ISSUE 13
SPRING 2026

Seek

THE ROCKEFELLER UNIVERSITY

Supercharging immunotherapy

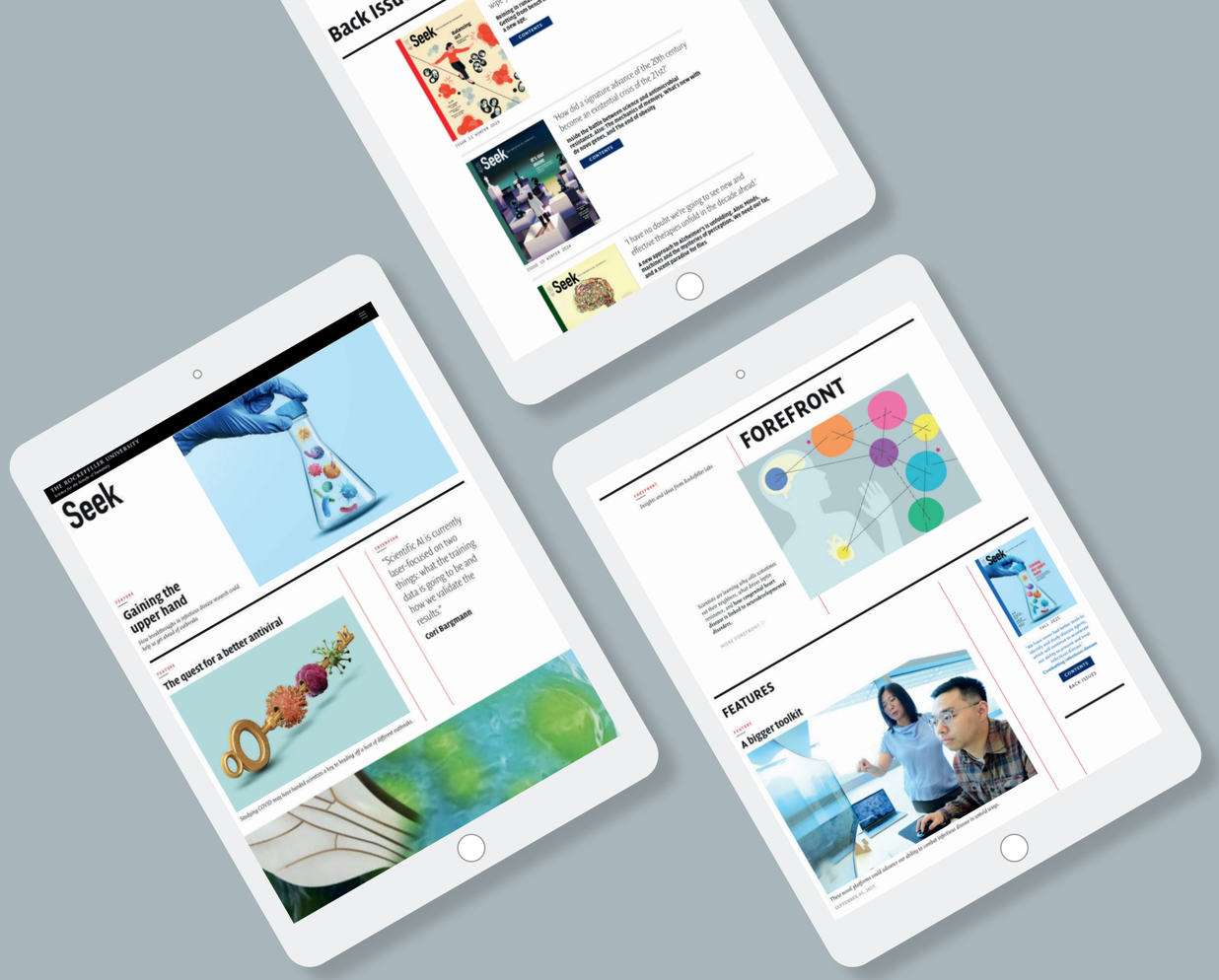
What we're learning about the immune system could transform how we treat cancer

ALSO

Deep dives into DNA

How does one brain understand another?

Building better vaccines



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CONTENTS

ISSUE 13 SPRING 2026

"We all want to convert more cancer patients into cancer survivors."

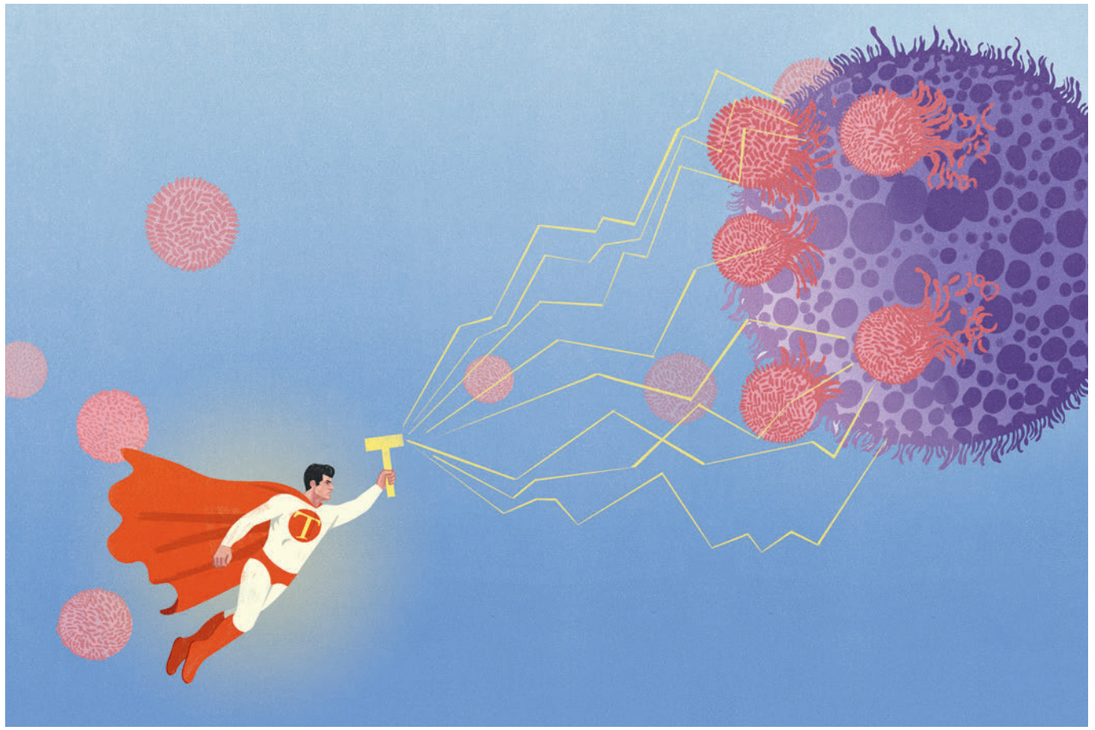
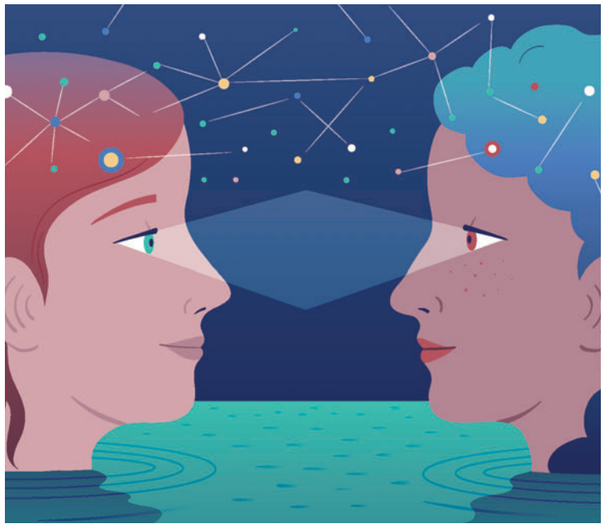


Illustration by Alessandro Gottardo



"Most sophisticated cognitive abilities probably evolved to support social interactions and social needs."

30
Secrets of the social brain

Probing the marvelous mystery of how brains are wired for communication and collaboration.

"Even partial deficiencies in these pathways can disrupt cell function and lead to disease."

40
The machinery of life

Scientists are studying the molecular machines that read, copy, repair, and package DNA. Their findings could impact how we prevent and treat a number of diseases.

Illustrations by Federica Bordoni; Petra Péterffy

16
Q&A

Neuroscientist Gaby Maimon wants to understand intelligence by studying one of nature's smallest brains.

"When you take a systematic approach, it can lead you to make unexpected links between different areas of biology and disease."

PAGE 28

CHRIS TAGGART

50
Building better vaccines

When is the best time to get a booster shot? How might B cells be contributing to neurodegeneration? What are broadly neutralizing antibodies, and can they cure HIV? Three immunologists discuss the enormous promise of next-gen vaccines.

Illustrations by Joel Kimmel; Jasu Hu

6

Why hair stem cells sometimes create skin, what turns on new genes, and ***the truth about mosquito mating.***

ON THE BACK COVER

The Rockefeller University by Michael Kirkham

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Game on. It's hard to believe that for nearly a decade, this green space was occupied by offices. Once the home of Rockefeller's IT dept. (since relocated to Weiss), this corner of campus, lying just south of the 66th and York parking lot, has been transformed into a new 7,200-square foot bio-based synthetic turf field available for soccer, volleyball, frisbee, and all manner of family fun—thanks to the generosity of Trustee Joelle Kayden. "The Kreek," as it's been affectionately rechristened, is named in memory of the university's pioneering addiction researcher, Mary Jeanne Kreek.

Photo by Lori Chertoff

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

FOREFRONT

Illustration by Jasu Hu

DISEASE VECTORS

Decoding the world's deadliest animal

MOSQUITOES AREN'T JUST irritating: As the primary vectors for malaria, yellow fever, Zika, and a host of other dangerous viruses, these tiny creatures are by far the most dangerous animals on the planet.

But deep dives into mosquito genetics and behavior by Leslie B. Vosshall's lab could change that. This year, Vosshall and her colleagues made two major advances: one that corrects a long-standing misconception about mosquito mating and another that reveals the insect's genetic secrets, cell by cell.

In the first study, postdoc Leah Houri-Zeevi uncovered the first evidence of what happens when a female mosquito chooses to mate for the one and only time in her life: a subtle movement of her genitalia that allows insemination to occur. This places the female firmly in control of copulation—a finding that overturns the decades-old assumption that male mosquitoes run the show.

"It's really profound that the field assumed for so long that the female must be passive," Vosshall notes. "Sometimes you need to pick apart an accepted dogma to see if there's actually evidence to back it up. In this case, there wasn't."

"If she doesn't make this movement, it doesn't matter what the male does."

In addition to upending decades of conventional wisdom, the discovery also helps explain why some mosquito species are outcompeting others. It could ultimately lead to new ways of interfering with mosquito reproduction, driving down the numbers of these deadly disease vectors. (A single female can lay more than 1,000 eggs over her lifetime.)

Achieving this breakthrough was no mean feat: A mosquito mating lasts for only 14 seconds, and the phase that includes the team's key finding takes only one or two.

But by combining high-speed cameras, artificial intelligence, and genetically engineered mosquitoes equipped with fluorescent sperm, Houri-Zeevi and her colleagues were ultimately able to determine what leads to a successful coupling: The male inserts structures called gonostyli into the female's genital tip and vibrates them; if she wants to mate, she elongates her own genital tip, permitting the male to transfer his sperm.

"If she doesn't make this movement, it doesn't matter what the male does—no successful mating will occur," says Houri-Zeevi. "And when previously mated females pair up with a male, no elongation happens. It's a one-and-done experience for her."

In the second study, Nadav Shai, a senior scientist in the Vosshall lab, led a global collaboration to create the first-ever cellular atlas of *Aedes aegypti*, which transmits more diseases than any other mosquito. The researchers used single-nucleus RNA sequencing to capture cellular-level gene expression in every single mosquito tissue, from the antennae down to the legs.

Their approach has already yielded new findings, including the widespread presence of supercharged sensory cells that can detect sweetness and fresh water, among other environmental cues. Disrupting mosquitoes' ability to detect those cues could help thwart their efforts to feed, breed, and bite.

"Whether they enable them to sense a human to bite, a flower for a sugar source, or a good water source for laying eggs, these multifunctional chemoreceptors are essential to mosquitoes' survival," Shai says.

Vosshall and her team hope that the atlas will help scientists around the world generate many more such insights into mosquito biology.

"We're excited to see the discoveries that will come from it," Vosshall says.

CHRIS TAGGART

ILLUMINATING DNA'S DARK MATTER

How new genes get switched on

WHEN LI ZHAO started her lab eight years ago, de novo genes—which spontaneously emerge from stretches of DNA that once encoded nothing at all—had only recently been discovered. She soon identified hundreds in fruit flies. But when Torsten N. Wiesel, a Nobel laureate and president emeritus of Rockefeller, asked her how de novo genes were regulated by transcription factors, she realized she had no idea.

"I was stunned," Zhao recalls. "I told him I did not know when we would be able to answer the question."

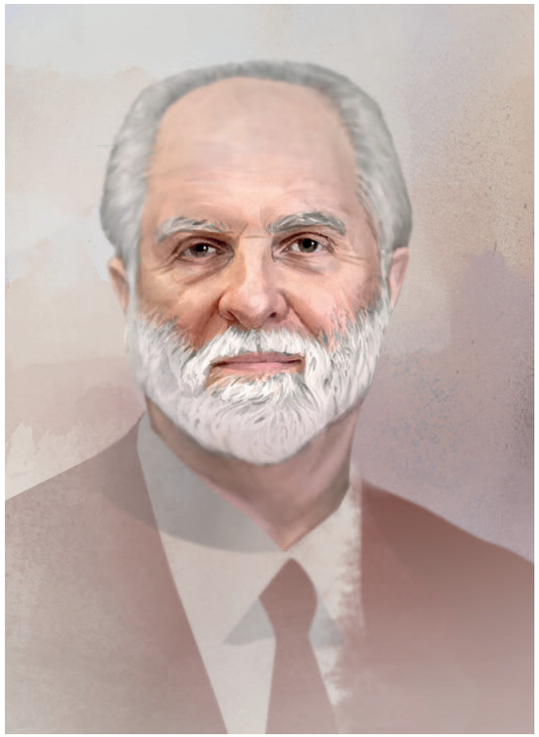
This year, Zhao finally did. By mastering new computational methods and advanced techniques such as single-cell sequencing, her team showed, for the first time, how transcription factors and genomic neighbors switch de novo genes on and integrate them into cellular networks.

The findings shed light on how new genes become functional, with broad implications for understanding evolutionary biology, gene regulation, and diseases that are born from gene dysregulation, such as cancer.

In one study of gene expression across hundreds of thousands of cells, Zhao's group, including Cong Li (pictured above), found that only about 10 percent of transcription factors—proteins that play a key role in activating and repressing genes—controlled the majority of de novo genes. In another, their analysis of gene expression patterns and other data revealed that de novo genes often share regulatory elements with adjacent genes, suggesting a mechanism of co-regulation amongst neighboring stretches of DNA.

Together, the findings begin to paint a picture of how gene networks evolve and how they can go awry, potentially benefiting the study of cancer and other diseases associated with gene dysregulation. And thanks to their relatively straightforward regulatory systems, de novo genes could also provide an accessible window into the trickier question of how the rest of the genome works.

"Expression and regulation are more complex than we think," Zhao says. "De novo genes may provide a simplistic model that helps us better understand gene expression and evolution."



IN MEMORIAM

He taught us how sound waves become brain signals

A. JAMES HUDSPETH devoted his life to explaining how we hear.

When Hudspeth began studying hearing in the 1970s, scientists understood how sound waves traveled through the outer and middle ear. But the process by which microscopic hair cells in the cochlea ultimately converted those sound waves into electrical signals that could be transmitted by nerves and interpreted by the brain remained unknown. Hidden deep within the spiral of the cochlea, hair cells were difficult to access and extraordinarily delicate. Yet working with animals such as bullfrogs and zebrafish, Hudspeth showed how tiny protrusions atop hair cells bent in response to sound, allowing the cells to transform mechanical vibrations into electrical signals.

Hudspeth went on to demonstrate that the process of converting sound waves into electrical signals was astonishingly fast and remarkably sensitive, with hair cells boosting and filtering incoming sounds to help the brain interpret complex soundscapes. These discoveries reshaped modern auditory science.

"While Jim's brilliant research inspired scientists everywhere, we knew him personally as a passionate investigator, deeply committed to his work and equally enthusiastic about sharing the wonders of science with children," says Richard P. Lifton, Rockefeller's president in a message to the community upon Hudspeth's passing. "He was known for his quick wit and as a generous mentor to students and postdocs, a thoughtful advisor to colleagues across the campus, and a fabulous communicator of complex scientific concepts to lay audiences. His deep intellect, integrity, and insistence on rigor set a standard for excellence that extended across our campus."

Late in his career, Hudspeth pursued new strategies to restore hearing, inspired in part by animals like fish and birds that regenerate hair cells naturally. Shortly before his passing, his lab published a paper presenting the first method for keeping a mammalian cochlea alive outside of the body—an advance that may accelerate the search for regenerative therapies.

Hudspeth, the F. M. Kirby Professor, died in August 2025. He was 79.

"His deep intellect, integrity, and insistence on rigor set a standard for excellence that extended across our campus."

