how RNA helps drive brain function.

Prior to Darnell's discovery, whatever suspicions molecular biologists may have harbored about the role of RNA in the brain, technological limitations prevented serious study of the subject: No method existed to explore RNA and its binding proteins in detail.

Darnell changed all that. His groundbreaking CLIP technology allowed him to produce detailed, high-resolution maps of where specific proteins attached themselves to RNA molecules, revealing the intricate regulatory networks that control gene expression.

That work markedly advanced the study of how RNA and RNA-binding proteins contribute to brain cell function—and, in the case of neurological disorders, dysfunction. Darnell, who is the *Robert and Harriet Heilbrunn Professor* and head of the Laboratory of Molecular Neuro-oncology, ultimately discovered that disorders such as autism, epilepsy, and neurodegenerative diseases all have strong connections to these proteins, revealing how disruptions in RNA regulation can lead to significant changes in the brain and establishing a whole new paradigm for understanding and addressing neurological conditions.

Darnell's work on RNA and its associated proteins not only deepened our

SETH A. DARST

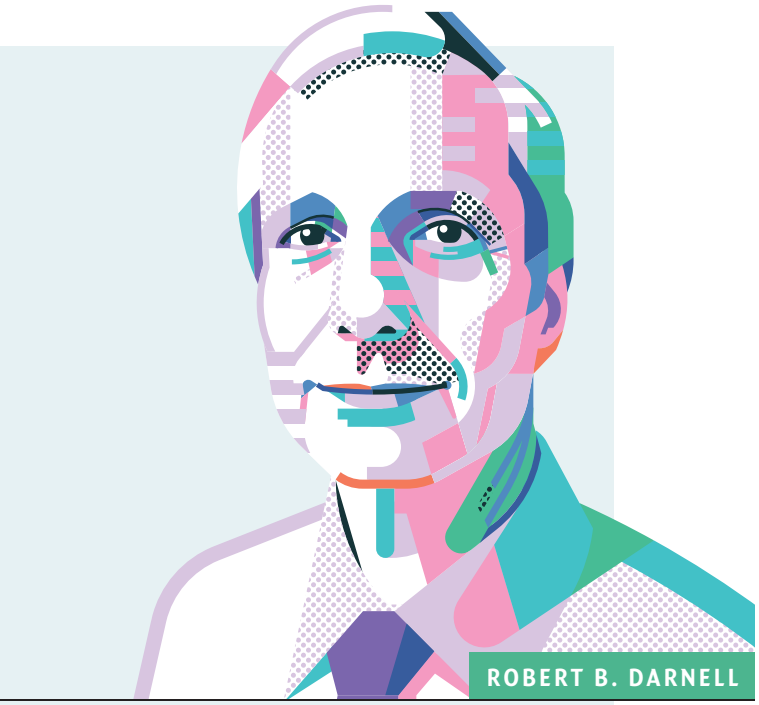
"Cryo-EM is revealing processes of the transcription cycle we've not yet seen, on timescales we've never achieved before.

LAMIA WAHBA

"We may get to a place where we sequence not only someone's genome but also their various epigenomes."

STEVE L. BONILLA

"Because RNA is involved in essentially every aspect of gene expression, it's also involved in every aspect of disease."



"There's a lot of hype around RNA. And I'm on the high end of the hype."

understanding of disease but also suggested entirely new treatments. For example, the insights that Darnell and his colleagues have gleaned into how RNA-binding proteins regulate neuronal gene expression and stress responses are paving the way for innovative therapies designed to slow or even halt the progress of Parkinson's disease. And their investigations into the role that RNA-binding proteins play in regulating immune responses have led to new therapeutic targets for rheumatoid arthritis.

It's an RNA-heavy docket for someone who once balked at studying the molecule at all. But Darnell has no qualms about where he wound up.

"There's a lot of hype around RNA," Darnell says. "And I'm on the high end of the hype." –JK

SETH A. DARST

Every cell on earth transforms its genetic code into marching orders through a precise three-step transcription cycle. Key to this process is RNA polymerase (RNAP), a hefty enzyme that builds RNA molecules from strands of DNA. Stopping RNAP in its tracks is a surefire way to interrupt the cycle; several antibacterials and antivirals work in just this way.

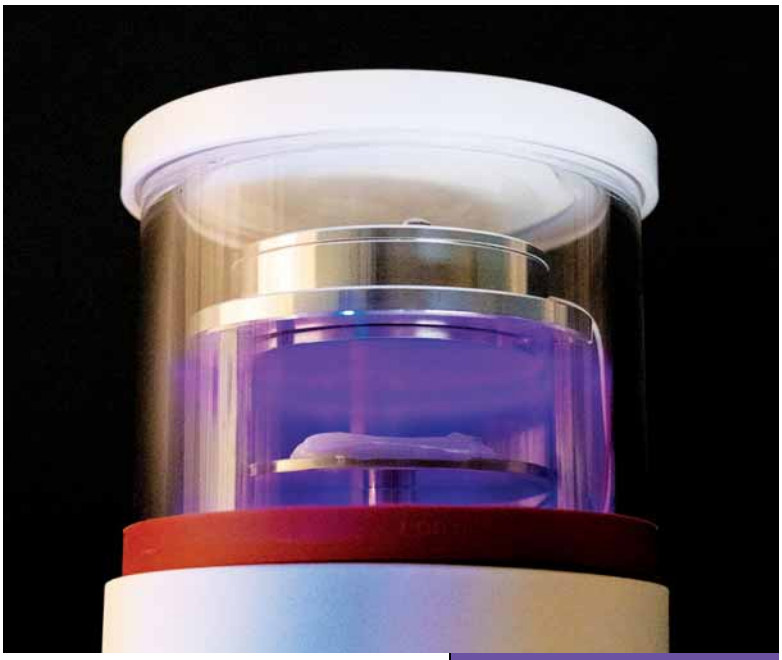
And yet well into the 1990s, the interior makeup of the RNAP used by bacteria remained a mystery. When viewed through a transmission electron microscope, it looked so much like a blurry smear that Seth Darst and his fellow structural biologists called their work "blobology." They eventually produced mildly sharper images they called Pac-Mans—"a cool nickname, but hardly informative in terms of molecular mechanisms," says Darst. But if they wanted to find fresh targets for new antibiotics—desperately needed in the face of growing antimicrobial resistance—they needed to reveal its inner structures.

