ISSUE 12
FALL 2025

Seek

THE ROCKEFELLER UNIVERSITY

Gaining the upper hand

How breakthroughs in infectious disease research could help us get ahead of outbreaks

ALSO

New tools to aid in the fight against disease

How AI could supercharge biomedical sciences

A better view of the brain

“We have never had better tools to identify and study disease agents, which will continue to accelerate our ability to prevent and treat infectious disease.”

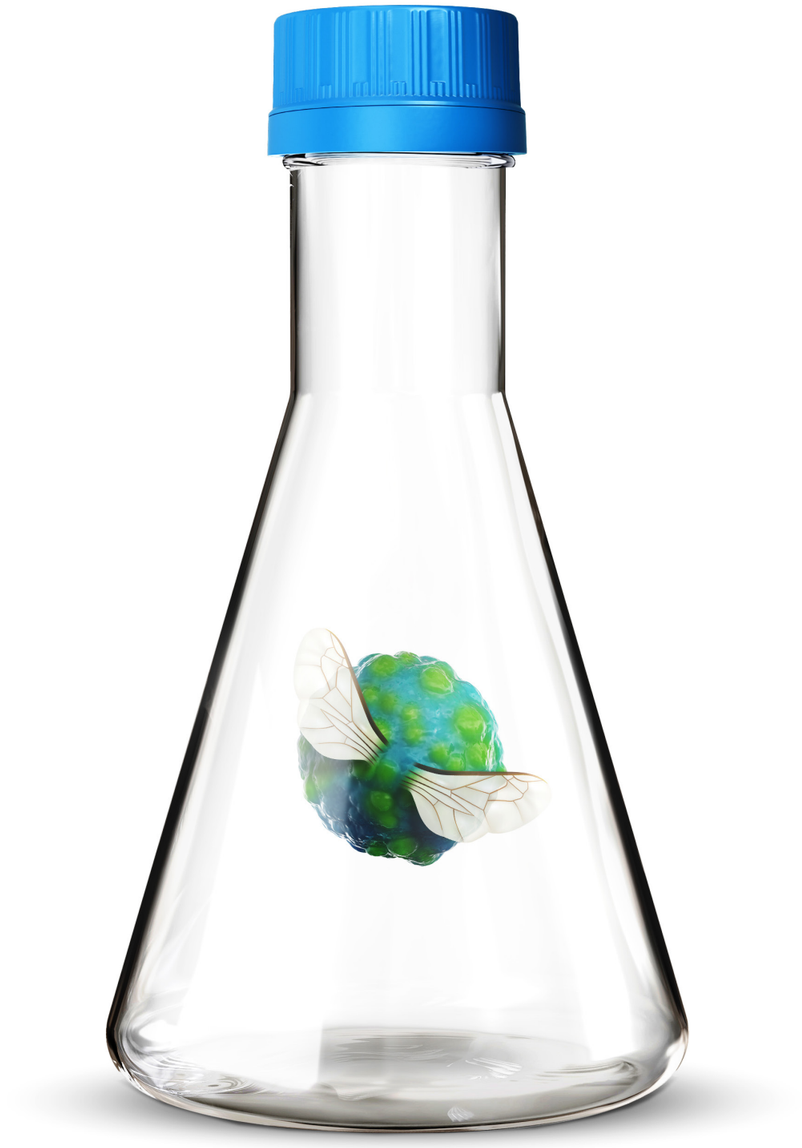

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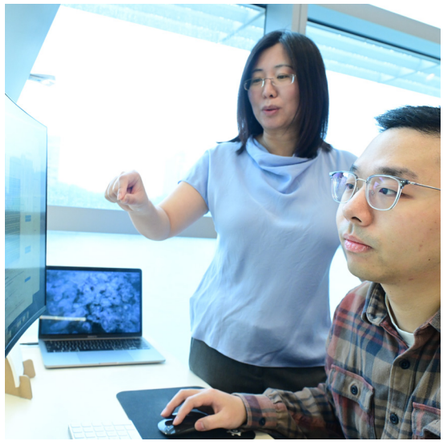
Illustration by Matt Chase



"We have a much better understanding than ever before of what holds people back from being cured."

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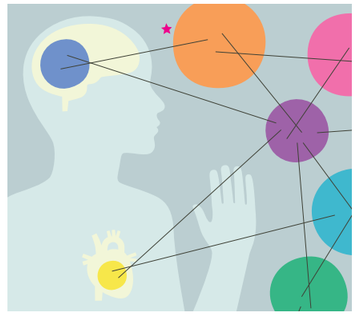

ON THE BACK COVER
The Rockefeller University
by Fien Jorissen

CHRIS TAGGART

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A polinator's oasis. Little bluestem, sea oats, butterfly weed, coneflowers, asters—Rockefeller's lush campus is dotted with a host of colorful perennials. But these plants aren't just beautiful; each one was carefully chosen by our landscaping team because it's hearty enough to thrive in the campus's fluctuating East River microclimate, where saline air and brisk winds can be tough on non-native species. Cultivating a space for this greenery to thrive among Manhattan's concrete canyons means that bees, birds, and other wildlife can find a hospitable environment as well.

Photo by Lori Chertoff

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

FOREFRONT

Illustration by Harriet Lee-Merrion

LANGUAGE

Finding our human voice

WERE MODERN HUMANS the first hominids capable of complex spoken language? If so, how did this unique capability evolve? New research by Robert B. Darnell and Erich D. Jarvis helps answer both of those questions, and could further our understanding of language and developmental disorders.