Illustration by HelloVon

GATEKEEPERS

At the core of the nuclear pore

EVERY MOMENT, MILLIONS of molecules pass in and out of a cell's nucleus through nuclear pore complexes (NPCs)—highly selective gateways that keep the precious genetic material nestled in the cell's core protected, while still allowing essential traffic to flow to and from the nucleus. When this system falters, diseases ranging from cancer to neurodegeneration can result; yet how NPCs do their essential work has been a subject of intense debate. Now, two complementary studies from Michael P. Rout's lab, conducted with longtime collaborator Brian T. Chait and an international team of scientists, help clarify how NPCs determine what shall pass and what shall not.

First, the researchers used vast quantities of disparate data to construct the most comprehensive computational model of NPC transport to date. They found that the pore interior is filled with a dense, highly dynamic, shifting array of flexible protein chains known as FG repeats. Tiny openings continually appear and disappear in this seemingly impenetrable barrier, allowing small molecules to slip through easily. But larger cargo can pass only when accompanied by specialized molecules called transport receptors that thread fluidly between the mobile protein chains.

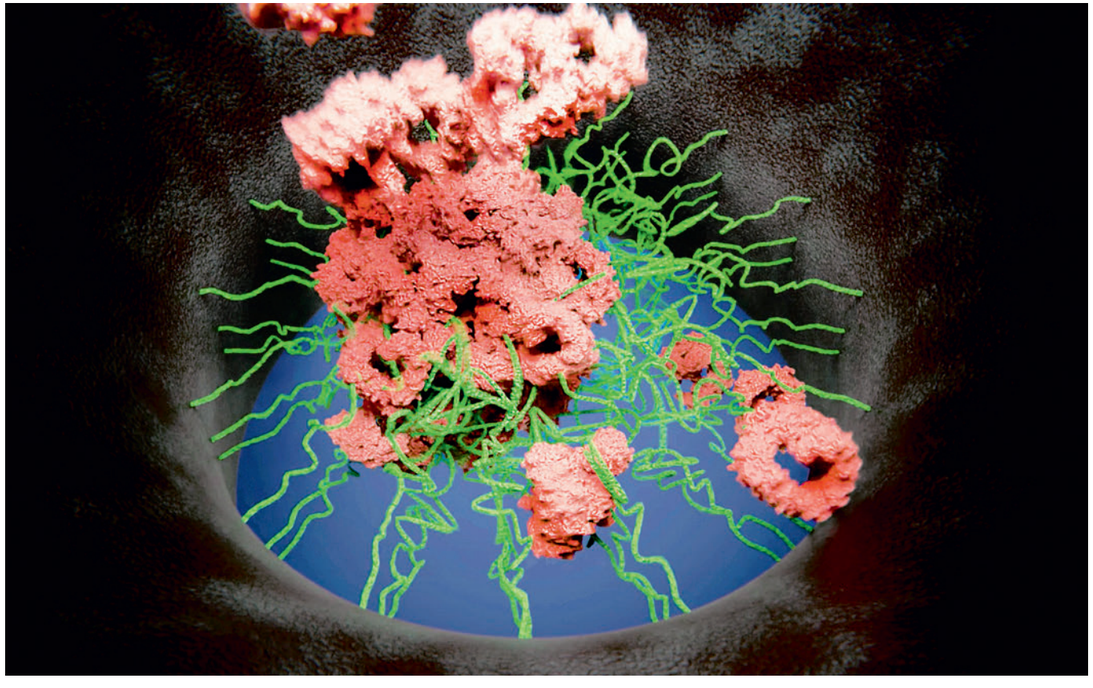
"The transport mechanism can be imagined as a vast, ever-shifting dance across a bridge."

"The transport mechanism can be imagined as a vast, ever-shifting dance across a bridge," Rout says. "The FG repeats form a dynamic, restless crowd that allows only those with the right dance partners—the nuclear transport receptors—to pass through, while pushing away those who cannot join the dance."

Their second study built on these findings with high-speed atomic force microscopy, which allowed the team to capture individual NPCs fluctuating in real time. After confirming that the center of the pore is packed with a shifting cluster of transport factors and cargo, the team built artificial nanopores and analyzed their behavior. They found that adding transport factors caused the same dynamic cluster to appear, indicating that the NPC is a self-organizing gate that is shaped by the very traffic that passes through it.

Together, the two studies resolve long-standing debates about how NPCs work and point toward new ways of understanding diseases linked to NPC dysfunction. They also offer a blueprint for engineering drug-delivery systems inspired by one of nature's most efficient molecular gates. But the work is not done.

"There still remain some big unknowns about how nuclear transport works at the molecular level," Rout notes. "And we're now in a position to ask those questions."



ENRIQUE SAHAGUN, SCIXEL

ANTIBACTERIAL RESISTANCE

The uncultured majority

"We finally have the technology to see the microbial world that has been previously inaccessible."

MANY OF THE antibiotics that we rely upon to beat back infections originally came from soil bacteria, and many more are undoubtedly lurking within the dirt, just waiting to be discovered. Yet the vast majority of soil bacteria cannot be grown in the lab, leaving most of Earth's therapeutic potential untapped. As drug-resistant infections surge and antibiotic pipelines run dry, the hidden chemistry of these buried treasures could offer a path forward.

Recent work from the laboratory of Sean F. Brady presents a strategy for discovering and future-proofing a new generation of soil-based antibiotics, combining new ways of harvesting them with novel methods for hardening them against drug resistance.

In one study, Brady and his colleagues tackled the core obstacle to deriving antibiotics from soil bacteria: access. By developing a new system for extracting exceptionally large DNA fragments directly from soil, Brady's team succeeded in assembling those fragments into full genomes even when they originated from microbes that had never before been grown or observed. Working from a single sample of forest soil, the researchers reconstructed hundreds of complete bacterial genomes, nearly all of them new to science.

The team then used a computational approach to predict the chemical structures encoded in the genomes. By synthesizing and testing the predicted molecules in the lab, the scientists discovered two potent antibiotics: erutacidin, which remains effective against multidrug-resistant germs, and trigintamicin, which attacks a rare antibacterial target.

In a separate project, Brady and his colleagues confronted an equally pressing problem: antibiotic resistance. Most antibiotics are defeated by bacterial resistance mechanisms that evolve rapidly in the clinic. But many of those mechanisms originated long before humans began using antibiotics: Soil bacteria have, on their own, evolved vast repertoires of resistance genes to battle one another for space and resources. Brady's team realized that this environmental "resistome" could function as an early-warning system—a way of identifying how bacteria might learn to disable a new antibiotic before the drug is ever prescribed.

To see how drug-resistant bacteria might one day defeat a promising antibiotic candidate called albicidin, the researchers scanned billions of DNA fragments from soil to find genes that could block the drug. When they tested this vast collection against albicidin, they uncovered eight distinct classes of resistance genes—many with mechanisms never seen before. The team then examined natural variants of albicidin and identified the chemical features that helped certain variants stay effective. Using those insights, they engineered improved versions of the drug that remained potent even in the face of the strongest resistance mechanisms.

Together, these findings reach deep into the microbial world to uncover new drug candidates while anticipating and disarming the resistance mechanisms that threaten them.

"We finally have the technology to see the microbial world that has been previously inaccessible," Brady says. "This is just the tip of the spear."

LABORATORY OF GENETICALLY ENCODED SMALL MOLECULES

HYPERTENSION

The link between brown fat and blood pressure

OBESITY IS A risk factor for high blood pressure, which, in turn, contributes to cardiovascular disease—the world's leading cause of death. But how does adipose tissue drive up blood pressure?

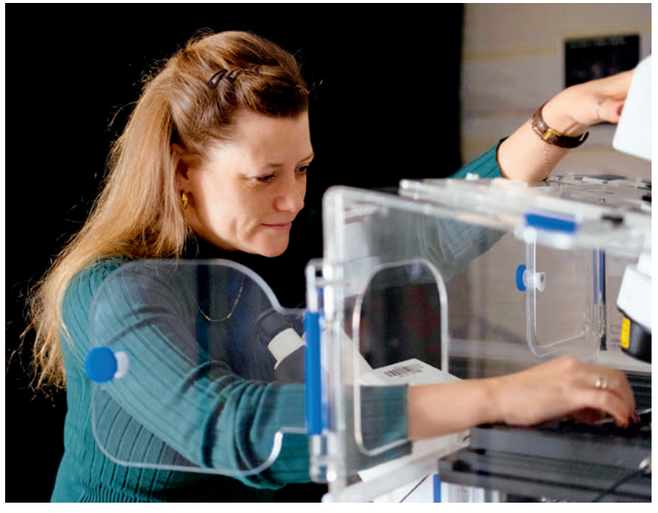
This year, a study from Paul Cohen's lab offered a surprising answer: It depends on the color of your fat.

Cohen's lab discovered that the culprit came down to a loss of beige fat, the heat-generating form of adipose tissue.

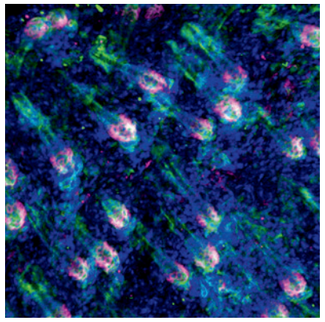
Building on earlier work showing that people with more brown fat have lower odds of hypertension, Cohen's team, including Mascha Koenen (pictured below), engineered mice that lacked beige fat—which is similar to the activatable brown fat found in adult humans—but were otherwise healthy. These animals developed elevated blood pressure, as well as many hallmarks of cardiovascular disease. So, his lab dug deeper, revealing that beige fat normally suppresses an enzyme linked to tissue remodeling known as QSOX1. Without beige fat, QSOX1 runs unchecked, triggering a cascade that leads to hypertension and vascular disease. To confirm that QSOX1 alone was responsible for this effect, the team then engineered mice lacking both beige fat and QSOX1. These mice, despite lacking protective beige fat, were protected from vascular dysfunction.

Now, Cohen's lab is searching for links between existing medications and brown fat activation and exploring how genetic differences may affect fat-driven disease risk. By uncovering a direct connection between brown fat and vascular remodeling, the findings open new avenues for precision medicine approaches to treating hypertension.

"These findings underscore the value of reverse translation," Cohen says. "We start with patterns we observe in people, then dig deep in the lab to uncover the molecular mechanisms. We can't design targeted therapies until we first conduct the basic science that explains what is behind the clinical observations."



LORI CHERTOFF; ROBIN CHEMERS NEUSTEIN LABORATORY OF MAMMALIAN CELL BIOLOGY AND DEVELOPMENT



SWITCH-HITTERS

When hair stem cells turn into skin

SKIN INJURIES ARE generally repaired by epidermal stem cells. But sometimes hair follicle stem cells (HFSCs), which ordinarily handle hair growth, lend a hand. So how do they know when it's time to step in?

Researchers in the lab of Elaine Fuchs showed that these cellular switch-hitters respond to a signal activated during a stressful situation—and their assistance accelerates the healing process.

The amino acid serine detects nutrient deficits in the skin, and a drop in serine levels activates a so-called integrated stress response (ISR) that directs stem cells to conserve energy for essential tasks. By subjecting HFSCs to a series of metabolic stress tests, the researchers discovered that when the serine tank is low, the ISR reorients them away from hair growth and towards skin repair.

"A missing patch of hair isn't a threat to an animal, but an unhealed wound is," says Fuchs.

Unfortunately for anyone with a balding pate, Fuchs and her colleagues also determined that simply boosting the amount of serine in the diet does not supercharge hair growth, so the applications for preventing hair loss appear to be limited. On the flipside, restricting serine levels could help accelerate wound repair.

"Our findings suggest that we might be able to speed up the healing of skin injuries by manipulating serine levels through diet or medications," says postdoc Jesse Novak.

BRAIN HEALTH

Detangling neurodegenerative diseases

ALZHEIMER'S DISEASE AFFLICTS more than 50 million people worldwide—a number that is expected to increase markedly in the coming decades. Yet effective treatments for this devastating form of dementia, whose principal hallmarks include amyloid plaques and tangles of tau proteins in the brain, remain frustratingly elusive. This past year, however, Rockefeller researchers made a series of discoveries that could lead to new treatments for Alzheimer's and other neurodegenerative diseases.

For more than two decades, Sidney Strickland's lab has investigated whether the vascular system contributes to the pathogenesis of Alzheimer's. This once controversial claim has gained traction in recent years, especially after the Strickland lab demonstrated that amyloid beta (Aβ), the molecule most associated with the disease, binds to fibrinogen, a major blood protein. Recently, the team discovered that when Aβ and fibrinogen bind even in small amounts, they form abnormal clots and trigger early signs of Alzheimer's such as neuroinflammation and synapse loss.

The findings suggest that targeting these Aβ/fibrinogen complexes could offer a new strategy for combating Alzheimer's. "Perhaps that would alleviate some of the pathologies, especially in combination with other therapies," says Elisa Nicoloso Simoes-Pires, a research associate in the lab.

"The science implies that our findings may potentially, down the road, allow us to slow down cognitive decline as we age."

LORI CHERTOFF

Meanwhile, Alexander Tarakhovsky's lab determined that a population of immune cells found in the brain may act as a natural defender against the disease.

A subset of microglia—the brain's resident immune cells—with a particular molecular signature can shift into an anti-inflammatory state that shields the brain from Alzheimer's-related damage. Enhancing this protective state in mouse models quieted brain inflammation, slowed the spread of toxic tau proteins, and reduced amyloid plaque buildup. It also preserved the animals' cognitive function and extended their lifespan, suggesting that the brain's own immune system could be trained to fight Alzheimer's and other forms of neurodegeneration.

"Perhaps reprogramming microglia into a protective state could present a new immunotherapeutic strategy," says Tarakhovsky.

For his part, Hermann Steller decided to focus on stimulating the machinery that prevents the buildup of toxic proteins in the first place, allowing them to clog synapses and congeal into plaques. Unwanted proteins are supposed to be removed by large enzyme complexes known as proteasomes, which function as a kind of cellular cleanup crew. When these molecular sanitation workers don't do their job properly, however, proteins can escape destruction and disrupt the flow of signals between brain cells. This causes a progressive cognitive dysfunction, from disrupting reasoning and language to memory and motor function.

Steller's team demonstrated in mice and fly models that boosting levels of PI31—a protein that keeps proteasomes on track—cleared away the abnormal tau deposits associated with Alzheimer's, preventing neuronal degeneration, restoring synaptic and motor function, and in some cases even extending lifespans fourfold.

Variants of the gene coding for PI31 are found in patients with Alzheimer's, Amyotrophic lateral sclerosis (ALS), Parkinson's, and several rare neurodegenerative diseases, which suggests that the team's findings could have a profound impact on a range of conditions.

"The science implies that our findings may potentially, down the road, allow us to slow down cognitive decline as we age," Steller says.

MOLECULAR MOVIES

How to build a ribosome

RIBOSOMES ARE THE molecular machines that make all other molecular machines, reading the genetic code and assembling the proteins that every organism needs to survive. But how are these master builders built in the first place? In a landmark study, Sebastian Klinge's lab recently captured a near-continuous molecular movie that reveals how cells construct a key component of the ribosome, step by step.

The team's findings cap more than a decade of work that began in 2013, when Klinge launched his lab at Rockefeller with little more in hand than a list of molecules, known as ribosome assembly factors, that were thought to participate in ribosome formation. Over the years, the team transformed that list into a timeline of when each factor appears, then into low-resolution structures and, eventually, into high-resolution snapshots of individual assembly states. A molecular movie of ribosome formation represents the natural culmination of that progression—revealing, at last, how the machine that builds all others is itself assembled.

Their latest work began not with experiments, but with artificial intelligence. Klinge's team used a powerful AI program called AlphaFold to predict more than 3,500 potential interactions between ribosome assembly factors. Based on those predictions, they constructed a roadmap to guide their experimental design and ultimately compiled a molecular movie that charts the step-by-step formation of a crucial portion of the ribosome known as the small ribosomal subunit. In addition to shedding light on how one essential machine is built, the results demonstrate the power of AI-driven structural biology, and open the door to visualizing other fundamental biological processes in similarly exquisite detail.

"The formation of ribosomes from nonliving matter is probably the closest thing to the origins of life that we know of," Klinge says. "Ribosomes are not quite alive, but when we study their biogenesis, we get a glimpse at the point at which something that isn't alive begins to feel alive."

"An improved understanding of embryogenesis can give people the best opportunities for building future families."

PHOSPHO BIOMEDICAL ANIMATION

NEW TOOLS

Shining new light on embryonic development

THE EARLIEST STAGES of human embryonic development hinge upon a brief and astonishing event: Only two weeks after fertilization, a flat sheet of embryonic stem cells suddenly folds into a living blueprint for where the head, spine, and limbs will eventually form. This fleeting transformation, known as gastrulation, has until now stood beyond the reach of science, occurring too early and deeply within the uterus to study directly.