In 1999, Darst, Rockefeller's *Jack Fishman Professor* and head of the Laboratory of Molecular Biophysics, captured the first high-resolution images of a bacterial RNAP structure. Since then, he's pursued a complete understanding of RNAP's structures, biochemical interactions, and regulators as it performs its role in the transcription cycle. Despite cryo-EM making their view of RNAP exponentially sharper than in the days of blobs and Pac-Mans, "there's so much we still don't understand about the chemical steps RNAP goes through as it adds one nucleotide at a time to an RNA chain. We also don't understand the likely hundreds of transcription factors that regulate the cycle."

His lab's insights into polymerase structures have revealed how rifampicin, a key component of tuberculosis therapy, works. During the COVID pandemic, his group, working with Elizabeth Campbell,

who now heads the Laboratory of Molecular Pathogenesis as the *Corinne P. Greenberg Women & Science Professor*, illuminated unknown characteristics of SARS-CoV-2 by creating an atomic-level resolution view of its replication system, and provided key evidence explaining how the antiviral remdesivir can work. Darst continues to sharpen the view of RNAP's inner workings. His lab is collaborating with researchers at Rockefeller and at the New York Structural Biology Center to build the next generation of tech: a time-resolved cryo-EM machine that takes RNA polymerase and DNA, mixes them together on a cryo-EM grid, and then freezes the stew in just 100 milliseconds.

"That can show us processes of the transcription cycle that we've never seen, on timescales we've never achieved before," he says. –JP



The Darst and Bonilla labs utilize glow discharge systems to prepare samples for advanced structural imaging.

STEVE L. BONILLA

RNA molecules are commonly depicted as squiggly lines, but they operate more like Swiss Army knives—multipurpose tools with complex structures and hidden features deployed only when needed. Like the proteins they help construct, these polymers fold into dynamically shifting 3D structures whose forms dictate their widely varying functions, including catalyzing chemical reactions and regulating gene expression.

But unlike proteins, the structural components of RNA molecules are little understood. Without deeper knowledge of these forms, we lack the ability to exploit these structures therapeutically.

"Because RNA is involved in essentially every aspect of gene expression, it's also involved in every aspect of disease," says structural biologist Steve Bonilla, who is at the forefront of efforts to identify its structures and the microscopic forces that mold them into shape. "If you can design small molecules or drugs that bind to a specific RNA 3D structure and somehow alter its shape or function, then it becomes a potential drug target for whatever process that particular RNA is involved in."

For Bonilla, that could translate into new ways of combating infectious disease. His lab studies how 3D structures encoded in the genomes of positive-stranded RNA viruses such as dengue, Zika, and West Nile play a role in the recognition—and hijacking—of the host cell's biochemical machinery. Blocking viral RNA from adopting the shape needed to commandeer the machinery might lead to new antivirals.

But it's a long and winding road between our current understanding and the ability to develop those drugs. Part of what makes pinning down RNA structures such a challenge is that they are constantly changing. "RNA does not behave like a static object. Instead, it behaves like an ensemble of objects moving in concert with one another," he says.

Bonilla, who heads the Laboratory of RNA Structural Biology and Biophysics, was one of the earliest researchers to use single-particle cryo-EM to capture the molecular choreography of small RNA 3D structures in viral genomes. Currently, he's freeze-framing additional dynamic ensembles critical to their replication. He hopes stringing together these snapshots could eventually help devise strategies for disrupting viral life cycles.

That's crucial, because while there are already thousands of RNA structures that need to be visualized, Bonilla believes many more await discovery. "There are many noncoding RNAs that we know

exist, but we just haven't figured out what their functions are," he notes. "Once we know what form they take, we can begin to identify functions that are yet unknown." –JP

LAMIA WAHBA

We know that genetic information is encoded in DNA and passed down to offspring. Changes, both adaptive and random, appear over time, morphing the species.

But scientists know DNA doesn't explain everything. Lamia Wahba is one of them. As head of the Laboratory of Non-Canonical Modes of Inheritance, she studies alternate mechanisms for passing down biological information. RNAs of all kinds are increasingly being seen here as key players.

Her early research homed in on a small class of non-coding RNA molecules called piRNAs. "They have a very well-established role in maintaining genome stability by tamping down elements that might otherwise repeat uncontrollably, leading to disease," she says. Through this work she discovered a new mode of nongenetic inheritance in roundworms, in which small RNAs that can silence specific genes are passed down.

But much remains unknown about these functions of small RNAs. How is the process regulated across generations? What promotes it, what limits it, and what are the long-term implications?