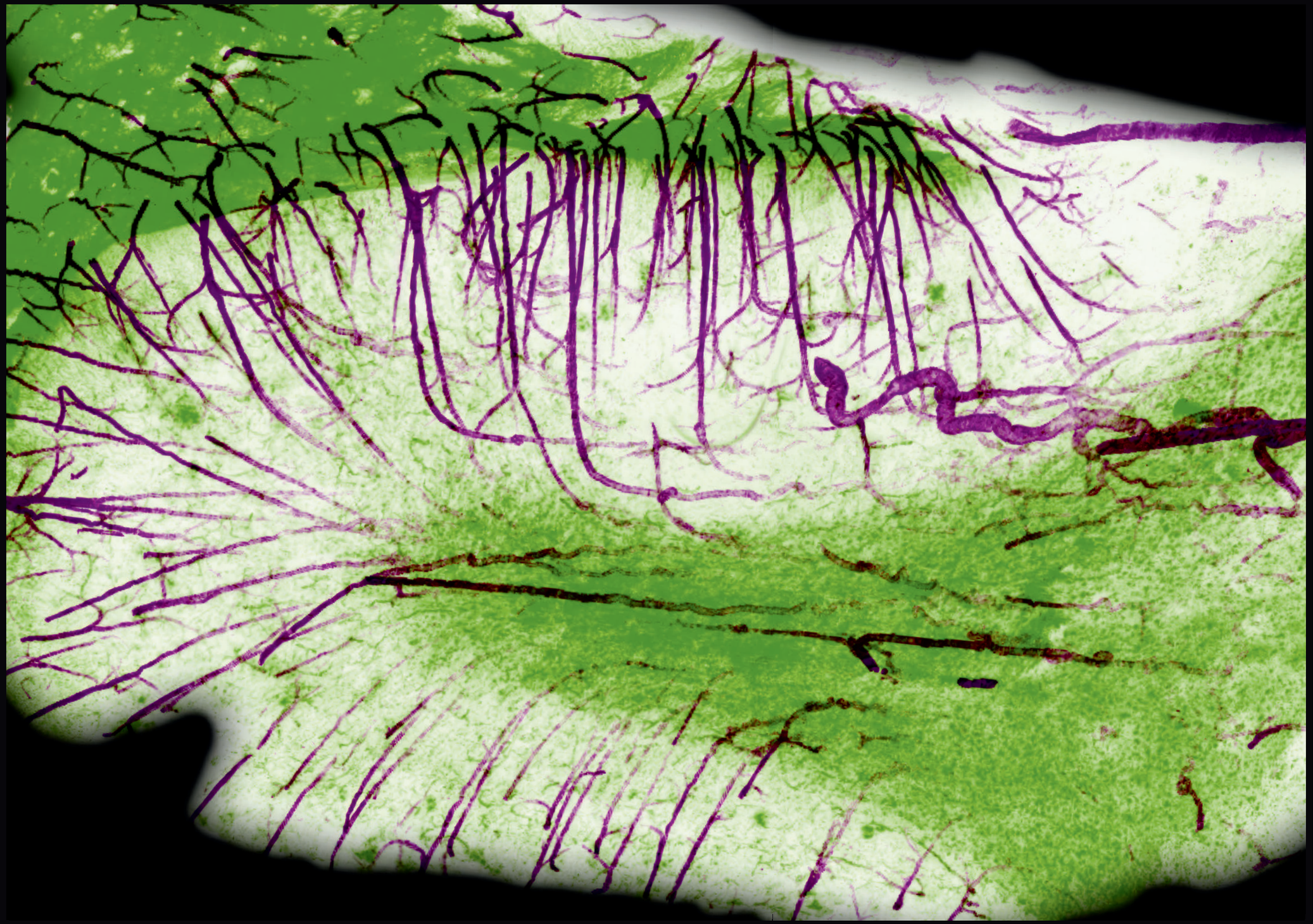
Recently, however, a team led by Ali H. Brivanlou—who has been investigating the mystery of gastrulation for decades—and Riccardo De Santis, director of the Human Pluripotent Stem Cell Resource Center at Rockefeller, in collaboration with theoretical physicist Laurent Jutras-Dubé, a former postdoc in Brivanlou's lab, used a new optogenetic tool and mathematical models to reveal surprising new details about this all-important stage in human development.

"We can now generate self-organization and different cell types just by shining light on them," says Brivanlou.

When aimed at human embryonic stem cells that the team engineered to respond to light, the tool allowed the researchers to activate developmental genes with extraordinary precision. Yet when they used this optogenetic tool to trigger the production of a key gastrulation-related protein known as Bone Morphogenetic Protein 4 (or BMP4), they found that chemical cues alone were not enough to prompt the transformation. Instead, gastrulation began only when the cells were also under the correct mechanical conditions.

The results revealed a fundamental interdependence between molecular signaling and tissue mechanics, offering a new framework for interpreting and modeling early human development that could advance regenerative medicine and lead to new fertility therapies.

"Our work focuses on fundamental biology and basic science, but an improved understanding of embryogenesis can give people the best opportunities for building future families," says De Santis.



LABORATORY OF MOLECULAR BIOLOGY

SNAPSHOT

Retracing missteps

RADIAL GLIA ARE the brain's most ephemeral cell type. Present only during embryonic development, they set the trajectory for the brain's vasculature, creating scaffolds for each newborn neuron to crawl along as it takes its place in the developing brain.

At the same time, radial glia also give rise to astrocytes, housekeeping cells that support neurons and maintain brain health throughout our lives.

Tatz Murakami, who studies brain tissue imaging as a research associate in the Heintz lab, suspects that scientists can find clues to neurological and psychiatric disorders by studying the patterns set by the radial glia. To that end, Murakami helped develop an open-source photobleaching technique that gives scientists a much clearer view of specific cells and structures—here arteries (shown in magenta) and astrocytes (shown in green) in adult brain tissue. One day, these winding paths may deepen our understanding of the mechanisms underlying conditions such as autism, obsessive compulsive disorder, addiction, and Alzheimer's, and help guide future therapeutic strategies.

The logic of a fruit fly

With Gaby Maimon

WHEN A FRUIT fly catches a whiff of rotting banana, it knows exactly how to home in on that appetizing smell: Even in perfectly still air, a fly can easily locate its next meal. This uncanny ability is more than a reflex; it's part of an adept strategy to survive and proof that even a brain with just 100,000 neurons (vs. the human brain's 80 billion) can chart a course through the world.

Most people see fruit flies as little more than kitchen nuisances that appear to buzz around aimlessly. But for Gaby Maimon, head of the Laboratory of Integrative Brain Function at Rockefeller and an investigator at the Howard Hughes Medical Institute, flies are windows into one of the most enduring questions in science: How do brains give rise to intelligence?

While human brains contain massive networks of cells, fruit fly brains are small, accessible, and surprisingly powerful. Over the past decade, Maimon's lab has helped reveal how flies build internal understandings of the world, carry out math as they navigate, and make decisions about where to move. By combining cutting-edge genetic tools and technology optimized to image minuscule brains, Maimon and his team are revealing, neuron by neuron, and circuit by circuit, how these brains work.

Maimon's basic research could shed light on how mammals, including humans, navigate the world and make decisions, as well as how these processes can go wrong in diseases like Alzheimer's.

Ultimately, Maimon's basic research could shed light on how mammals, including humans, navigate the world and make decisions, as well as how these processes can go wrong in diseases like Alzheimer's.

We spoke with Maimon about why he turned to flies, what his lab has uncovered, and why understanding these insects could help us understand ourselves.

CHRIS TAGGART

To the average person, fruit flies don't seem very smart. What makes them a good model for studying intelligence?

We always like to say that fruit fly brains may be small, but they're not simple. Per neuron, the fly brain does as much or more than a mammalian brain. For instance, if a fly is hungry and it smells something good, logically, it turns upwind—a behavior that helps it arrive at its favorite environment: a rotting fruit. But what's even more impressive is that if the wind dies down, we recently found that flies will use a working memory of the direction from which the wind was last coming to keep heading along that angle for a few minutes. And if a group of flies is hungry and they have no cues at all—no wind, no smell—they each pick a random direction and travel in a long, straight path, sticking to that direction for hours, effectively organizing a search party, where the hope is that at least a few flies chance upon a morsel of food and survive.

Alongside these navigational capacities, flies can be genetically modified with incredible precision, reproduce quickly, and have been studied for over a century to reveal fundamental principles of genetics, development, and evolution. This unique combination of experimental tractability and deep biological knowledge makes them an ideal system for investigating the brain from multiple perspectives. This is why, in 2006, I switched from studying primates to flies.

These flies' brains are the size of poppy seeds. How do you study them?

When I began working with flies, methods existed to secure them in place and electrically record their brain activity. It wasn't possible, however, to record electrical activity during behavior. So, as postdocs, my colleagues and I came up with a method to tether a fly in place and record both its wingbeats and the electrical activity of its neurons. Now, we typically use microscopes to image neural activity as flies walk on tiny floating balls, which act like spherical treadmills that allow them to navigate around a visual virtual environment. These methods, alongside other developments related to manipulating neuronal activity and characterizing the anatomy of the fly brain in fine detail, have opened a new window into understanding how neuronal circuits regulate behavior.

What have you discovered about how they work?

In the middle of every fly brain is a structure called the ellipsoid body, which literally looks like a donut. This structure has a set of neurons that break it up into sectors, like pizza slices divvying up a pie. When you measure the activity of these neurons, only a few neighboring ones are active at a time, creating a localized activity "bump" in one section of the donut. When a fly turns, the position of this bump rotates correspondingly, like a compass needle tracking the fly's orientation in the world.

Our first major finding, in 2017, described a dedicated neuronal circuit that functions to rotate the ellipsoid-body compass signal at just the right speed to match how fast flies are turning in the world. In 2021, we further found that the fly brain calculates not just angles (like the compass direction) but also vectors, which are mathematical quantities that combine an angle and a length. Specifically, we found that another structure in the fly brain—called the fan-shaped body—encodes vectors and can add or rotate them as the fly moves through space. The fan-shaped body can calculate the direction in which a fly is traveling, and it does so via vector arithmetic. This traveling-direction signal is particularly important when the ellipsoid body compass is indicating one direction (which the fly is facing), but she is walking or flying in another direction.

More recently, we discovered how the same system can turn an internally generated goal into a motor action. Here, the goal is the direction in which the fly wants to progress forward, and the motor action is that act of turning so as to align the body with the goal direction. The circuit we discovered provided the first biological example of how a brain can convert a navigational goal into a steering signal.

Do human brains work the same way?

Humans don't have the same brain structures as flies, but some of the core computational principles might be similar across nervous systems. The ellipsoid-body compass in flies, for example, works nearly identically to "head direction cells" that have been discovered in mammals. Other mechanisms might fundamentally differ between the fly and human brain, and our work could help to reveal these differences too.

"If we can figure out how memory works in the fly, it could reshape how we think about memory in all brains."

What do you want to find out next?

We want to understand the nature of spatial memory. To this end, we are focusing on how flies can remember a direction or location over seconds, minutes, or even days. As part of this research direction, we're building apparatuses that allow flies to live for weeks in a virtual environment while we simultaneously image their brain activity. Overcoming the significant technical challenges involved in this project is worth it, I think, because if we can figure out how memory works in the fly, it could reshape how we think about memory in all brains.

Where do you hope this work will ultimately lead us?

Brains remain fundamentally mysterious. Rigorous explanations of how sets of neurons give rise to function are still rare. By gaining a detailed understanding of how a small region in the middle of the insect brain works, our research provides a road map for how to go about achieving a similar understanding of bigger brains, like our own. Also, the insect brain holds a beauty all its own. Most species that share our planet are insects, and to understand how they master the art of living, in my view, deepens our own humanity. This sense of wonder is also why we pursue this work, and where such curiosity-driven science takes us is not wholly predictable.

In Control

Empowering the immune system to more effectively fight cancer

Illustration by Alessandro Gottardo

Immunotherapy has proven to be a wonder drug—for certain patients, against certain cancers. For others, it doesn't work at all. Can striking new insights into the immune system help immunotherapy finally live up to its full potential?

By Alexander Gelfand

THERE WAS A TIME, recalls Rockefeller scientist Sohail Tavazoie, when metastatic melanoma—an advanced form of skin cancer that has spread to other parts of the body—was almost universally fatal.

"It was basically a death sentence," says Tavazoie, head of the Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology. "You would be given chemotherapy, but you would soon die."

The advent of modern immunotherapy treatments, which were first approved in 2011, changed that: Fifteen years ago, the median survival rate for patients with metastatic melanoma was just six and a half months. Today, more than half stand to survive cancer-free for a decade or more.

Such benefits have gradually spread to a wide range of cancer patients. Immunotherapies, which enlist the body's own immune system in the fight against cancer, are now approved for malignancies ranging from renal cell carcinoma to Hodgkin lymphoma, extending millions of lives and in some cases, effectively curing patients after conventional treatments like radiation and chemotherapy have failed.

Revolutionary though it may be, however, immunotherapy still has limitations—and risks.

For one, not all patients respond to it. Oncologists like Tavazoie estimate that modern immunotherapies work, to some degree, on perhaps 25 percent of patients who try it. And they have little to no effect on certain tumors, including aggressive forms of pancreatic, liver, and most breast cancers. (This comes at a time when rates of some common forms of cancer have been rising—largely among young people, and for reasons that are not yet well understood.)

What's more, while scientists often hail immunotherapy as a "clean" form of cancer therapy compared to treatments like radiation and chemotherapy, manipulating the immune system can lead to severe side effects.

"Immunotherapy is transformative. It is exciting," says Tavazoie. "But it can also be quite toxic."

Checkpoint inhibitors—the most common variety of immunotherapy drugs—block certain proteins that act like brakes on the immune system. Under ordinary circumstances, these molecules prevent T cells from going after healthy cells. But tumors can also shield themselves behind checkpoint proteins. And therein lies the trade-off: Removing that shield boosts the body's immune response to cancer, but it also removes an important safeguard, exacerbating autoimmune disorders in people who already have them, and triggering them in people who don't.

As a result, immunotherapy treatments must at times be blunted with the same immunosuppressant drugs that are given to organ transplant recipients. Even still, the ensuing complications can become so severe that, in rare cases, they turn fatal.

But new research is beginning to show that immunotherapy needn't be a double-edged sword. For example, Tavazoie, who also treats patients as an attending medical oncologist at Memorial Sloan Kettering Cancer Center, developed a drug that has demonstrated promising results in early-stage clinical trials: Trial data published last year indicated that the compound dubbed abequolixron shrank tumors in a clinical trial of patients with metastatic lung cancer who hadn't previously responded to other forms of immunotherapy with no serious side effects. "It was incredibly exciting and rewarding to see patients' metastases shrink," says Tavazoie, who explains that the therapy works by killing abnormal immune cells that suppress T cell activity inside tumors.

That sense of excitement is shared by a growing community of Rockefeller scientists who are working to extend the benefits of immunotherapy to more patients and better manage its downside. Ekaterina V. Vinogradova, for instance, employs sophisticated chemical tools and mass spectrometry-enabled platforms to search for new targets and drugs that can reinvigorate immune cells that have lost their cancer-fighting mojo. Kivanç Birsoy has devised a compelling new approach to identifying not only drugs but also dietary interventions that can prevent tumors from outsmarting T cells. And Jeffrey V. Ravetch is engineering antibodies to beat back some of the most intractable forms of the disease.

These new strategies for treating cancer were born out of striking new insights into the mechanics of the human immune system and the differences between healthy and unhealthy cells. And each new breakthrough further untangles the intricate web of genetic, molecular, and biochemical factors that have thus far prevented immunotherapy from living up to its full promise.

> "Immunotherapy is transformative. It is exciting. But it can also be quite toxic."
>
> TAVAZOIE

> "Our goal is to target cancer's metabolism—what cancer cells eat, how they generate energy—so immune cells can kill them more effectively."
>
> BIRSOY

Birsoy's lab studies the intersection of metabolism, cancer, and the immune system.

ROSHNI KHATRI

TAVAZOIE, RAVETCH, VINOGRADOVA, AND BIRSOY all receive support from the Weill Cancer Hub East, a joint venture between Rockefeller, Weill Cornell Medicine, Princeton University, and the Ludwig Institute for Cancer Research that seeks to improve immunotherapy by investigating how metabolism affects the immune system's ability to recognize and control cancer.

"It's an area that's really been understudied," says Tavazoie, who serves on the Hub's scientific steering committee.

Birsoy, who heads the Laboratory of Metabolic Regulation and Genetics, has been working to rectify that situation longer than most: For more than a decade, he has explored the intersection between metabolism, cancer, and the immune system, along the way producing a string of profoundly new insights.

When Birsoy and other scientists talk about metabolism, they mean all the chemical reactions carried out within our cells. At the macro level, metabolism begins with the food we put in our mouths; at the micro level, it includes the molecular machinery that transports nutrients across cell membranes and turns them into fuel.

"Our goal is to target cancer's metabolism—what cancer cells eat, how they generate energy—so immune cells can kill them more effectively," he says.

That task is complicated by the fact that every form of cancer appears to have its own unique metabolism based on its tissue of origin (liver, pancreas, brain) and the genetic mutations that drive it.

Nonetheless, Birsoy is making impressive progress. In 2024, for example, he published a study demonstrating that an aggressive form of pancreatic cancer that does not respond to checkpoint inhibitors exploits the fatty substances known as lipids to hide from the immune system. Better still, he showed that an FDA-approved drug could render it visible again.

Scientists have long known that high lipid levels go hand-in-hand with the growth and spread of cancer. But they tended to assume that that was because cancer cells were using the fatty molecules as fuel. Birsoy, however, established that in the case of at least one form of pancreatic cancer with a specific genetic mutation, the cancer cells were instead using lipids as a kind of cloaking device.

The lipids in question, known as sphingolipids, are commonly found in cell membranes. Working with animal models, Birsoy and his team showed that by cranking up the sphingolipid content of their own membranes, cancer cells were able to interfere with the molecular signals that immune cells normally rely upon to perceive them. Genetically blocking the production of sphingolipids allowed the immune system to "see" the cancer cells again, and administering checkpoint inhibitors together with a drug called eliglustat that inhibits sphingolipid production caused the animals' tumors to shrink substantially.

Eliglustat was originally approved as a treatment for Gaucher disease, a metabolic disorder that causes sphingolipids to accumulate in various organs. Its ability to boost the efficacy of checkpoint inhibitors supports Birsoy's hypothesis that interfering with cancer metabolism could improve immunotherapies. Birsoy has since found another sphingolipid that appears to perform the same cloaking function for an aggressive form of liver cancer that is also resistant to checkpoint inhibitors, suggesting the possibility of a similar treatment.

But sphingolipids aren't just found in cell membranes: They are also found in the foods we eat, like red meat and chicken. And that suggests there might be ways of modifying patients' diets, from adding supplements to eating more of certain foods and less of others, that could help improve the efficacy of immune therapies—modifications that could be moved into human testing much more quickly than new drugs, and that would come without potentially harmful side effects.

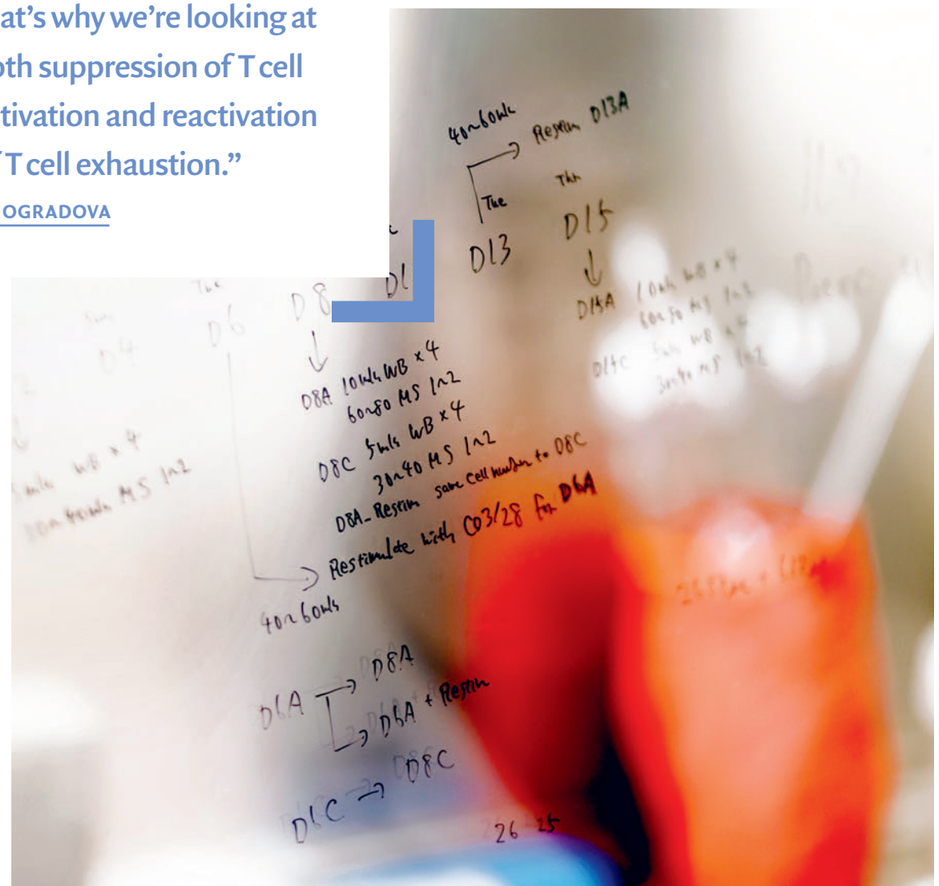
"What we're learning in my lab could lead to dietary regimens that increase the effectiveness of immune therapies," Birsoy says.

Birsoy suspects that most metabolically oriented immunotherapies will complement rather than replace other treatments, if only because cancer is such a wily and multifaceted adversary that metabolic factors cannot fully explain what's going on.

But that holds true for all the approaches being pursued across campus: More often than not, the ultimate goal is to combine multiple therapies, achieving synergistic effects and improving outcomes for the largest possible number of patients by filling in yet another piece of the immunotherapeutic puzzle.

"We're all coming at this from different angles," Birsoy says. "That's how you create a full picture."

> “It’s always a balancing act. That’s why we’re looking at both suppression of T cell activation and reactivation of T cell exhaustion.”
>
> VINOGRADOVA



ROSHNI KHATRI

Because the proteins Vinogradova is probing aren’t targeted by current immunotherapies, her work could lead to a whole new class of drugs.

(Opposite) Charlotte R. Wayne is a postdoc in the Vinogradova lab, which has developed a platform for examining the inner workings of human T cells.

Birsoy is trying to help battle-ready immune cells root out and kill tumors that are hiding in plain sight. But what can be done to refresh battle-weary ones that have become too tired to fight in the first place? And how can you avoid overstimulating them to the point where they begin attacking healthy tissues?

Ekaterina Vinogradova, head of the Laboratory of Chemical Immunology and Proteomics, is trying to solve both those problems at once.

T cells that are chronically stimulated can eventually become exhausted, losing the ability to wage war against whatever they’ve been fighting. This phenomenon poses a major challenge to immunotherapy: One of the telltale signs of T cell exhaustion, for instance, is an increase in the checkpoint proteins that suppress T cell activity; and while checkpoint inhibitors can overcome that to some extent, most patients either don’t respond to the drugs or eventually develop resistance to them. Even the enhanced T cells employed in CAR-T therapy, which genetically modify a patient’s T cells so they can better recognize and attack cancerous ones, become exhausted after a while.

New ways of rejuvenating exhausted T cells are therefore badly needed. But finding them will require a better understanding of the mechanisms behind T cell exhaustion, and of the fundamental differences between exhausted T cells and normal ones.

Towards that end, Vinogradova has developed a platform for probing the inner workings of human T cells using amino acids called cysteines. The latter play important biological roles and can simultaneously provide insights into dynamic changes in the structure and function of T cell proteins, which in turn affect the cells’ ability to do their jobs.

Cysteines readily form chemical bonds with a particular kind of small molecule, but their reactivity changes depending on the state—functional or dysfunctional, healthy or diseased—of the proteins they are embedded in. By probing the cysteines inside T cell proteins with specially designed small molecules, Vinogradova can use them as sensors to gather information on the biochemical differences between normal and exhausted T cells.

Because therapeutic drugs are also made from small molecules, this approach can help identify potential targets for new T cell treatments at the same time: If a small-molecule probe reveals that a particular protein plays a role in T cell exhaustion, a small-molecule drug that targets the same protein could help reverse or prevent the condition. And because the proteins Vinogradova probes aren’t targeted by current immunotherapies, her work could lead to a whole new class of drugs.

“We’re trying to understand basic mechanisms, but ultimately these findings can be used to develop therapeutics,” she says.

As a postdoc at The Scripps Research Institute, prior to coming to Rockefeller, Vinogradova mapped more than 3,400 reactive cysteines distributed throughout more than 2,200 T cell proteins. Some of her probes measured the overall reactivity of the cysteines, while others tested their suitability as potential drug targets. Vinogradova was able to compare data from activated T cells with data from quiescent ones, which are idling but ready to jump into action. She then went a step further and identified several chemical compounds that suppressed activated T cells through a variety of mechanisms, which could lead to new methods for corralling the overactive T cells involved in autoimmune disorders.

Since coming to Rockefeller in 2020, Vinogradova has continued to refine and expand her platform with an eye towards finding drugs that can prevent and reverse T cell exhaustion without causing the immune system to run amok.

Together with colleagues at Memorial Sloan Kettering, she is developing additional platforms for comparing quiescent, activated, and exhausted T cells that will shed even more light on the molecular pathways that drive cellular dysfunction. Her lab is also applying improved methods to map the proteomic differences in T cells directly from cancer patients. And she is collaborating with Birsoy to better understand how metabolism affects cysteine reactivity and T cell function.

Even as the scope of her investigations grows, however, Vinogradova's objective remains the same: to identify novel drugs that can reinvigorate the immune system without causing collateral damage.

"It's always a balancing act," she says. "That's why we're looking at both suppression of T cell activation and reactivation of T cell exhaustion: Understanding both parts of the equation will help us to develop better therapeutic strategies."

Research Assistant Finley Barber at work in the Ravetch lab, which studies health implications that arise from one region of a human antibody.

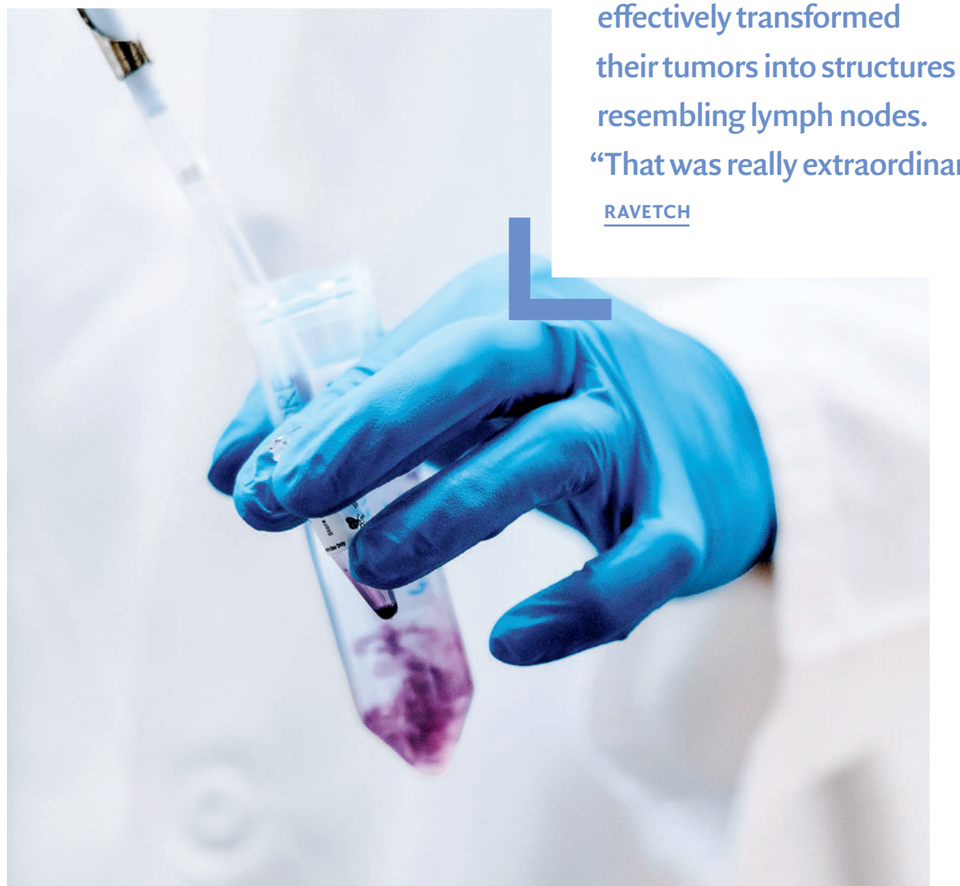
JEFF RAVETCH'S INTEREST IN cancer sprang from his long-standing fascination with antibodies, which serve not only as one of the body's principal tools for fighting disease but also as the primary ingredient in many immunotherapy treatments.

As head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology, Ravetch has spent decades identifying a wide range of health implications that arise from one piece of a human antibody, known as the fragment crystallizable (Fc) region. Most immune cells have special receptors that either trigger or suppress inflammation by binding to this pivotal region, which lends the Fc an outsized role in ramping up and tamping down immune responses to all kinds of perceived threats. When the antibody-based anticancer drug Herceptin was first introduced in the 1990s, for example, scientists thought it worked by blocking a protein that fuels the growth of a particularly aggressive form of breast cancer. Ravetch, however, showed that the drug's tumor-shrinking powers were tied to its ability to bind to a particular Fc receptor, an insight that allowed drug developers to increase the effectiveness not only of Herceptin but of several other antibody-based cancer treatments.

Now, Ravetch has leveraged the Fc to build an entirely new type of antibody-based immunotherapy.

The drug targets a receptor called CD40 that is found on various immune cells, including the dendritic cells that help activate T cells. In the early days of the immunotherapy revolution, several major pharmaceutical companies tried to develop cancer treatments using antibodies that could rouse the immune system by binding CD40. But while those antibodies showed therapeutic promise in mice, they didn't work particularly well in people. Instead, they severely sickened patients, damaging their livers and blood.

Working with one such antibody, Ravetch and his colleagues determined that the molecule worked in mice but not in humans because it could only bind mouse Fc receptors and not human ones. By modifying its Fc, Ravetch was able to increase the antibody's potency against tumors containing human receptors by a factor of 10.



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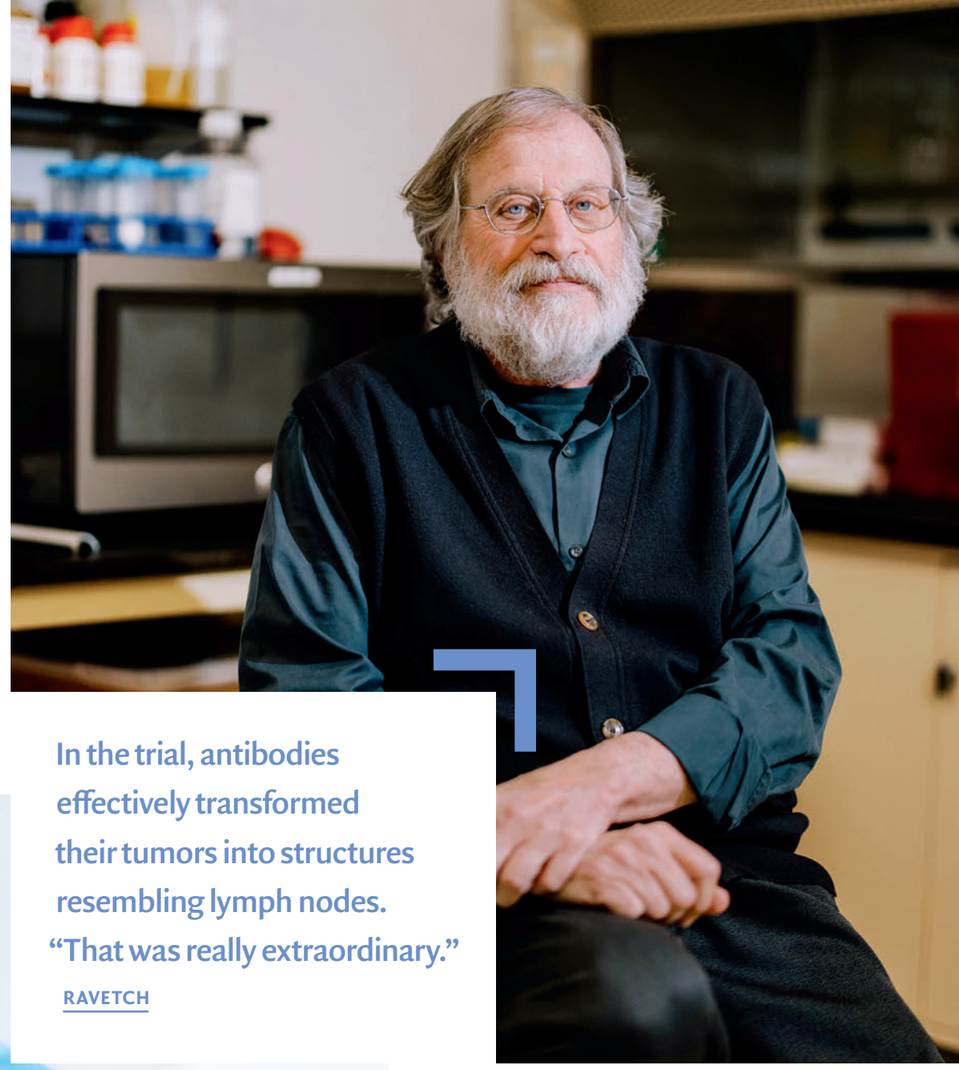


Ravetch has leveraged the Fc to build an entirely new type of antibody-based immunotherapy.

In the trial, antibodies effectively transformed their tumors into structures resembling lymph nodes. "That was really extraordinary."

RAVETCH

At first, those more powerful antibodies were also more toxic. But Ravetch surmised that this stemmed from the fact that CD40 is found on many non-immune cells as well, embedded in all manner of tissues throughout the body. So Ravetch proposed administering his antibodies locally instead, injecting them directly into the tumors of cancer patients in a clinical trial conducted at The Rockefeller University Hospital. Even with targeted injections, he reasoned the treatment might produce wider vaccine-like effects, prompting the immune system to seek out and destroy cancer cells wherever they lurked.

The trial, which ran from 2020 to 2024 with support from the Robertson (now Black Family) Therapeutic Development Fund, proved Ravetch right on all counts: Of the 12 patients enrolled, six saw their tumors shrink significantly, while two more saw the tumors that had spread throughout their bodies disappear completely. One of them had a form of metastatic breast cancer that generally doesn't respond to immunotherapy at all, but after a series of injections to a tumor in her armpit, the tumors in her liver and lungs disappeared as well. None experienced severe side effects from the treatment.

"It was absolutely exceptional to see what was happening in patients," says Juan Osorio, a medical oncologist at Memorial Sloan Kettering and a visiting assistant professor in Ravetch's lab who was lead author on a paper that described the study in the journal *Cancer Cell* this past summer.

The researchers were also surprised to discover that the antibodies effectively transformed their tumors into structures resembling lymph nodes—immune system factories that are packed full of dendritic cells, T cells, and antibody-producing B cells. "That was really extraordinary," Ravetch says.