These mechanisms can put evolution on a fast track, with dramatic changes appearing in a short period of time and immediately handed down to descendants, Wahba says. "This can crop up in microbial drug resistance and mutation-driven diseases, so understanding more about these mechanisms could help us find ways to counter their effects," she notes.

Wahba's research could help explain why so few genetic diseases have a definitive origin. "There are some diseases where the relationship is really one-to-one: If you have this mutation, you get this disease and can potentially pass it down to your children," she says. "But for most, the relationship is much weaker, with a known link identified only about 20 percent of the time." As for that missing 80 percent, Wahba suspects some of the culprits to be proteins, epigenetic chromatin marks, and foremostly RNAs.

Her findings may also improve CRISPR, the most promising gene-editing tool discovered to date. She's identified a gene essential to the formation of three-stranded tangles called RNA:DNA hybrids, whose mixed nature makes them useful guides. "Boosting this gene's output might increase CRISPR's efficiency by helping the tool bind better to the target site," she says.

Expanding our knowledge of these profound nuances of inheritance will lead us toward more precision in medicine, she believes. "We may get to a place where we sequence not only someone's genome but also their various epigenomes, and that information collectively will give a much better predictability of their likelihood for certain diseases, and how we might be able to intervene," Wahba says. "To me, that's the next wave." –JP

Crayola modeling clay is ideal for holding custom needles designed by the Wahba lab for gene editing experiments on one-mm-long nematodes.

Mahsa Shirani (left), a postdoc, with Skye Ryan, a fibrolamellar hepatocellular carcinoma (FLC) patient who joined the Simon lab in 2024 and is currently working on a project utilizing CRISPR-Cas9 to search for mechanisms that allow FLC to develop unchecked.

LAB

By Bethany Brookshire

Photography by Roshni Khatri


PARTNERS

At 18, Willow Pickard was an open-hearted, artistic soul.

Willow Pickard at 21, working in Simon's lab.

COURTESY OF SIMON LAB

She loved drawing and painting, and jam bands like Phish. The slender girl in a tie-dyed t-shirt—with a mop of curls just like her mother's—befriended everyone, especially those who needed it most. "The word 'protective' comes to mind," says Julie Newcomb, Willow's mother, a medical coding analyst based in Livonia, New York. "People that would get bullied or picked on, or people that are a little bit different… she would sort of put her wing around them."

For years, Willow had been plagued by strange symptoms. Abdominal bloating, strange feelings of fullness, stomach discomfort. "The symptoms were so vague, that's part of the problem," Newcomb says. Blood work showed nothing, the doctors could feel nothing. Clinicians blamed hormones or anxiety. "Who the heck isn't anxious in this day and age?"

The symptoms persisted, but doctors followed protocol and nobody suggested imaging. By the time there was imaging, Willow was 18 and had just started her first year at a community college in Rochester, New York. She had a boyfriend and had started art classes. Now, she also had a diagnosis: Stage IV fibrolamellar hepatocellular carcinoma, sometimes shortened to "FLC," or just "fibrolamellar."

Fibrolamellar is not like most other cancers. It is incredibly rare, diagnosed in one out of every five million people. It is a liver cancer that erupts in people who are seemingly healthy. They are also young—most patients are between 11 and 25. In the United States, only a few hundred people are living with it. By the time of Willow's diagnosis, she already had FLC tumors elsewhere in her body.

Doctors tried multiple surgeries. They tried chemotherapy. Willow got a part-time job at a juice bar and began thinking deeply about wellness. "She was on the computer a lot, researching her diagnosis and some treatment options," Newcomb says. In the process, she came across the work of Sanford M. "Sandy" Simon, a cellular biologist and biophysicist at Rockefeller. Simon's lab has focused on FLC since 2009. But it isn't just the focus on such a rare disease that distinguishes his lab. It also operates in a unique way: Simon makes a point of welcoming FLC patients into his lab, whether they want to just visit or pick up a pipette themselves.

Willow visited the lab, participated briefly in research, and donated blood and tissue from her surgeries to Simon's work. She passed away in 2018 at the age of 21. But meeting patients like Willow "makes you realize your research isn't just a job," says Mahsa Shirani, a postdoctoral researcher in the lab. "You want to do something important, because you see the application." The sense of urgency, she says, is palpable.

In turn, the lab's distinctive approach to research collaborations has resulted in a stunning run of discoveries—leading to new avenues for treatment and clinical trials. When Simon began his research into fibrolamellar, the disease was a black box. Ten years later, his team has already found the specific mutation that causes the cancer and has identified promising drug candidates to shrink tumors and attack the mutated molecule that causes it. Moreover, they are finding that their deep study of one rare cancer is generating insights that could advance understanding and treatments for others.

DOGGED PURSUIT OF KNOWLEDGE

Before 2009, Simon's Laboratory of Cellular Biophysics had been focused on basic cell biology. With training in cell biology and biophysics, Simon, who is Rockefeller's *Günter Blobel Professor*, was interested in how proteins in a cell move from one location to another. He also was curious about how viruses assemble, studying diseases such as HIV and Ebola.

Ten years ago, this cancer was a black box. The past decade has seen a stunning run of discoveries.

All that changed when his daughter Elana was diagnosed with FLC in 2008. The cancer had no recommended therapies. It was rare—any university or hospital had only a few cases and little information about them. One of the few published studies had survival at five years close to zero.

After the removal of her FLC mass in 2008, Elana has remained cancer-free. But Simon found himself dismayed by just how little was known about FLC. He began to pivot the focus of his lab—starting with Elana, who worked in the lab through high school—and helped discover a DNA mutation common to every studied case of FLC. Simon's team never looked back.

"I think [Simon] really made the major contribution to the understanding of the disease in the last 20 years," says Michael LaQuaglia, a pediatric surgical oncologist and collaborator of Simon's at Memorial Sloan Kettering Cancer Center.

The DNA mutation that Elana helped reveal is one of several breakthroughs. It's a joining of two genes. The genes usually lie next to each other. The first, *DNAJB1*, contains the code for part of a heat-shock protein that responds to cell stress. The second codes for part of the enzyme protein kinase A—a critically important protein that helps control the actions of other proteins in the cell.

In FLC tumor cells, however, the genes don't lie next to each other. The gap between them has been deleted, and the two get transcribed and translated into a protein conglomeration—a chimera. The lab has since shown that the mutation is spontaneous, not something that can be inherited.

This sudden cellular chimera can kickstart tumors. So one angle Simon's lab is pursuing is to attack the rogue protein itself using something called a PROTAC—a proteolysis targeting chimera, or molecule that will grab the rogue proteins and label them as cellular trash. Another method is using specialized RNAs to silence the RNA that makes the bad protein.

Both of those research pathways have been successful, but Simon wanted something faster—an already approved drug that doctors could add to their toolkit now, instead of waiting years for clinical trials and approval. Instead of assuming their own scientific genius would find a new compound, he says, why not "just screen every drug that's ever been safety tested for any condition?" The lab went on to screen roughly 7,000 drugs—and found a few that shrank FLC tumors. A combination of one of those drugs and one PROTAC is currently moving toward a clinical trial.

Every patient that passes through the doors of the Simon lab affects the researchers there.

PATIENTS AND PERSISTENCE

Rare cancers are especially hard to study; with few patients, there's little information, and very few samples are available to learn more. That was, in part, why Simon and his wife, Rachael Migler, started the Fibroregistry. The patient-community-based group's goal is to bring science to the patients,

After his daughter's diagnosis more than a decade ago, Simon pivoted his group's research to FLC.

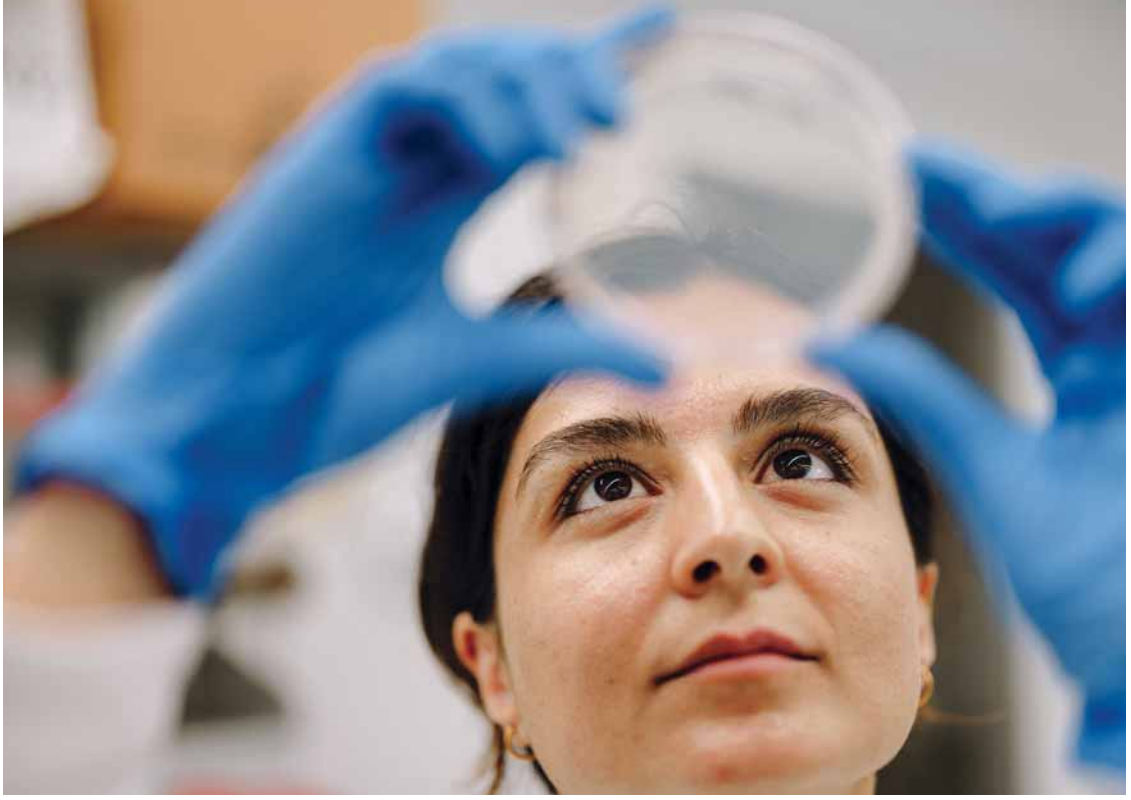
and the patients to the scientists. If specific institutions didn't want to share their data, patients could do it on their own. Information on their history and outcomes could be shared across institutions and even countries. Since it was being run by the patient community, the registry could stay in touch with patients long after they left the hospital or finished a clinical trial. Currently, about 250 patients have completed the questionnaire to join the registry. It's not a light lift. "There are several hundred questions," Migler says. The questions can seem utterly random, each trying to pull out any tiny piece of information that might be valuable. Was the patient bitten by an animal at any point? Was it a squirrel? A monkey? Does the patient have pierced ears? Wounds on their feet? "It is basically our attempt to find the needle in the haystack."