Additional trials are now underway at Memorial Sloan Kettering and Duke University to see how these modified antibodies fare against bladder, prostate, and brain cancer, and Ravetch and Osorio are looking at the possibility of further improving their efficacy by combining them with other therapies. They are also searching for biomarkers that could help explain why some patients respond to the antibodies while others do not—information that could be used to identify patients who would benefit from the treatment, and to develop ways of turning those who don't into ones who do. "All of us here have the same end goal," Ravetch says, "We all want to convert more cancer patients into cancer survivors."

Along the way, he and his colleagues may wind up doing even more; for as history has demonstrated time and again, basic research tends to pay unanticipated dividends.

For instance, Vinogradova's work on T cell exhaustion may prove relevant to diseases as disparate as multiple sclerosis and tuberculosis, just as Birsoy's work on metabolism and the immune system could lead to fresh strategies for treating metabolic disorders. Ravetch's Fc research has already led to a novel potential treatment for autoimmune disease that is entering phase 2 trials. And Tavazoie's tumor-shrinking drug grew out of his serendipitous discovery that a gene associated with Alzheimer's disease also drives metastasis—a finding that could lead to a better understanding of Alzheimer's itself.

"That's what's wonderful about science," Tavazoie says. "When you take a systematic approach, it can lead you to make unexpected links between different areas of biology and disease." ◎

ROSHNI KHATRI

NEW INSIGHTS INTO THE STRUCTURE OF THE T CELL RECEPTOR COULD IMPROVE IMMUNOTHERAPIES

Key to most cancer immunotherapies is the process of T cell activation, which prompts the body's immune cells to target threats. Activation of a T cell starts with triggering the T cell receptor, but scientists don't understand precisely how this receptor activates. If they did, drug developers could create immunotherapies that kill more cancers in more patients. T cell receptor (TCR) and chimeric antigen receptor (CAR) T cell therapies, for instance, train patients' T cells to specifically recognize cancer antigens. But while they work well on liquid tumors, response rates are below 25 percent for solid tumors, and no one knows why.

Recently, Rockefeller scientists made a major breakthrough in understanding TCR activation that could go a long way toward designing more effective T cell therapies. Thomas Walz, a leading cryo-electron microscopy expert who heads the Laboratory of Molecular Electron Microscopy, and Ryan Notti, an instructor of clinical investigation in the lab, were curious to uncover what mechanisms underlie the all-important signaling system that kicks off T cell activation. So they devised a new approach to image structural changes of the TCR, which sits inside the cell membrane.

Their findings resolved a decades-old debate about structural alterations a TCR undergoes as it activates. Previous studies suggested that the receptor retains a single shape, or conformation. But when Notti and Walz reexamined the fundamental biology at play, they revealed that TCR has at least two: a closed, resting one, and an active, open one.

With this new information in hand, drug developers may be able to boost T cell activation, extending the benefits of immunotherapy to more patients.

"Our study is a great example of how basic science is essential or accelerating improvements in the clinical space," says Notti, who has since imaged even more of the receptor's conformational states.

Illustration by Veronica Falconieri Hays

Brains in Conversation

Rockefeller scientists are putting their heads together to learn what drives social behavior

By Sarah CP Williams

On the edge of a city sidewalk, hundreds of ants march in a line toward an enemy colony's nest. High above, two birds trade snippets of song back and forth in a call-and-response conversation. On a bench nearby, a mother locks eyes with her baby, and both feel an irresistible pull to smile—a response so automatic it bypasses conscious thought.

These moments, spanning species separated by hundreds of millions of years of evolution, share something fundamental: They are all driven by brains that have been sculpted by social pressures.

"Most sophisticated cognitive abilities probably evolved to support social interactions and social needs," says Vanessa Ruta, Howard Hughes medical investigator, professor and head of Rockefeller's Price Family Center for the Social Brain. "That's true not only in humans, but in much simpler organisms as well."

Yet despite the importance of social behavior to life itself, scientists don't fully understand how our brains let us connect, communicate, and coordinate with each other. How are we wired to so quickly read the energy of a room when we walk into a meeting? What neuronal computations let us predict other people's actions or read their body language? How do memory and attention enable conversation?

Established in 2021 with a gift from Michael and Vikki Price, the Price Center brings together Rockefeller labs using diverse approaches and diverse organisms—from ants and flies to birds and primates—to gain insight into how brains drive social behaviors. Ultimately, these scientists want to not only shed light on the deepest roots of connection

Illustrations by Federica Bordoni

but also explain what happens when those roots falter. Disorders from depression and schizophrenia to autism and Alzheimer's disease can be thought of, at least in part, as disorders of the social brain.

"There is a hope that when we understand these building blocks across organisms, we will understand what are the core features of the social, the specializations that make us human, and what happens when the human social brain goes awry," says Ruta.

The search for answers begins with some of the planet's most social creatures, and with researchers who are starting at the most basic level: watching what happens in the brain when one organism interacts with another.

Ants in synchrony

NEARLY HALFWAY AROUND the world from their native home of Okinawa, Japan, clonal raider ants scurry across containers lining the walls of Daniel Kronauer's Laboratory of Social Evolution and Behavior. Each colony is genetically identical, but the ants don't all act the same. In one setup, worker ants bustle around a collection of pale, rice-grain-sized larvae, gently grooming them and hauling back food from foraging raids. In a second colony, the same ants live without larvae. These workers are less exploratory, less aggressive, and do not leave the safety of their nests while they lay eggs instead.

"The presence of ant larvae completely changes not just the behavior of the adult ants, but their physiology, their metabolism," says Kronauer, also an investigator at the Howard Hughes Medical Institute, whose lab is one of several connected with the Price Center. "In some ways, it's a little bit reminiscent of mammals, but of course, an ant brain is much, much simpler and easier to study."

It's a striking example of how the presence of other organisms can change behavior—we all act differently around a newborn, a close friend, or our boss. But Kronauer's ants also model something else that's key to social animals: Individuals coordinate with each other to benefit the greater collective. In the ant colony that houses larvae, ants specialize. Some care for larvae, while others forage for food.

A decade ago, studying the links between ants' brains and this social behavior seemed nearly

"How do you go from a solitary animal to something that has this rich communication system and complex society?"

KRONAUER

ROSHNI KHATRI

impossible. Ant brains are tiny (smaller than a poppy seed) and encased in a hard exoskeleton. Social neuroscientists had long ignored ants in favor of genetically more tractable model organisms like mice, so the tools didn't exist to breed, study, or genetically alter the insects. But Kronauer, who had carried out field work on ant behavior from the deserts of Arizona to the rainforests of Kenya and Venezuela, was fascinated by the unique—and often humanlike—ways that ants interacted.

To investigate what drove both their cooperation and their competition, Kronauer focused on clonal raider ants. Most ants are incredibly difficult to breed in the lab; only queens lay eggs. But clonal raider ants are asexual and don't have queens. Instead, they all lay eggs, and each new larva is an identical clone of the parent—making them uniquely suited to certain kinds of experiments.

"We can take thousands of genetically identical ants and put them in very different social environments and see how it affects their behavior," Kronauer explains. "It's like a massively scaled-up identical twin study."

But first, his team had to develop ways to record brain activity from individual ants. By engineering the ants' brain cells to light up with fluorescence when they become active, the researchers can now watch the animals' brain activity in real time through powerful microscopes. Using this approach, Kronauer's group found the particular clusters of brain cells that become active when an ant senses alarm pheromones—chemical signals used for communication. This is the first step towards deciphering the neural link between chemical signals and behavioral responses.

But Kronauer's recent work has revealed something even more sophisticated: The neural representation of pheromones in the ant brain changes as the ants age and take on different roles. A young nurse ant responds differently to pheromones than an older forager, even though they're genetically identical. Kronauer says that this could help explain the difference in behavioral tendencies between young and old ants, and he sees parallels with humans. Just as in ants, our preferences and inclinations change as we get older.

Much of his current work focuses on this broad question of how specialized functions evolve in a social species. In ants, the majority of the brain is devoted to processing chemical signals, similar to how large regions of human brains are dedicated to processing speech. Both represent evolutionary solutions to the same challenge: how to create complex societies through sophisticated communication.

"We're interested in how that evolves," Kronauer says. "How do you go from a solitary animal to something that has this rich communication system and complex society?"

Reading faces

JUST AS A single alarm pheromone can commandeer an ant's brain and trigger coordinated colony-wide action, primates have their own irresistible social signals. But instead of chemicals floating through the air, we rely on something far more complex: reading other people's emotions through their faces and body language. When you catch the eyes of another person, for instance, it can hijack your emotional state, activate memories, and even force your own face muscles to mirror what you're seeing.

This phenomenon captivated Winrich Freiwald as he watched interactions between the macaque monkeys in his Laboratory of Neural Systems. A dominant monkey's threatening stare would instantly change the behavior of others nearby. A playful expression could shift the entire social dynamic of the group. Like Kronauer's ants responding to chemical signals, the monkeys seemed unable to ignore these visual cues.

"When you look at a face, that face manipulates you," says Freiwald. "If a baby smiles at you, you have to smile back. You're completely defenseless against this. It actually alters your emotional state and can even control your motor system."

In his work with macaques, Freiwald homed in on what he calls a "mini-brain"—a contained and interconnected area of brain cells in primates that evolved just to process faces. In monkeys, this system is as large as a mouse's entire brain, but it's dedicated to just one task: extracting social information from faces.

Within that mini-brain, Freiwald has mapped distinct specialized regions, each with its own role. Some clusters of brain cells help primates identify individuals they know, while some cells track where other animals' eyes are looking or show activity when the monkeys watch social interactions between other sets of animals. Still others provide direct links between recognition and emotion—explaining why

"When you look at a face, that face manipulates you."
FREIWALD

you might smile the instant you see a familiar face, or feel a sense of dread when you spot an ex-partner across a crowded room.

Freiwald thinks that instantaneous connection between what you see and what you feel could offer a new way to understand the deepest core of human emotions. He already knows which brain cells are active with face recognition; probing what circuits those cells connect to when someone feels a rush of emotion would help him map the brain's emotional wiring.

"What really is a feeling?" Freiwald says. "We don't know a lot about what happens in the brain when we experience emotions, and that makes it very difficult to understand conditions like depression."

But a new understanding of exactly which brain cells are activated with emotions—like sadness, hope, and trepidation—could dramatically advance treatments for depression. By mapping the individual circuits where seeing becomes feeling, Freiwald envisions an approach capable of homing in on specific targets within specific regions using techniques like deep brain stimulation. Precisely placed electrodes could boost activity in just those areas of the brain to restore healthier emotional responses.

"Major depressive disorder is so destructive, and it's become so prevalent," says Freiwald. "But it's also a challenge that I think, through basic research on the brain, we're getting closer to being able to solve."

Learning to communicate

FOR A HANDFUL of the most social species, like humans, reading faces isn't the only thing that forms the backbone of the rich information networks that hold societies together. We have also developed ways to carry out back and forth exchanges of information with our voices. Understanding how this vocal communication evolved, and how it's wired in the brain, could reveal the biological foundations that made human civilization possible.

"The ability to imitate sounds likely started out as a way to show others how intelligent an individual is," says Erich D. Jarvis, head of the Laboratory of Neurogenetics of Language and investigator at the Howard Hughes Medical Institute, pointing out that in certain bird species, males that can make more complex sounds are selected for in mating. "But, over time, in some organisms, it evolved into a way of communicating much more complex social messages."

Most species are born with a fixed set of vocalizations; a dog's bark or a cow's moo don't change much throughout their life. But for those known as vocal learners—a limited set of animals including humans, songbirds, parrots, dolphins, whales, and some bats—learning to produce new sounds represents a unique evolutionary adaptation and signals more flexible cognitive abilities.

For years, Jarvis has used songbirds to study how the brain allows vocal learning. His lab has uncovered what parts of the birds' brains help them learn new songs and has shown that songbird species with more advanced vocal learning abilities are also better problem solvers and have larger brains. Most recently, his group has found that only vocal learning species can learn to dance, synchronizing their movements to a musical beat.

But there is a larger lesson that ties Jarvis' various findings together: Vocal learning comes as a cognitive package deal. Species that can imitate sounds have more direct connections between a brain region involved in learning (the cortex in the forebrain) and brain cells that control movement (motor neurons in the brainstem).

"The evolution of spoken language is associated with more complex cognitive behaviors," Jarvis says. "These genetic changes with vocal learning are influencing other cognitive pathways, which may help explain how spoken language allowed human civilization to flourish."

For Jarvis, vocal learning and language aren't quite the same thing, though they're deeply connected. It appears that the ability to hear sounds and reproduce them lays the biological foundation that makes complex spoken language possible. In other words, the brain circuits that allow a songbird to learn new melodies are evolutionarily related to those that let humans learn to speak.

But his research goes beyond just understanding how we communicate through sound. He's learning how the same genetic pathways that enable vocal learning also seem to enhance other cognitive abilities—pattern recognition, problem-solving, even the ability to learn dance rhythms.

"We think vocal learning is a window into how the brain adapts and forms new connections," Jarvis explains.

ROSHNI KHATRI

"The evolution of spoken language is associated with more complex cognitive behaviors."
JARVIS

Understanding how brains learn to imitate sounds could shed light on how to boost the brain's ability to learn other things, communicate better, or heal. To achieve this, Jarvis has turned to mice—normally not a vocal learning species. But in his lab, genetically modified mice are doing something that should be impossible: They're producing more complex sounds and sequences of sounds. When he plays back the animals' ultrasonic vocalizations, the females prefer more complex sounds.

"When you pitch it down to our range, mice's ultrasonic vocalizations almost sound like songbirds'," says Jarvis.

The key to the mice's melodies: Jarvis and his team locally shut off a gene in the brain that usually prevents connections between their forebrain and motor neurons. Without the gene, the mice's forebrain cells grew new, humanlike connections, the animals modified the control of their vocal muscles, and then they started producing more complex sequences.

Next, Jarvis wants to study humans more directly, using MRI scans to gauge brain activity in people as they imitate new phrases or songs. That's part of his research with the Price Center's support.

"Very few people have studied the mechanisms of vocal learning in human brains," he says. "They study speech production and processing, but not the actual imitation of sounds."

The research has immediate clinical relevance. Stroke patients who lose language abilities can sometimes recover through intensive practice. Jarvis learned that bird brains with damaged song-learning regions initially caused the animals to stutter. But, over months, these birds gradually recovered, as new neurons integrated into the damaged circuits. Understanding this repair process could improve rehabilitation strategies.

A potential connection to autism is equally compelling: Many genes the Jarvis team has identified in vocal learning pathways show variations in children with autism, potentially explaining communication difficulties. These findings could eventually point toward treatments that strengthen or repair these brain circuits.

The attention filter

PICTURE A FATHER chatting with his toddler as they walk across a busy street. A car suddenly speeds around the corner; he instantly stops talking and pulls the child closer. It's a split-second shift that requires the brain to filter out one stream of information and amplify another—a process called sensory gating that happens thousands of times a day. Without this ability, every sound, sight, and sensation around us would compete equally for our attention, making it impossible to focus on any one thing.

"This ability to quiet distracting inputs while amplifying important ones is crucial for navigating social situations," explains Priya Rajasethupathy, whose Laboratory of Neural Dynamics and Cognition studies memory and attention. "You need it to focus on a friend's voice in a noisy restaurant, or to notice when someone's facial expression shifts during a conversation."

When sensory gating fails, social interactions become overwhelming. People with autism often describe feeling bombarded by sounds or textures that others barely notice. Those with schizophrenia may struggle to distinguish between external voices and internal thoughts. Even ADHD can make it difficult to track group conversations or pick up on subtle social cues, raising questions about how our increasingly noisy environment might be affecting many people's social abilities.

Rajasethupathy became interested in these connections when a graduate student in her lab, Zachary Gershon, started studying attention in mice. Some animals were clearly better at filtering distractions than others. When trained to respond to specific tones for food rewards, focused mice reacted quickly, while others were slower to notice the cue. Working with hundreds of genetically diverse mice, Gershon scanned the genome and pinpointed one gene that had a large contribution to their attention: *Homer1*. Mice with lower levels of *Homer1* were much better at focusing and faster to earn their reward.

"What was really striking to us is that most drugs for ADHD stimulate the brain," says Gershon. "But *Homer1* works by quieting the noise in the brain.

> *"The ability to quiet distracting inputs while amplifying important ones is crucial for navigating social situations."*
>
> RAJASETHUPATHY

ROSHNI KHATRI

In both cases, you're changing the signal-to-noise ratio, but this gene is doing that in a different way."

Gershon notes that humans with ADHD often have mutations in genes that work alongside *Homer1*. *Homer1* itself is rarely altered in these conditions, but the genes it partners with—like spokes connected to a central hub—often are. In addition, the gene is associated with schizophrenia and autism in humans, suggesting that early dysfunctions in sensory gating may underlie a range of symptoms including hypersensitivity, hallucinations, and social-motor compensations. *Homer1*, Rajasethupathy says, could be altered with therapeutics in the future.

"For patients where stimulants are not effective, or have ceiling effects, *Homer1* may be an effective alternative target," she says.

To test that theory, postdoc Manoj Kumar is growing human cells into small clusters of neuronal tissue, referred to as 3D brain organoids. By adjusting *Homer1* levels in these human brain organoids and measuring their electrical activity, researchers can study exactly how the gene filters neural signals to noise and whether pharmacological compounds can mimic this effect.