The results have been invaluable for both patients and clinicians. Now, scientists and patients have learned that if caught early enough, tumors can be taken out with surgery, or a patient may receive a liver transplant. These patients have a 44 to 68 percent chance of surviving for another five years. However, if surgery isn't an option, or if the tumors have spread to too many other parts of the body, survival after five years drops to two to 17 percent. And while chemotherapy can help in other cancers, the registry has shown that for FLC, most chemotherapy has no effect or actually reduces chances of survival.

The registry, doctors, Facebook groups, and internet searches all lead patients to Simon's lab. He receives four to five emails per week from patients and their families. He replies to each, answering questions, sharing papers, and offering what comfort he can. In turn, contributions of information to the Fibroregistry—whether information or patient tissue—have resulted in four research publications on the disease. The studies explore topics ranging from which patients have better odds of survival, to creating organoids from patient cells to better study the cancer, to the clinical outcomes of treatments like immune inhibitors.

The lab is always looking for new angles on the disease. Jeannie Carreiro, a first-year bioscience graduate student in Simon's lab, is hoping to use gene-editing techniques like CRISPR to determine what, exactly, allows FLC tumor cells to thrive. But any knowledge she obtains, she notes, is worth it: "We know from our past successes that any detail matters; any detail can help."

These details could be critical to more than FLC. For instance, tumor-suppressor genes were originally found in retinoblastoma, a cancer just as rare as FLC. Mutations in those tumor-suppressor genes are now known to play important roles in breast cancer, colorectal cancer, prostate cancer, and more. The enzyme isocitrate dehydrogenase plays an important role in cell metabolism. Mutated forms of it were identified in a rare glioblastoma, but they have now been found in other cancers such as acute myeloid leukemia. By digging deep into FLC, Simon hopes that some of the findings could translate to other cancers—both rare and common. As part of that, his team has formed an international consortium of scientists, working together as part of the Cancer Grand Challenges program. The goal is to apply the Simon



Shirani (top); Ryan with colleague Jeannie Carreiro, a graduate student working with CRISPR-Cas9 (middle).

lab's approach of making PROTACs, or degraders, to other cancers, such as Ewing sarcoma, rhabdomyosarcoma, and neuroblastoma.

Sometimes, patients coming to visit the lab end up staying to work—weighing in on projects and conducting research, as their treatment schedules permit. Simon tries to treat them like every other lab member, while accommodating some of their medical needs—many of which are side effects of the chemotherapy drugs or surgical recovery.

That includes making sure patients get a full New York City experience. During one of Willow's visits, for example, Simon found out that the band Phish would be performing in Madison Square Garden. Because of her treatments at the time, however, a regular ticket would have been impossible for Willow. She had to be within 10 feet of a bathroom.

Simon, who used to play in a band, realized his old connections could be of use. "I said to my friends, 'Listen…I know there are these corporate suites, where they've got their own bathroom in them,'" he says. "'Do you know anybody who can get me two of those tickets?'"

He found a suite; Willow got her Phish show.

Simon hopes some of the findings could translate to other cancers, both rare and common.

A RARE CANCER, A RARE LAB

Simon's spacious, airy lab is right on the water and has stunning views of the East River from every desk. But lab members don't spend much time staring out the window. They are planning experiments, conducting research, and analyzing data. Occasionally, when a new patient's donated tissue comes in from a surgery, the lab is all hands on deck, processing precious samples as fast as possible. Shirani has, like other lab members, on occasion, curled up for a refresher nap in the dark, quiet patient records room. Like all members of the lab, she knows that fibrolamellar patients are relying on her. Not on scientists in general, but on them specifically.

Shirani came to Simon's lab after doing her graduate work with Barbara Lyons, a chemist at New Mexico State University in Las Cruces. Lyons's lab had focused on breast cancer. In 2015, her son, Jackson Clark, then 20, was diagnosed with FLC. A devoted chemist like his mother, Jackson went on to pursue a master's degree in chemistry at Cornell University in Ithaca, New York, in between his surgeries and treatments. He also spent a summer in Simon's lab, working on the chimeric protein that causes the disease. His work contributed to a 2023 paper showing that fibrolamellar tumor cells behave differently compared to normal liver cells—they produce much larger amounts of ammonia. FLC patients frequently die from the effects of ammonia buildup in the brain; the paper explains why conventional therapies have not worked, and what might. Jackson's lab work could one day help prevent these deaths.

Jackson passed away in 2020. His mother, Shirani, and Simon are still publishing together, investigating how the fusion gene so key to FLC leads to tumor development, and identifying new immunological targets for potential treatment.

Like Willow, Jackson contributed tissue, blood, and more to Simon's efforts. Shirani knew him well, and one day she found herself working with his cells. "I remember I was imaging Jackson's sample at some point," she says. "And [Lyons] was in the lab. And we were just looking at the picture." She wanted to tell Lyons that they were Jackson's cells. She could not make the words come out.

The presence of patients also encourages lab members to work together, not in competition with each other. Lab culture at some institutions can get very competitive, says Jaelyn Vigee, a first-year graduate student in cancer immunology. "We don't have that. I feel like we're all just very much trying to work together," she says.

Michael Ortiz, a pediatric hematologist-oncologist and collaborator of Simon's at Sloan Kettering, sees other ways such a close connection to the project impacts the science. For instance, calling a new drug the "most effective treatment yet" for treating a cancer might not be wrong. But it might also leave patients with false hope of a cure. The new drug might stop the cancer from growing, or slow it for a while, and then it might grow again. Saying it that way "is less exciting, but is more honest and comprehensive," Ortiz notes. "My impression is that having someone in the lab with that very cancer helps to ensure more nuanced kinds of claims are made."

But the success of these collaborations is attributable to Simon himself, a person who is driven, but also kind, say colleagues. "Sandy is unique," notes Lyons.

Newcomb would agree. Willow has been gone for seven years now, but Newcomb still receives notes from Simon when he publishes new studies on FLC. "It gives me chills," she says, "because she's part of these findings." ◎

Increasingly, pharmaceutical and biotechnology companies are looking to academia to find their next big medical breakthrough.

Industry players

By Joshua A. Krisch

All scientists are driven by curiosity, and biomedical researchers are no exception to that rule. But pursuing basic science doesn't just mean unpacking nature's mysteries: It frequently results in scientific discoveries that lead to new medical treatments to relieve suffering and save lives.

For instance, some recent studies have estimated that more than 25 percent of new medications coming to market originated in academia, with public sector contributions rising rapidly over the past decade. Whether looking for the next novel antibiotic or a first-in-class gene therapy, industry has come to keep a close eye on research from the public sector. Yet, that path from bench to bedside remains long and winding. Success requires time, money, and the cooperation of many disparate groups, from researchers and investors to pharmaceutical and biotechnology companies. At the earliest stages, however, it often falls to the institution itself to spot the potential. Without internal support building the case for commercialization, promising scientific research may never get the wider exposure it deserves.

"If that happens, the public misses out on findings that would make life better," says Jeanne Farrell, associate vice president overseeing the Office of Technology Transfer at The Rockefeller University.

Farrell is one of several individuals fostering the bridge between academia and industry at Rockefeller. With the ultimate goal of helping academic discoveries become products with tangible societal benefits, this team lays critical groundwork to pave the way for commercialization, by working closely with inventors on the filing of patents, coaching scientists as they frame their ideas for investors, and partnering with researchers to think through all the myriad possibilities. In streamlining the larger translational pipeline and leveraging Rockefeller's considerable resources—from internal funding sources to an on-site startup incubator—Farrell and her colleagues are "looking to light that spark which will create an opportunity."

We explored what it takes to create that kind of vibrant entrepreneurial ecosystem in a roundtable conversation with Farrell and her colleagues Bruce Conway and Carlo Yuvienco. Farrell's team looks for ways to create commercial opportunities for discoveries made at the university, from partnerships to new businesses.

Illustration by Michael Kirkham

Conway is the founding director of the Black Family Therapeutic Development Fund at Rockefeller (formerly the Robertson Therapeutic Development Fund), where he draws on his background in the pharmaceutical industry and the startup world to create internal de-risking funding opportunities and provide mentorship for researchers looking to best position their work for advancement outside of the university. Yuvienco is the director of the Ford Center Incubator at Rockefeller, where he brings in promising early-stage life science companies spinning out of Rockefeller labs and beyond.

First things first: What are the raw ingredients needed to create a fertile environment for commercialization?

CY: For any kind of economic development, you need three factors: capital, resources (meaning a physical infrastructure that makes discovery convenient), and people. But you also need that X factor: inspiration. The three of us come at this from different angles: I'm working to create a new kind of space on campus, one that supports startups during that tenuous moment when they transition from an academic environment to the marketplace. I used to work for the City of New York under the de Blasio administration, serving as deputy director of life sciences at the NYC Economic Development Corporation. We studied what elements were common across the most effective incubators, and proximity to academic institutions turned out to be paramount. Yet before we launched earlier this year, there were no incubators focused on biomedical science on Manhattan's Upper East Side, despite the incredible concentration of top biomedical institutions.

JF: A lot goes into setting the stage. Externally, you have to develop strong relationships with companies and investors, and internally you have to really know your scientists and their science. Only then can you build the story and the strategy that help bridge those two worlds. You also need a team that's flexible, creative, and nimble—these projects can take years to develop, with a lot of pivoting along the way. Having leadership that appreciates how bringing products to market aligns with the institution's mission has allowed us the latitude to do that.

BC: The funding piece is huge here. Look at any number of startup companies or IP licensing deals that made it to market, and you'll see a huge reason their technology advanced was because the group had access to directed funding. We recognized that, and so in recent years, we found ways to fund great research that wouldn't necessarily be considered fundable using traditional mechanisms, such as through the NIH or NSF. Traditional funding also has a big lag time between being awarded the money and receiving it. We've turned that cycle upside down. The system we have in place can fund promising projects just weeks after a researcher's proposal is approved. That keeps the momentum going.

Investors and other industry players aren't always good at seeing the therapeutic significance of basic research. And not all scientists are born entrepreneurs. How do you help both parties recognize real-world applications?