The Rajasethupathy lab is also using such human brain organoids to test the function of genes they've identified as key to memory processing. The organoids provide a way of confirming whether genes identified in mouse studies work similarly in the human brain. They also provide a high throughput platform to identify new pharmacological compounds to target these genes, which may be helpful with memory disorders, or even the normal forgetfulness of aging.

The research on attention and memory both reflect something deeper. Many psychiatric conditions that we consider social disorders may actually stem from disruptions in the fundamental brain processes that make social interaction possible. If sensory gating develops abnormally early in life, for instance, Rajasethupathy suspects it creates a cascade of other problems; children with autism or attention deficit disorders who can't filter distractions struggle to focus on faces, voices, and social cues during times their brains should be learning to navigate our social world. And that potentially exacerbates difficulties that then persist into adulthood.

"A huge part of our cognitive capacity is meant to serve our social function," notes Rajasethupathy. "So much of what we use these systems for is social."

Lessons from fruit flies

OVER HUNDREDS OF millions of years, evolution has run the same experiment again and again: How do you wire a brain for social life? The solutions are wildly diverse—chemical communication in ants, vocal learning in songbirds, face processing in primates. Yet beneath this diversity lie shared principles that different species use to predict, communicate, and cooperate.

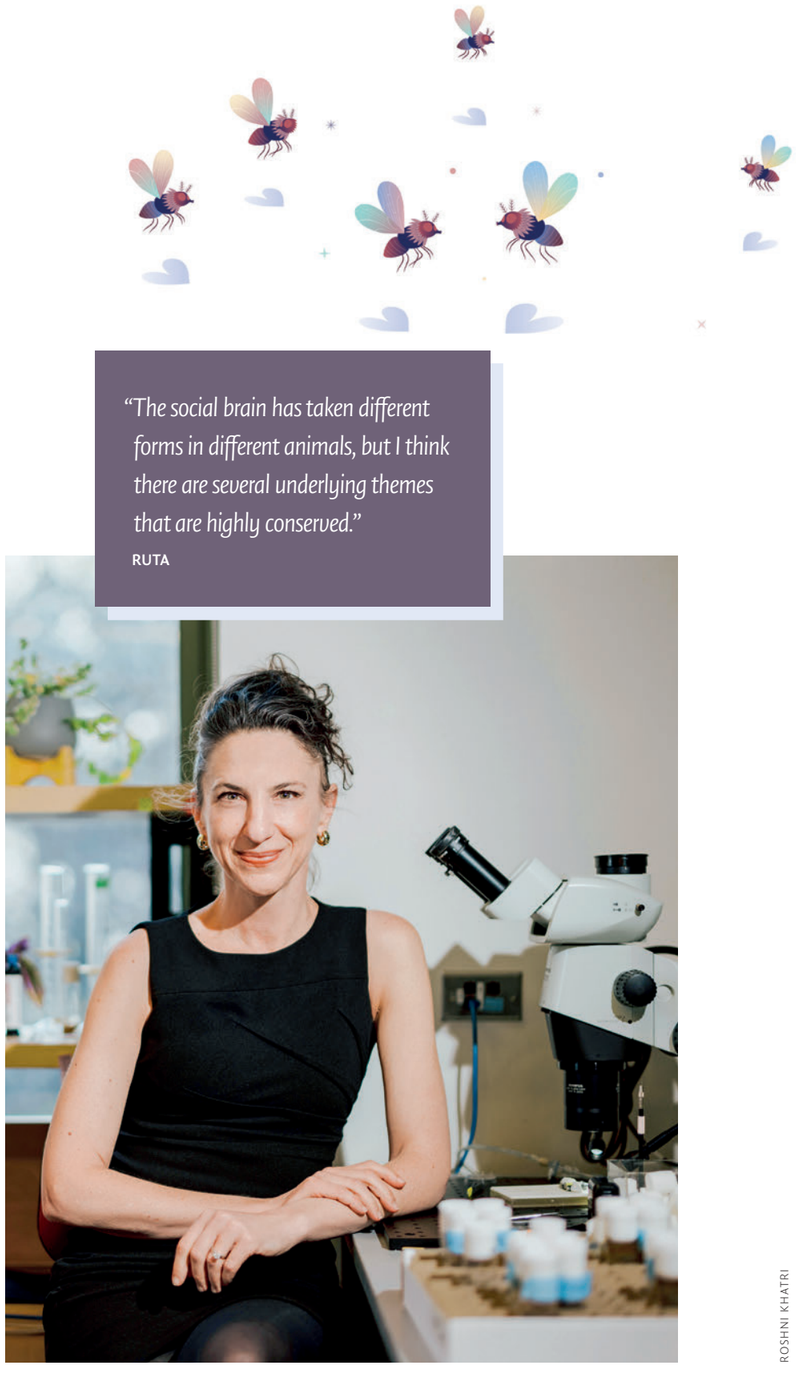
That's why Ruta's choice animal model—tiny *Drosophila* fruit flies—makes perfect sense for asking big questions about social behavior. Their brains contain only 100,000 neurons, yet they court mates, compete for territory, and make split-second social predictions. By studying how such a simple brain accomplishes sophisticated social feats, Ruta can identify the essential computational building blocks that likely operate in all social species, including humans.

Ruta, head of the Laboratory of Neurophsiology and Behavior, is particularly interested in the innate, hardwired aspects of social behavior—the built-in circuits that don't require learning. These are likely driven by ancient brain pathways that have remained largely the same between species and only produce distinct types of behaviors because of small evolutionary tweaks.

"What makes social interactions so valuable to study is that animals naturally engage in these rich social behaviors," says Ruta. "In the vast majority of species, including flies, animals don't have to be trained to fight or to mate."

Like Kronauer's work with ants, Ruta has developed ways to measure fly brain activity during social interactions. Her lab also pioneered machine learning approaches to track how animals move with millisecond precision and developed virtual reality systems that let researchers control what a fly sees in its social environment while recording its brain activity. Using these techniques, she recently pinpointed the neurons that help male flies balance aggression and courtship when competing for mates.

"One of the things we have been really interested in is how the internal state of an animal shapes the way it responds to social cues in the environment," explains Ruta.



"The social brain has taken different forms in different animals, but I think there are several underlying themes that are highly conserved."

RUTA

ROSHNI KHATRI

It's a phenomenon humans know well; when you're in a good mood, a colleague's neutral expression might seem warm and inviting, but when you're already angry, that same expression can feel cold or dismissive.

Her team showed how this kind of shift happens in the fly brain. Once male flies become sexually aroused, Ruta discovered, they perceive even simple moving targets—like two-dimensional dots projected onto the floor—as potential mates. In the flies' brains, it turned out, visual neurons became more sensitive during this time.

In ongoing experiments, her lab is exploring how, during courtship, male flies don't just react to females; they predict where females will move next and position themselves accordingly. It's a rudimentary form of the same social prediction that lets you anticipate when someone will finish speaking or where a friend will sit at a familiar table.

"The social brain has taken different forms in different animals, but I think there are several underlying themes that are highly conserved," says Ruta. "These basic building blocks of what a social brain has to carry out—communication and coordination—are the same across social species."

Understanding how fly brains carry out these social calculations might eventually hint at how primate brains accomplish similar feats. The more basic principles emerging from her fly studies—like how they integrate different pieces of information in order to make split-second decisions—likely apply across the animal kingdom.

Labs in conversation

FROM THE CHEMICAL trails that coordinate ant colonies to the neural circuits that help humans decode facial expressions, a common thread runs through this research: deciphering how individual brains work together to create something larger than themselves. Just as social brains require constant communication between individuals, understanding those brains requires constant communication between researchers.

Each Rockefeller scientist approaches the puzzle from a different angle, but their insights converge, underscoring the ancient roots of the social brain. Kronauer, for instance, discovered that an ant version of oxytocin—the human "bonding hormone"—shapes ants' social behavior. In brain pathways important for vocal learning in songbirds, Jarvis and his team have turned up some of the same genes Rajasethupathy's team has discovered to be involved in memory in mice.

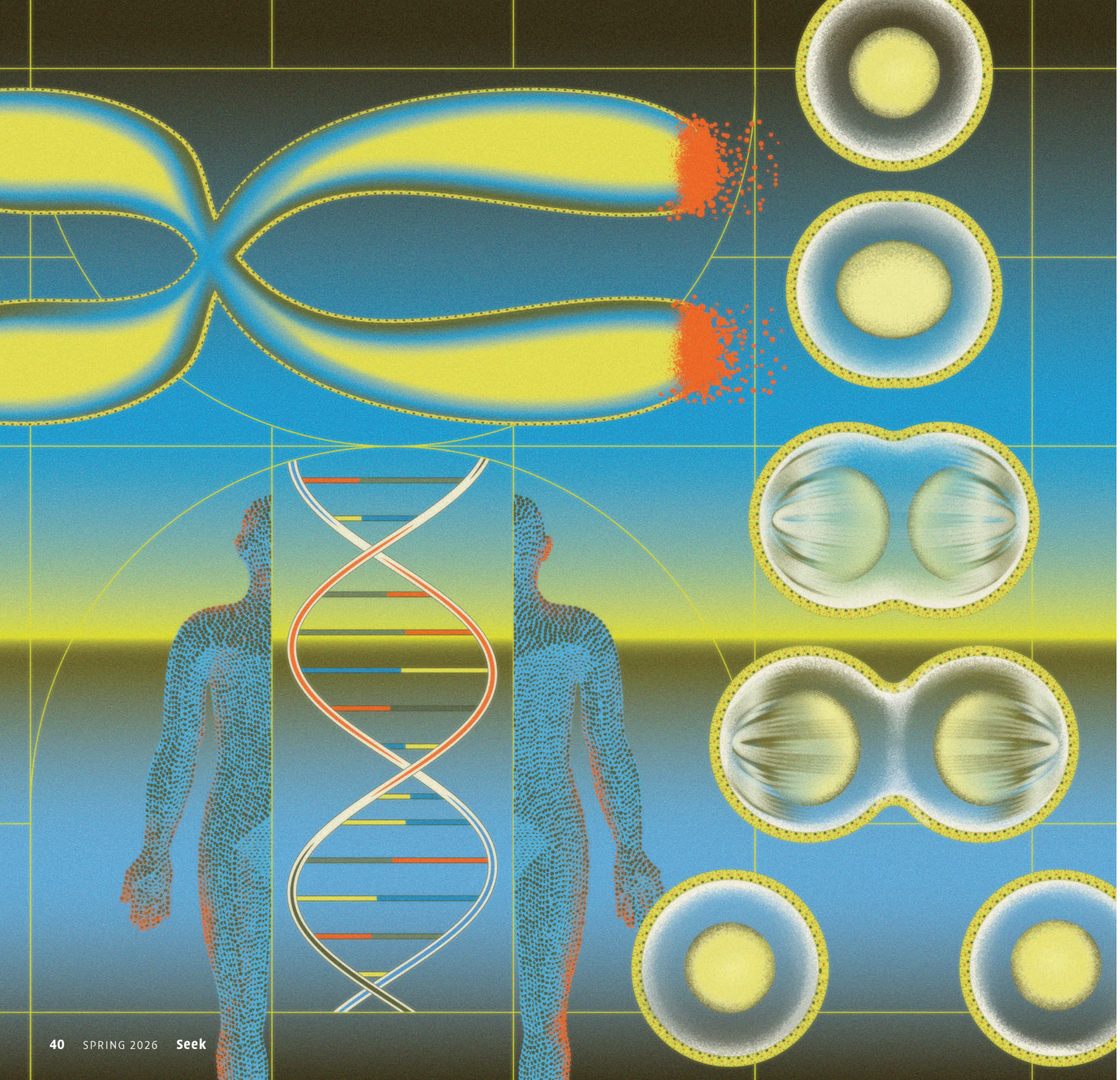
These kinds of links often emerge from casual conversations at meetings and seminars—as did the need for collaborative approaches to overcoming common technical obstacles. "The challenges we face in studying social behaviors are similar across species," adds Ruta. "Whether you are tracking ants, flies, or primates, you need ways to quantify complex, dynamic behaviors and relate them to what's happening in the brain."

Recognizing this shared challenge, Price Center researchers have been pooling their expertise to develop tools that accelerate discoveries across the entire field. For instance, machine learning algorithms that track individual ants in a colony can be adapted to follow flies during courtship or monitor facial expressions in monkeys.

And as each discovery lays the foundation for the next, their collective work further illuminates one of the most entrancing mysteries in neuroscience.

"You will never see or hear or touch or taste anyone else's thoughts or feelings or intentions, but you're making all these inferences," Freiwald notes. "The most complex thing for your mind to understand is the mind of someone else. Because that mind is just as complex, and as you're trying to understand it, it's trying to understand you."

Such is the marvel of our social brain. ◎



Scientists are studying the molecular machines that read, copy, repair, and package DNA. Their findings could change how we prevent and treat diseases, including cancer.

THE MACHINERY OF LIFE

Right now, in nearly every cell of your body, microscopic machines are copying your DNA. Clusters of proteins glide down each strand of genetic material, racing to assemble a full replica of your genome before the cell divides. Six billion base pairs are duplicated in about eight hours.

At the same time, other molecular machines are repairing DNA that's been damaged by sources including ultraviolet light and pollution, reading the genetic code to produce proteins, and reorganizing how DNA is packaged to control which genes stay active and which fall silent. In every cell, DNA is under constant management by dozens of tiny machines that copy it, fix it, read it, and protect it.

These machines keep us alive. When they falter, the consequences are severe: Genetic mutations that go unrepaired or genes that are inadvertently turned on or off can accelerate aging and trigger cancer, spiral into neurodegeneration, or give rise to devastating inherited diseases.

"DNA repair and maintenance are absolutely crucial for life," says Agata Smogorzewska, the Skoler Horbach Family Professor and head of Rockefeller's Laboratory of Genome Maintenance. "Even partial deficiencies in these pathways can disrupt cell function and lead to disease, including cancer."

For more than eight decades, Rockefeller has been mining the mysteries of these minuscule machines. In 1944, physician-scientist Oswald Avery and his Rockefeller colleagues Colin MacLeod and Maclyn McCarty were the first to demonstrate that DNA carries genetic information, a discovery that launched the entire field of molecular genetics. Now, researchers across the university are dissecting how cells process, protect, and use that genetic material. What they're learning could one day lead to targeted therapies that may allow us to repair damage in cancer cells, aging tissues, and genetic disorders.

Illustration by Petra Péterffy

GENETIC COPY MACHINES

THE REPLICATION FORK is the region where the DNA double helix separates into two single strands so that each can be copied; it's one of the most dynamic sites in the cell. At each fork, proteins move along the exposed templates, reading the genetic sequence and synthesizing new DNA at an average rate of about 50 nucleotides per second in human cells. This is where DNA replication happens—it's also a major source of potential errors that must be corrected by a wide variety of repair proteins, or corrected "on-the-spot" by the replication machinery itself. If a replication or genomic repair protein becomes mutated, the outcomes can be lethal.

If scientists could fix damaged genes or remove cells with harmful mutations, they could help cells stay better protected when DNA replication and repair systems fail or become overwhelmed. In fact, DNA replication and repair lie at the heart of many diseased states. For example, when abnormal amino acid is present within the replicative DNA polymerases, that can render them far less accurate than normal, leading to mutations during cell division that are associated with cancer.

Polymerases aren't the only potential vulnerabilities; there are numerous DNA repair factors and other DNA replication proteins that, when mutated, can also contribute to cancer and a wide range of other diseases, including conditions associated with premature aging."There's much we have yet to learn, but understanding all the complexity of how DNA replication and DNA repair machinery works will ultimately lead to new medical breakthroughs," says Michael O'Donnell, head of the Laboratory of DNA Replication and an investigator at the Howard Hughes Medical Institute.

O'Donnell has spent more than 30 years patiently teasing out the staggeringly complex dance of DNA—what mechanisms govern its replication and what factors keep errors in check—to explain not just what missteps lead to rapid aging and cancer, but also neurological disorders. Early on in his research, he discovered the first protein known to encircle DNA; later studies have shown that it plays a role in all cellular life. This ring-shaped protein, known as proliferating cell nuclear antigen (PCNA), slides along DNA, physically tethering other proteins to the DNA to help them stay attached until their task in replication or repair is complete. O'Donnell and other scientists have also

> "There's much we have yet to learn, but understanding all the complexity of how [this DNA] machinery works will ultimately lead to new medical breakthroughs."
>
> ● O'DONNELL

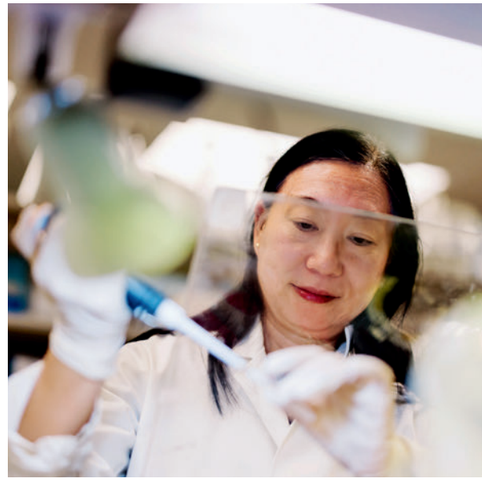
ROSHNI KHATRI

revealed how the PCNA ring gets loaded onto DNA—another protein complex called replication factor C (RFC) opens the ring, positions it around the double helix, and snaps it shut. Then, according to every previous model, RFC drifts away.