JF: Rockefeller is focused on important scientific questions in the context of academia, but often discoveries from that kind of research lend themselves to the creation of new chemical entities, biologics, devices, research tools, and other enabling technologies that have application in the commercial world. We do whatever we can to protect the integrity of the science while clearing the hurdles to commercialization. One main focus of my team is promoting and giving visibility to work that might otherwise not get enough attention from investors and industry players. Once we see that potential and visualize what the application could be, in collaboration with

"A lot goes into setting the stage. Externally, you have to develop strong relationships with companies and investors, and internally you have to really know your scientists and their science."

Yuvienco (left), Farrell, and Conway use complementary strategies to find paths to commercialization.

Photography by Chris Taggart

our scientists, we look for good industry partners. Sometimes established pharma companies see the discovery as not mature enough to go straight into their development pipeline, and so creating a startup company may be the best way to advance it. That's where the partnership with our scientist inventors comes into play. Starting a company is a long, difficult road that isn't for everyone. We aren't asking our scientists to be entrepreneurs, but just to be open to that road as a way to move a discovery further.

BC: A lot of my focus has been on helping researchers hone their pitches—put simply, helping them learn to speak the same language as investors. How someone talks about their proposed research project is so important. And it pays off not just when it comes to securing funding in those individual instances. I've seen how transformative this has been on a larger scale. When our academics learn to communicate in this way, industry has really taken notice. These conversations are a big reason why there is this growing network of external experts in commercialization who are excited about what the university is doing.

I also work with researchers to conduct the kinds of experiments—generating the specific kinds of data—that a pharmaceutical company needs to recognize a wise investment. My team has been doing this for over a decade now. Rockefeller was one of the first institutions to step in and say, when we see a promising therapeutic target, we'll do this kind of extra R&D to expedite it.

Entrepreneurship is often seen as a numbers game—we own this many patents, our labs have spun out this many companies, and so on. But focusing on those stats can obscure the actual level of impact. How many of those companies are viable? How many of those patents led to viable products? Knowing that, how do you focus on creating a translational culture that generates real, lasting benefits?

BC: Our university's global ranking in high-impact citations regularly outranks larger scientific institutions such as Harvard, Stanford, and MIT. Across the board, the emphasis at Rockefeller is quality, not quantity. We think about patents in the same way; we're not interested in just filing as many as we can. We want to maintain that quality in the translational work we do in-house, which means being selective about the projects we work on.

CY: Likewise, we aren't afraid to challenge incubator applicants and ask whether their business proposal is really the best shot at solving an unmet need. One of the things that attracted me to Rockefeller is the focus on creating stronger, better companies, not just a high volume of patents. In turn, investors will know that companies coming out of here are better positioned to succeed in the market.

JF: Just starting more companies than the year before or having more patents granted than the year before doesn't say a lot about progress or quality, so it's important to understand what you're measuring when you're looking at metrics for success. We think of success in highly individualized terms. Sometimes that means filing a patent alongside publication, which helps create an incentive structure for companies to then invest time and money in developing the potential product. Sometimes there isn't a role for what our office does, and the best way to get the discovery implemented is through a great publication. Every instance is different and has to be thought through carefully. We operate under the philosophy that, since we're often at the cutting edge of new fields that don't yet have any reference point or clear path for commercialization, we have to be bold and willing to take a smart risk on a new idea.

"Every project is different and has to be thought through carefully. We have to be bold and willing to take a smart risk on a new idea."

Can you talk about some of your favorite recent success stories?

JF: In 2023, my team hosted an invitation-only Startup Summit specifically for Rockefeller startup companies that were still in the conceptual stage, but far enough along to be ready to seek management and funding. We wanted to help them keep up their momentum by connecting them with investors at that crucial juncture. One of the eight companies pitching that day received backing less than three months later from an investor we'd brought to the summit. Similarly, we were also proud to nominate another startup company for a pitch day at Alexandria Real Estate Investments, a major venture capital firm, the same year. Our company won, and they got a rent-free year in their laboratory space as just one of their prizes. It's notable that this company's technology was initially funded with several awards from the therapeutic development fund—showing how all of these pieces work hand in hand.

CY: We've got a lot of exciting things happening at the incubator right now—I'm just not allowed to talk about them publicly yet, due to confidentiality agreements. Broadly speaking, I will say something interesting I've seen is how much more active investors are today than they were 10 to 20 years ago, in terms of funding and establishing companies in NYC. That's been exciting to watch, and it's interesting to think about how we can contribute to that momentum.

There are lots of moving parts here, some more esoteric, some very practical, from seeing promising ideas to imagining the applications and connecting with investors and licensing opportunities. How do you juggle that?

BC: We work together closely. The Office of Technology Transfer is the eyes and ears for the rest of us. I'll attend Jeanne's staff meetings to keep abreast of new developments, and we bring her team in when we're reviewing a proposal, to help them understand what investors might have to say about a project in progress. I also lean on Carlo's expertise for several projects, and Carlo will often invite me over to meet with investors who are involved in the incubator.

CY: It's no wonder that most biotech startups—like most startups in general—fail. How does one increase the odds of success? Jeanne, Bruce, and I all contribute our expertise in different ways. This is why it's been essential to have them participate in the incubator's selection process, providing complementary insights from the numerous angles from which startup opportunities must be assessed.

JF: As you can see, there's a lot of cross-talk here. My team in the tech transfer office tries to engage before there's an invention to speak of, by learning about the research in a lab and getting connected to the researchers.

A big part of our job is establishing credibility with the investigators. Sometimes we're the first people outside of the lab to see new data. That can be a very special moment, but nobody is going to share that moment with us unless they first trust us and understand how my team plays a role in creating an early and implementable strategy around potential commercialization.

When there is something that can benefit the public good coming out of this research, we all have an interest in doing our best to make that happen. In serving as a liaison between academic science and industry, we're most effective when we work in collaboration with our researchers; after all, they know their research best. I always say to them, just come talk to us—early and often. ◎

1,000+ channels

The mass spectrometer was invented in 1912 by English scientist J.J. Thomson (famed discoverer of the electron). Ever since, it's been a lab standard, the go-to tool for deducing the chemical composition of scientific samples.

The problem is, as it became more sophisticated, it also became more cumbersome. "Instead of doing everything simultaneously, as early machines could when the whole process was simpler, each step must now be completed one after another," says Brian T. Chait, Rockefeller's *Camille and Henry Dreyfus Professor* and head of the Laboratory of Mass Spectrometry and Gaseous Ion Chemistry. Thus: First the mass spec ionizes a sample; then it determines that sample's mass-to-charge ratio; finally it measures the outcome. This costs scientists precious time, because each run through the apparatus accommodates only a minuscule fraction of a given sample, which are often precious commodities, like donated cancer cells. "Mathematically, it's the equivalent of trawling Niagara Falls, looking for rare species of a teeny fish with a tiny bucket."

So, Chait and Andrew Krutchinsky, a senior research associate in Chait's lab, developed a tool that reintroduces the concept of parallel analysis, potentially increasing the mass spec's processing capacity 1,000-fold. Rather than blasting samples through one at a time, their prototype—a cubic device hand soldered, assembled, and retrofitted by the duo—adds 1,000 channels for weighing and sorting molecules in parallel.

Chait and Krutchinsky can't wait to work faster. It took Chait and collaborator Michael P. Rout, Rockefeller's *George and Ruby DeStevens Professor*, 30 years to piece together a comprehensive, 3D model of the nuclear pore complex—a cellular gatekeeper that's implicated in diseases as diverse as cancer and Alzheimer's. "We needed an expediting tool, because we want to see more of how this pore behaves in action," says Chait. "Plus, there are thousands of other biomolecular machines we have yet to explore."

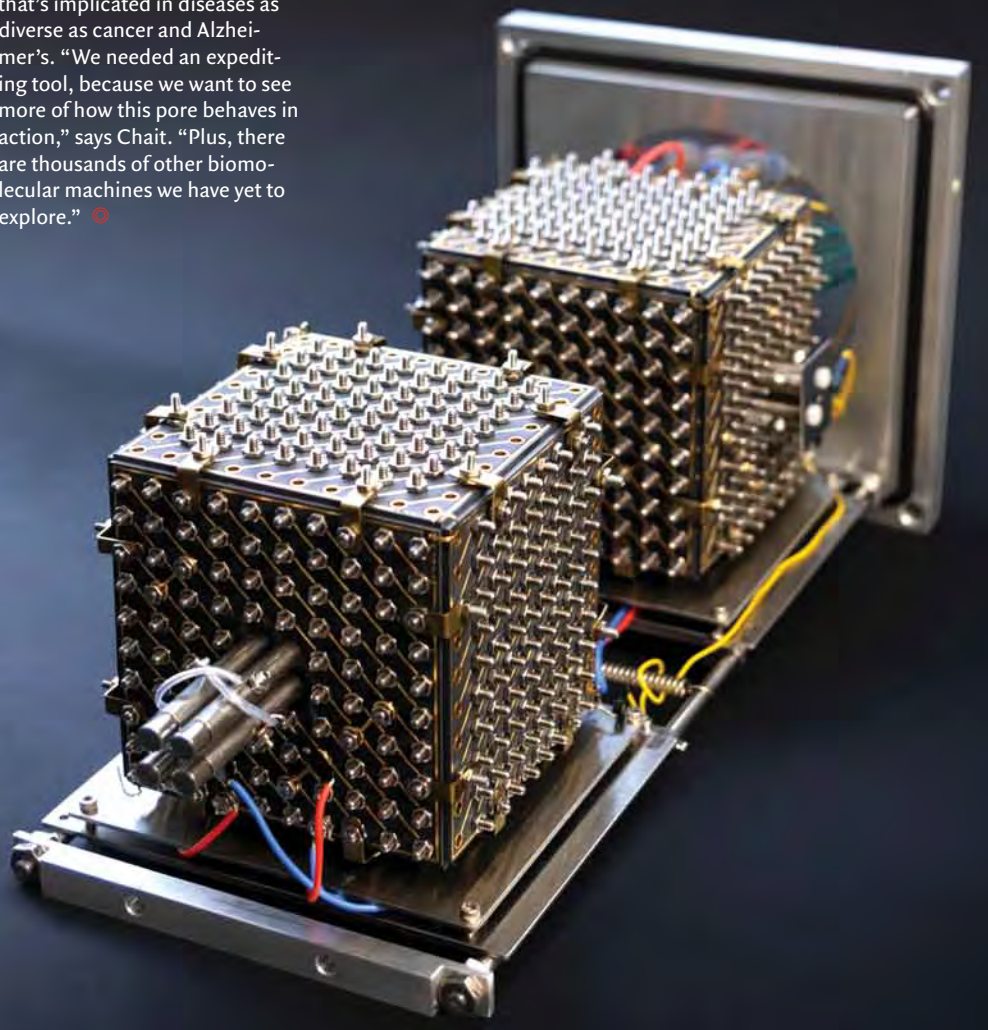


Photo by Lori Chertoff

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