But O'Donnell suspected that if he took a deeper look at RFC, he'd find more to this story. Recently, he teamed up with Shixin Liu, head of the Laboratory of Nanoscale Biophysics and Biochemistry, to study the details of how and when RFC and PCNA interact with DNA. They stretched a single strand of DNA between two microscopic beads held in place by lasers. Then they added RFC that glowed green and PCNA that glowed red. Under the microscope, the researchers spotted a dot of yellow—red and green merged in the same place—moving along the strand of DNA. The new data suggested that RFC remains bound to PCNA throughout the entire replication process, traveling down the DNA together as its own complex.

"It's not a result that a lot of people were expecting," says Gabriella Chua, a postdoc in O'Donnell's lab and former graduate student in Liu's lab. "RFC was thought to do its job and leave the scene—and now we know that it remains bound and plays a functional role."

Work like this has helped PCNA emerge as a potential drug target for cancer. Because it serves as a hub that binds dozens of different DNA replication and repair proteins, it acts like a master switch. Block PCNA's interactions, and you could simultaneously prevent cancer cells from copying their DNA and repairing chemotherapy damage.



Nina Y. Yao, a research associate in the O'Donnell lab which studies the molecular mechanisms of DNA replication, recombination, and repair.

THE DNA FIX-IT CREW

CHILDREN BORN WITH Fanconi anemia face devastating complications from birth: missing thumbs, malformed bones, and heart defects requiring early surgery. Later in childhood, their bone marrow begins to fail, and they develop aggressive mouth and throat cancers usually only seen in lifelong smokers. Their health challenges are all because of a single molecular failure: Their cells cannot repair a type of DNA damage known as interstrand cross-links, where the double helix's two strands become glued together when they should separate for copying.

The damage that causes this disease may sound severe, but it's actually routine—it occurs constantly, in every person's DNA. Ultraviolet light from the sun, air pollution, grilled meat, and alcohol chemically alter DNA. Even normal everyday activities in our cells, such as turning food into energy or controlling gene activity, generate reactive molecules that attack the genome multiple times each day.

"The only difference between the DNA damage that is accumulating in people with Fanconi anemia and in the rest of us is that most of us have a functioning system for repairing the damage," Smogorzewska points out.

Cells have evolved an intricate surveillance system—molecules that detect damage and dispatch repair crews to fix problems before they become permanent, or stop cells from dividing when they've accumulated too much genetic wear and tear. In most people, this fix-it crew keeps us healthy most of the time. But when these systems fail, it has huge implications: newly introduced

genetic mutations can drive cancer, accelerate aging, trigger neurodegeneration, or derail development before birth.

Smogorzewska has identified some of the 23 genes that, when mutated, lead to the inability to repair DNA cross-links, resulting in Fanconi anemia. Thus, studying these genes, she says, not only could lead to treatments and earlier diagnoses for patients, but offers a window into how DNA repair works when it's functioning properly.

Understanding how to make the cross-link repair pathway more active or less active could also inform therapies. Turning up the pathway would be a boon to people with Fanconi anemia—their cells could begin repairing the damage so it doesn't accumulate. Many labs are working on gene therapy to correct the underlying genetic problem. A huge challenge there, however, is ensuring these therapies reach cells all over the body.

For those patients with normal DNA repair, on the other hand, turning down the Fanconi anemia pathway could help eliminate tumors: Cancer cells would die when unable to repair cross-links induced by chemotherapy drugs. But at the moment, selectively targeting this pathway remains extremely challenging. Many dividing cells in the body rely on cross-link repair machinery to survive daily DNA damage. Turning the pathway down in stem cells could trigger mutations leading to cancer.

Another avenue for therapeutic intervention in Fanconi anemia patients is preventing the damage from occurring in the first place. To that end, learning more about the cells' own sources of DNA damage could inform strategies for reducing or blocking this damage before it occurs. While the Smogorzewska lab is working on the disease-driving processes, they're simultaneously developing ways to halt and even reverse cancer at early stages of its development

Work in the Smogorzewska lab has led to the identification of genes that repair DNA interstrand crosslinks.

ROSHNI KHATRI

> "The only difference between the DNA damage that is accumulating in people with Fanconi anemia and in the rest of us is that most of us have a functioning system for repairing the damage."
>
> ● SMOGORZEWSKA

in Fanconi patients. Thus far, her group has identified biomarkers that they will test in a cancer prevention trial that her lab will soon be starting.

DNA cross-links, of course, represent just one type of obstacle the replication machinery encounters. Other types—breaks in the DNA itself or extra chemical groups stuck to a strand—must also be repaired or avoided while DNA is being duplicated, to prevent the errors from being passed to new cells. Often, the copying machinery pauses while a repair mechanism swoops in to fix the problem.

O'Donnell and Liu have studied this machinery with their single-molecule approach. Their data suggested that when the replication machinery encounters a lesion, one of its key components—the Cdc45-Mcm2-7-GINS (CMG) helicase—doesn't simply stay at the replication fork. Instead, it leaves the fork yet stays attached to the DNA. Once the damage is fixed, the molecule reenters the fork and reassembles the machinery to continue copying. It is a feat, they found, made possible by CMG's ability to shapeshift on DNA.

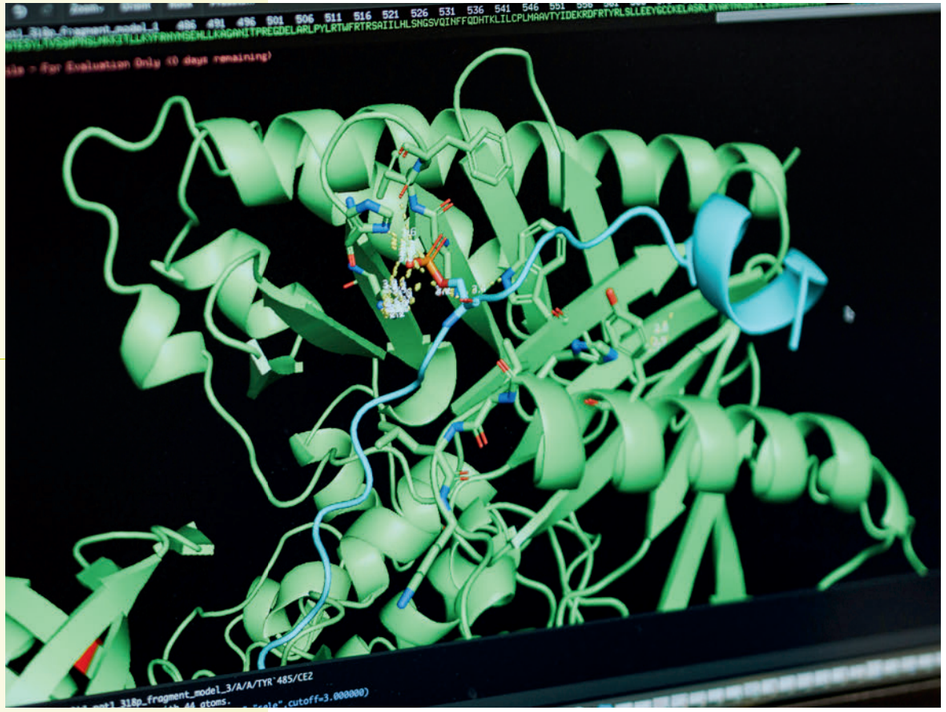
O'Donnell's team also uncovered how Polymerase Alpha, the enzyme that initiates each new DNA strand, can bypass certain common types of damage on its own. It's a strategic trade-off that keeps replication moving when repair isn't fast enough, allowing damage to be fixed later.

● CHROMOSOME CARETAKERS

SOME CHANGES IN our DNA are not due to the onslaught of mutagens or mistakes in DNA replication, but occur slowly with each cell division. When the machinery that duplicates DNA gets to the end of a chromosome, it stops before it has copied the last few dozen base pairs. This process gradually shortens the chromosome's protective caps, called telomeres, which are regions composed of a repeated sequence and the specific protein complex shelterin. If the number of repeats is sufficient, shelterin can bind and protect the chromosome ends. Without shelterin's protection, cells respond to their telomeric ends as if they are DNA breaks, which stop cell division or lead to genome instability.

When cells have undergone many divisions, the telomeres become very short, and there is no longer enough telomeric DNA for shelterin to hang on to. As a result, cells stop dividing and undergo a process

> Anything critical to telomere length regulation may well be critical to cancer prevention too. This is a major focus of our lab.”
>
> ● DE LANGE



The de Lange lab studies the role of telomeres in cancer.

ROSHNI KHATRI

called replicative senescence or die. “This is actually a great thing, because it keeps cells from dividing indefinitely,” says Titia de Lange, the Leon Hess Professor and head of the Laboratory of Cell Biology and Genetics. “In fact, we now know that telomere shortening is one of the most powerful barriers to cancer development.”

For this cancer barrier to work, telomeres need to have the right length at birth: not too short and not too long. If telomeres are too short, cells stop dividing sooner, and this limits tissue maintenance and repair. If the telomeres are too long, early cancer cells can undergo many more divisions before they reach the barrier, frequently leading to tumor formation. “How the length of our telomeres at birth is regulated is poorly understood,” de Lange says. “Because of the importance of this issue to cancer prevention, this is a major focus of our lab.”

On the other hand, many cancers find a way to circumvent the telomere barrier by activating telomerase, the enzyme that can add telomeric DNA to chromosome ends. “Telomerase is a great target for cancer therapy,” de Lange says. “Past worries about the effect of telomerase inhibitors on stem cells may have been unfounded. It would be wonderful if somebody found a good small molecule inhibitor of telomerase to test in preclinical models.”

● SPEED CONTROLS

COPYING DNA IS only the beginning. To turn DNA’s instruction book into the proteins that carry out much of the molecular work in living tissues, cells rely on an enzyme called RNA polymerase II (Pol II), which was first identified over 50 years ago by Robert G. Roeder, head of Rockefeller’s Laboratory of Biochemistry and Molecular Biology. When a gene is activated, Pol II latches on to the beginning of the gene and scans the code, churning out a corresponding strand of RNA through a process called transcription that can be shuttled to protein-making machinery elsewhere in the cell.

The speed at which Pol II moves along DNA, it turns out, matters a lot. After it latches onto a gene, Pol II first crawls slowly, often pausing near the start. Then regulatory proteins kick in, propelling it into high-speed transcription mode. Near the gene’s end, it decelerates again to finish cleanly. This pacing must sync seamlessly with the machinery that processes and packages RNA. Move too fast or too slow, and RNA molecules emerge malformed or misprocessed, and the risk of genome instability increases. Failure to properly control transcription speed has been linked to developmental disorders, neurodegenerative diseases, and cancer.

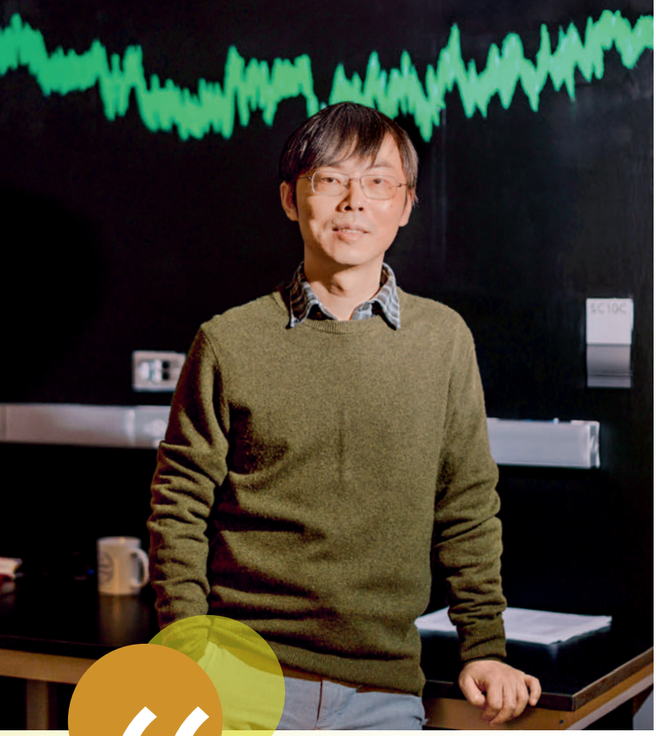
“I’m often asked: As long as it can make RNA and we know how it does it, do we really care about the speed of the machine or whether it pauses?” says Liu. “We care because we know that the altered kinetics of transcription are linked to various diseases.”

To learn more about how cells control the speed of Pol II, Liu recently collaborated with Joel E. Cohen, head of the Laboratory of Populations, and a group of scientists in China. Their labs built a unique platform that reconstructed an entire transcription system using purified proteins—not just Pol II, but all of the other proteins that play a role in the process at the same time. This allowed scientists, for the first time, to watch these molecules move on DNA and produce RNA in real time.

The result was an incredibly precise view of a molecular engine in action, revealing exactly when and where Pol II accelerated, paused, or shifted gears, and which other proteins helped control each transition.

“Our platform allows us to objectively assess when this machine shifts gears, and how fast it goes,” explains Cohen.

The team opened up a molecular gearbox: a hierarchy of regulatory proteins working in concert to



control speed. One protein acts as the master switch, chemically modifying Pol II to unlock its activity. Others serve as accelerators, stabilizers, or brakes, each binding at specific moments to push the enzyme faster or hold it back.

"What's really striking is how this machine functions almost like a sophisticated automobile," Liu says. "It has the equivalent of multiple gears, or speed modes, each controlled by the binding of different regulatory proteins. We figured out, for the first time, how each gear is controlled."

The hierarchy also reveals potential drug targets. One of the master control proteins, positive transcription elongation factor B (P-TEFb), was already known to be a promising target for leukemia and solid tumors, including breast, pancreatic, and ovarian cancers; blocking it can keep the cancer cells from expressing their malignant genes. But scientists have struggled to do so without toxic side effects on healthy cells. Understanding exactly how it fits into the larger speed control system could enable more precise therapeutics.

"Our work may offer clues for designing more specific therapeutics, and a better understanding of what could go wrong in disease," says Liu.

"What's really striking is how this machine functions almost like a sophisticated automobile. It has the equivalent of multiple gears, or speed modes, each controlled by the binding of different regulatory proteins."

● **LIU**

● GENOME ARCHITECTS

DNA ISN'T JUST a long flat string of genetic code. It's carefully wrapped around proteins called histones, which are organized into chromatin—a complex packaging system that controls which parts of the genome are active and which should be silent by determining which sections can be accessed by molecular machines. This architecture makes it a challenge for replication, repair, and transcription machineries to access the genetic code.

Viviana I. Risca, head of the Laboratory of Genome Architecture and Dynamics, has developed ways to map the organization of chromatin proteins inside cells. She has shown how changes in this architecture can alter cancer cell biology—work that could contribute to the development of new cancer therapies.

Risca's lab is investigating the mechanism by which loss of function of proteins associated with chromatin organization—including linker histones, which help compress histone-wrapped DNA into its most compact form—can alter gene expression, which other groups have shown contributes to the emergence of blood cancers.

ROSHNI KHATRI

"The importance of linker histones in compacting chromatin in blood cells agrees very well with human patient data where linker histones are some of the most highly mutated genes in lymphoma cases," Risca says.

These mutations can trigger a cascade of events: chromatin regulation fails, genes or stretches of repetitive "junk" DNA that should stay silent become active, and DNA repair systems cannot keep up with the onslaught of damage from all this activity on DNA. The Risca lab's work showed that the molecular mechanism by which the chromatin regulation fails involves unfolding of chromatin throughout the genome, which has context-dependent effects on genes. As a consequence, a cell's ability to maintain a stable identity—say, a B cell's ability to remain a B cell—is compromised. The gene expression patterns suggest that it reverts to a more primal state that divides uncontrollably and becomes cancerous.

Risca's work has also revealed something unexpected about cancer treatment. When breast cancer cells are treated with standard chemotherapy, most tumor cells die, but some persist in a kind of resting state known as senescence. As the cells enter senescence, Risca and Justin Rendleman, a postdoc in her lab, discovered that the cells begin expressing genes not usually active in adult tissues. These aberrant genes mark the drug-resistant cancer cells like a red flag and present a potential opportunity to target them with additional therapies that will kill them without harming healthy tissue. The Risca lab is currently exploring such avenues and working to understand how the rearrangement of tumor cell chromatin during drug-induced senescence turns on such marker genes. It's just one example of how understanding chromatin architecture could unlock new therapeutic strategies.

The broader lesson from chromatin research is that DNA management operates at multiple levels simultaneously. Cells must not only copy DNA accurately and repair damage quickly; they must also organize the genome so that the right genes are accessible at the right times, repair machinery can reach problem sites, and transcription machinery moves at appropriate speeds.

When any of these levels fails—replication, repair, transcription, or packaging—the whole system can unravel. Understanding how they work together, and how they fail individually, is essential for developing therapies that target disease at its molecular roots.

"Just as the work of Avery, MacLeod, and McCarty ignited the molecular revolution by revealing DNA as the basis of heredity, current research at the university aimed at understanding the fundamental biology of genome maintenance will drive future therapeutic breakthroughs," says Smogorzewska. "The impact on human health could be equally revolutionary." ◎

LORI CHERTOFF

"Linker histones are some of the most highly mutated genes in lymphoma cases."

● **RISCA**

INTERVIEW

A deep understanding of how immune cells respond to infection could revolutionize vaccine design.

How basic biology helps build better vaccines

By Megan Scudellari

Vaccines are one of the most impactful public health interventions in human history. Today, a child younger than 10 years old is 40 percent more likely to survive until their next birthday than they would be in a hypothetical scenario in which childhood vaccination did not exist.

Since the 1790s, when Edward Jenner first observed that dairymaids who had been infected with cowpox were protected against smallpox, rigorous research by scientists exploring the basic biology of the immune system has sparked breakthrough after breakthrough, resulting in the development of vaccines for dozens of infectious diseases, from chicken pox to COVID-19.

While those successes are to be celebrated, much work remains. For instance, we still do not know why many potential vaccines fail, why some are effective for a lifetime but others only for a few years, or how one might coax the immune system to better control cancer cells or HIV infection.

Today, immunologists have new ways to address these pressing questions, using advanced analytic and experimental technologies to test and design vaccine components from scratch. They can also directly measure how vaccines affect immune system cells, including B lymphocytes—or B cells—which create antibodies.

We invited three of Rockefeller's immunologists—Michel C. Nussenzweig, Marina Caskey, and Gabriel D. Victora—to discuss how research into the intricate details of immune system function can help improve today's vaccines and unlock the next generation of preventative and therapeutic immunizations.

Nussenzweig is Rockefeller's Zanvil A. Cohn and Ralph M. Steinman Professor, head of the Laboratory of Molecular Immunology, an investigator at the Howard Hughes Medical Institute, and co-director of the SNF Institute for Global Infectious Disease Research. His work explores the molecular

Illustration by Rose Wong

aspects of the immune system's innate and adaptive responses. Caskey is a professor of clinical investigation in Nussenzweig's lab, where she develops and evaluates novel therapies for infectious diseases. Victora is the Laurie and Peter Grauer Professor, head of the Laboratory of Lymphocyte Dynamics, and a Howard Hughes Medical Institute investigator. He studies the processes by which the immune system refines its response to infection.

What are your current research interests, and how do they relate to vaccine development?

Gabriel D. Victora: Designing a vaccine or a therapeutic intervention requires fundamental knowledge of all the different parts of the immune system and how they work together. We're interested in that biology: We investigate in depth how B cells behave and try to find out how to get the best antibodies out of those cells. This serves as a basis for any future clinical exploration by others of how to elicit a particular antibody response. If we can more thoroughly understand the function and evolution of B cells, it will enable the development of vaccines that prompt the immune system to produce the best B cells to fight off infection.

Michel C. Nussenzweig: With chronic infections of viruses such as HIV and hepatitis B, some people have immune systems that are able to control the infection. We are working on understanding how the immune system does that, so the knowledge can be used to craft vaccines to help prevent infection or control it with a single shot, rather than a lifetime of medications.

We continue to do a lot of basic work to understand antibody response to infection in mice, and in humans as well. We study how certain B cells decide to respond to an infection, and, once engaged, what they do in order to develop an optimal response. We hope that knowledge will help create better vaccines for evolving viruses. Right now, vaccines for these types of viruses have to be given every year, such as with the flu and COVID-19. That's not ideal. If we can understand how and when B cells produce a long-lasting antibody response, we can potentially prompt the immune system to make antibodies that have a more lasting impact.

Marina Caskey: My main focus of research has been HIV, though we now have projects related to hepatitis B as well. One of the big challenges of HIV is that the virus can change itself very rapidly. It modifies its structure over time so that previously existing

Marina Caskey

Gabriel Victora

Michel Nussenzweig

antibodies can no longer bind to it. This dynamic turns into a competition between the virus and the immune system. Unfortunately, the virus usually wins the race and escapes from the immune system. That's why there is no current effective vaccine against HIV.

To both treat and potentially prevent HIV with a vaccine, we are exploring the use of broadly neutralizing antibodies (bNAbs). These are antibodies that recognize and attach to many different forms of HIV because they are able to target parts of HIV that need to be conserved. We are working to identify the right combination of bNAbs to use as a therapy to reduce the so-called "reservoir" of HIV infection, so that HIV levels become undetectable in patients. Additionally, if we identify the right antibodies, we can use them as a blueprint to design a vaccine that prompts the immune system to make its own bNAbs.

What are the biggest mysteries you're trying to solve about the immune system?

MCN: So far, the field does not know enough to design vaccines against some truly important pathogens, such as HIV and norovirus, plus we do not have a universal flu vaccine that protects against all strains of influenza. Many of these pathogens are adroit at evading typical immune responses. For example, pathogens that evolve rapidly, like flu or HIV, change bits and pieces on the outside of the viral particle that the immune system would normally recognize. Finding and targeting viral elements that cannot change is part of what we do.

Several years ago, our lab identified two broadly neutralizing antibodies that target those conserved viral elements on HIV in the blood of people whose bodies have successfully combated HIV without the help of drugs. Now, in collaboration with Marina, we have been testing those antibodies in clinical trials. Last March, we showed that participants who received a treatment with these two bNAbs just once

"By studying and understanding a pathogen's tricks, we can learn to design vaccines to overcome them."

had undetectable levels of virus for up to 20 weeks. By studying and understanding a pathogen's tricks, we can learn to design vaccines to overcome them.

GDV: Currently, if you get a measles vaccine, you are protected forever, but if you get any type of protein or mRNA vaccine, the protection lasts only a certain amount of time and antibody levels decline after that. We don't know what makes a response last forever, and that's essentially a B cell biology question. What is the biology of these B cells that last forever?

We study tiny clusters of cells in the lymph nodes called germinal centers, in which B cells multiply and mutate—a form of high-speed evolution—to produce antibodies with the highest affinity for an invading pathogen. By understanding how B cells control rounds of mutation and proliferation, we can better understand how an immune response matures over time, changing again and again until it reaches an ideal response, with B cells that are long-lasting.

For example, we recently used imaging techniques to spot bursts of single B cells dividing rapidly and taking over a germinal center. We found that when these B cells are proliferating, they skip the cell cycle phase in which mutation takes place, suggesting that they are safeguarding successful mutations and avoiding deleterious mutations. Principles like these shed light on exactly what the immune system is doing to produce effective antibodies. That knowledge can help researchers design vaccines that prompt the immune system in the right way to produce the most effective antibodies against an infection.

There are additional areas of medicine in which B cells play a role that is important but not entirely understood. In allergies, why is it that some people's B cells make an antibody called IgE that generates severe allergic responses? In autoimmunity, why is it that some people's B cells attack their own organism instead of attacking foreign pathogens? If we can understand how and why B cells are reacting in these abnormal ways, perhaps we can guide those reactions, preventing them from producing antibodies that generate severe allergy and autoimmune reactions.

How can basic research help address current challenges in vaccine development?

MCN: There are two ways we can do better in vaccine development. One way is to find rare individuals who avoid or suppress infection naturally and study them to find out how they are doing it and try to replicate it. In the case of COVID-19, for example, we collected

Illustration by Joel Kimmel

blood from volunteers who had recovered from infection. Most of the samples had a weak antibody response to the virus, but we identified three distinct antibodies that could potently neutralize the virus. Cloning those antibodies in the lab is one way to work backwards to learn how to make those antibodies for other people.

Another approach is to do the fundamental research on how immunity and immune responses develop in order to understand the whole process well enough to be able to design therapies and vaccines based on underlying principles. We recently discovered that B cells can store advantageous mutations, to produce antibodies with a stronger affinity to a pathogen, by cloning themselves instead of continuing to mutate. In this way, they strategically produce the most effective antibodies. If we understand the system well enough, perhaps we can engineer vaccines to produce the same response.

GDV: In order to make vaccines better, we need to know the underlying biology of what happens when a person receives many doses of vaccines, such as five doses of the COVID-19 vaccine. Say you get three doses of a vaccine against the original strain, then one dose against a different strain, and then another dose against another different strain. How does the immune system react when it is exposed to a series of immunogens? Does it max out at some point?

To understand that biology, we've been exploring a phenomenon called "original antigenic sin." This occurs when the immune system reacts most strongly to the first viral strain it encounters, and then responses to later variants are blunted. That's very important in flu immunizations, where we keep getting updated vaccines over and over.

We developed a molecular fate-mapping approach in which we tracked antibodies from different B cell cohorts in mice. We discovered that if a booster shot contains an antigen that is sufficiently different from the original antigen, then the immune system will reset and produce antibodies from new B cell populations, not the old B cells. If the same rules apply to humans, booster vaccines might work best if we wait until a virus strain is sufficiently divergent from the original strain.

"Booster vaccines might work best if we wait until a virus strain is sufficiently divergent from the original strain."

Instead of preventing disease, some vaccines are used to treat diseases. What work are you conducting in therapeutic vaccines?

MCN: In therapeutic cancer vaccines, we've only recently been able to sequence cancers and learn enough about them to possibly produce something tailored to an individual. And the mRNA platform needed to produce a therapeutic cancer vaccine fast enough is only recently available. We're at the very, very beginning of that whole process.

We do know immune manipulations, such as PD-1 and CTL4 immunotherapies, are game changers in therapy. You can think of them as global vaccinations, as ways of enhancing immune responses. That's what a vaccine does, just in a specific way.

For HIV, we're learning about how the immune system can help control the infection. Understanding that will be an essential part of trying to create a vaccine that can be therapeutic. But before we can do that, we need to understand what people who actually control HIV really do in order to control it. This is something that is just evolving now.

MC: We are currently finishing a couple studies with broadly neutralizing antibodies as a treatment. In a study of people with HIV, we combined the antibodies with another drug that enhances immune system activity. We want to see if the antibodies can keep the virus suppressed, even without standard antiretroviral therapy, and to see if this combination of antibodies plus an immune-stimulating drug can enhance a person's own immune response. The hope is that even once the antibody washes out, the immune system can continue to suppress the virus on its own. If we are successful, our approach could put the possibility of a functional cure for HIV back on the table: a finite course of combination treatments inducing durable remission, in place of lifelong antiretroviral therapy.

GDV: I'm very interested in how the immune system is involved in diseases such as cancer, autoimmune disease, and neurodegeneration. In these conditions, B cells appear to be present and involved, but no one yet understands what role these cells are playing. What is it that B cells do in cancer—why are they so present inside some tumors and not others? And do B cells play a pivotal or secondary role in these conditions, including multiple sclerosis, where the best current drugs are treatments that target B cells? These kinds of questions are still wide open, and revealing the underlying mechanisms of B cells in these conditions could lead us to potentially stunning breakthroughs in vaccine development.

B cells may also help lead toward treatments as we continue to study the role of the immune system in the gastrointestinal tract. With my colleague Daniel Mucida and his team here at Rockefeller, we identified how specific gut cells communicate with T cells, triggering them to either attack or ignore antigens from food and pathogens. Next, we want to know what B cells are doing in the gut. Understanding the logic of the gut immune system will help us better understand, and potentially treat, conditions like inflammatory bowel disease and colitis.

"New technologies allow vaccines to be rationally designed, with a specific purpose, to induce a specific immune response."

When you look to the future of vaccines, what areas of vaccine development are you excited about?

MC: Historically, the majority of vaccines have been developed empirically, by means of observation, without much knowledge about how a protein structurally interacts with the immune system. Now, new technologies allow vaccines to be rationally designed, with a specific purpose, to induce a specific immune response. This is still very new; we are just in the beginning of this type of vaccine design.

For infections like the flu, mRNA vaccines are a good platform because modifications can be done very quickly. But they are not a solution for everything because the immune response that mRNA induces may not be adequate for every type of pathogen. There is still more to be learned about mRNA vaccines and how to best apply them.

GDV: Today's vaccines are based on rigorous scientific testing supported by a deep understanding of the immune system. The vaccines that have already been designed with the knowledge we have are amazing, and if we get answers to the questions we're asking now, we could do phenomenal things in the future.

Right now, we know how to give an organism an antigen and let the organism's immune system target whatever part of the antigen it wants. If that spontaneous targeting works out, we have a vaccine. If it doesn't, as in the case of HIV, we don't. In the future, we can be better at guiding the immune system to target the conserved part of a virus, rather than a random location.

To do that, an active area of research for the field has been germline-targeting vaccines, designed to guide B cells to produce specific, potent antibodies that bind to a conserved site on a pathogen. In this case, it's not so much about the formulation of the vaccine, whether it's RNA, DNA, or protein. Instead, the focus is on engineering the antigen we're going to expose the immune system to, so that it elicits the exact response we want: B cells that produce antibodies targeting a specific, conserved place on a pathogen.

It will be much harder to make a germline-targeting vaccine if we don't understand how antibodies work and what kind of cells make them. The more we understand the basic rules of how the complex, intricate immune system works, the better we will be at devising interventions. That's the value and beauty of basic science.

The mosquito leg tickler

New scientific gadgets are often developed to meet an unmet need. At the Laboratory of Neurogenetics and Behavior, headed by Leslie B. Vosshall, scientists needed to "tickle" mosquito legs.

Why? These bugs possess the ability to taste with their legs and feet, so gaining a better understanding of how they sense chemicals via neurons in their appendages could help researchers develop better insect repellents.

To achieve that feat, graduate student Jacopo Razzauti has been developing a device to image neuronal activity at varying distances and upon contact. The device is composed of a blunt needle attached to an actuator on an adjustable mount that is connected to a high-throughput microscope. Crafted by Nick Belenko at the Gruss Lipper Precision Instrumentation and Technologies facility, this servomotor can be programmed and adjusted with micron-level accuracy. (For scale, a micron is about 75 times thinner than a strand of human hair.)

Researchers manipulate the tickler via a joystick control and touch-screen monitor at the Frits and Rita Markus Bio-Imaging Resource Center (BIRC). BIRC staff also assist in recording images of mosquito neurons responding to Razzauti's different variables. "It might sound wacky, but it is a far less expensive and more precise platform than existing tools," he says. "Only at Rockefeller could I come up with a crazy idea like this and find experts in our resource centers who are talented enough to make it a reality." ◎

Photo by Lori Chertoff

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125
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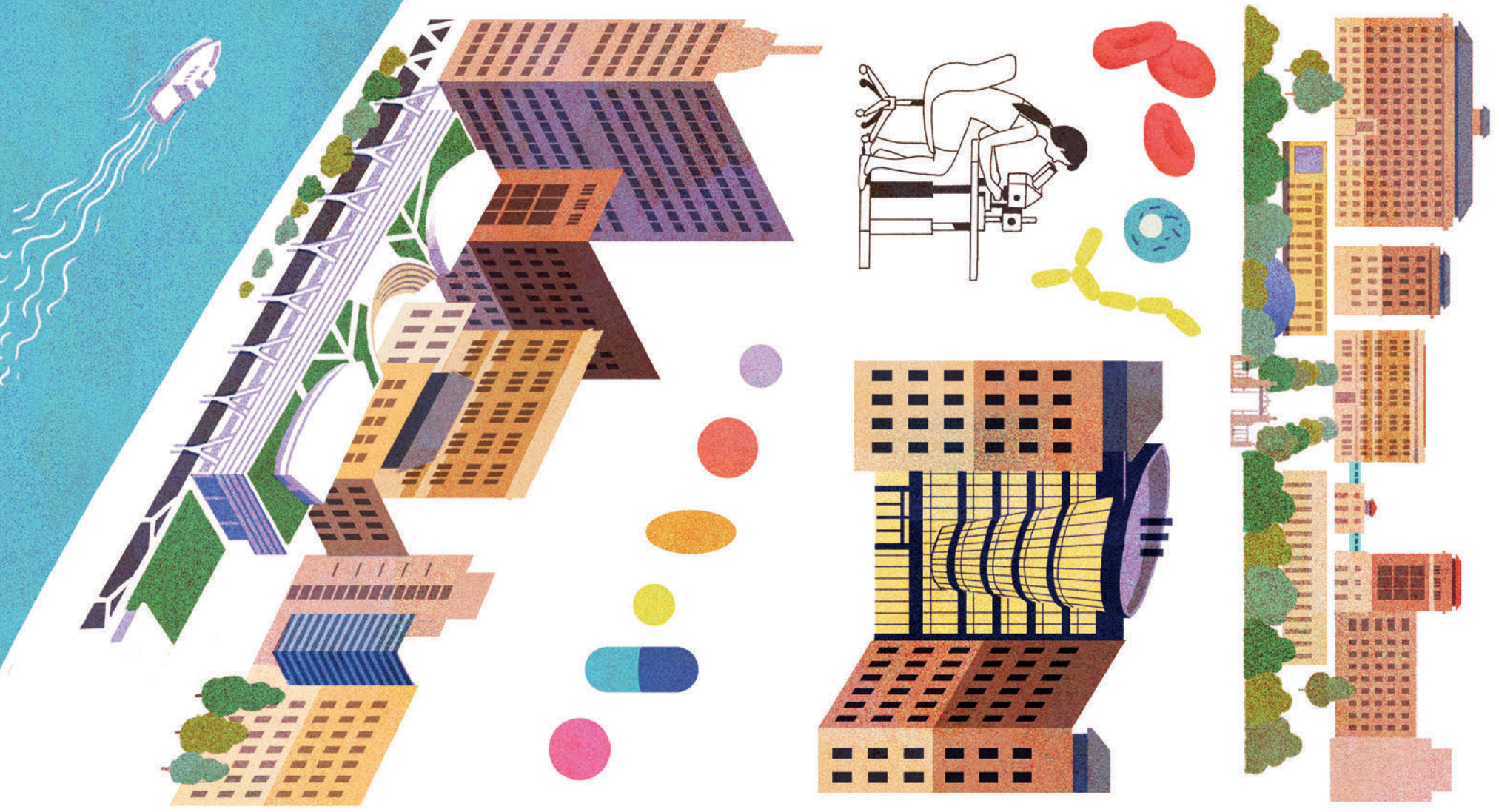

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