Darnell, who specializes in studying how RNA-binding proteins regulate gene expression, has spent more than three decades investigating a particular RNA-binding protein called NOVA1. NOVA1 is vital to brain development and neuromuscular control—Darnell has identified cases in which variations in NOVA1 are associated with developmental language and motor difficulties—and while it is found in animals ranging from mammals to birds, a particular variant of the protein, known as I197V, appears only in humans.

Yoko Tajima, a postdoc in Darnell's lab, used CRISPR gene editing to replace the common NOVA1 protein found in mice with I197V. Intriguingly, the human-specific variant specifically affected RNA binding at sites related to vocalization.

Probing deeper, Darnell joined forces with Jarvis, who studies the molecular and genetic mechanisms underlying vocal learning. Over the next few years, the researchers documented altered vocal patterns among adult male mice and mouse pups of both sexes that carried the human variant.

"The single amino acid change in NOVA1 may make it a bona fide human 'language gene,'" Darnell says. "Though certainly it's only one of many human-specific genetic changes."

To understand the potential influence of I197V on human evolution, the team compared the genomes of modern humans with those of our nearest relatives, the hominids known as Neanderthals and Denisovans. While these archaic relatives had the same version of NOVA1 found in nonhuman animals, the human-specific I197V variant was found in 650,052 of 650,058 modern human genomes analyzed, underscoring how it has become nearly ubiquitous, and suggesting it arose early in Homo sapiens' evolution.

"Our data show that an ancestral population of modern humans in Africa evolved the human variant I197V, which then became dominant perhaps because it conferred advantages related to vocal communication," Darnell says. "This population then left Africa and spread across the world."

The team's findings advance our understanding of when and how humans acquired their unique linguistic abilities. And by clarifying the role that NOVA1 plays in regulating language along with neural development and motor control, Darnell and Jarvis could also help scientists better understand a wide array of illnesses and impairments.

"Our discovery could have clinical relevance, ranging from children with language and developmental disorders to neurodegenerative disease," Darnell says. ◎

BACTERIA VS. VIRUS

There's more to CRISPR than we knew

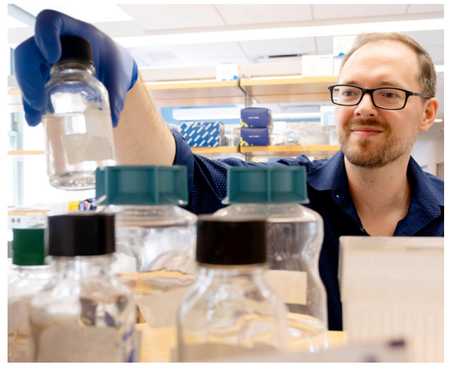
BACTERIA HAVE EVOLVED powerful defenses against the viruses that prey on them. The most famous such defense, CRISPR-Cas9—a kind of molecular scissor that can snip away at viral DNA—was adapted to create the first FDA-approved genetic editing tool. But Luciano Marraffini, who helped identify CRISPR's potential for genetic engineering, keeps finding more.

Most recently, Marraffini and his colleagues in the Laboratory of Bacteriology partnered with Dinshaw Patel at Memorial Sloan Kettering Cancer Center's Structural Biology Program to study a class of molecules called CARF effectors that leap into action when bacteria are infected.

In the past year, the researchers have identified three CARF effectors that take different approaches to achieving the same goal: stymying viral propagation by bringing cellular activity to a grinding halt. Cad1 triggers a sort of molecular fumigation, flooding infected cells with toxic molecules. Cam1 slows their growth by altering their cell membranes. And Cat1 depletes a metabolite essential for cellular function, which cuts off the viral invader's fuel supply.

"The range of both their enzymatic activities and structures is quite amazing," says Marraffini, who adds that much remains to be learned about how these molecules work their antiviral magic. "It will be fascinating to see where this work leads us next." ◎

LORI CHERTOFF



GENOME STABILITY

This enzyme heads off "transcriptional catastrophe"

CELLS EXPRESS THEIR genetic instructions by transcribing DNA into RNA. Sometimes, though, that process goes dangerously awry, destabilizing the genome and contributing to a whole host of diseases.

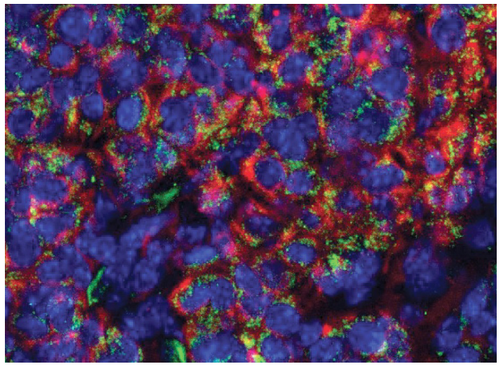
A recent study from Seth Darst's lab reveals how a particular enzyme helps prevent this kind of transcriptional catastrophe from occurring in bacteria—a finding that could inspire new strategies for targeting illnesses linked to genome instability.

All living things rely on an enzyme called RNA polymerase (RNAP) for transcription. While RNAP normally releases DNA after transcribing it, the enzyme sometimes remains clamped in place, reinitiating the process and creating potentially dangerous molecular structures called R-loops unless another enzyme called RapA intervenes.

Darst and colleagues demonstrated that the RapA enzyme functions as a bacterial Jaws of Life, prying open RNAP to stop it from inadvertently producing R-loops. Using advanced imaging techniques and a realistic substitute for bacterial DNA, the researchers captured the moment when RapA forces RNAP to let go of DNA. They also showed that *E. coli* bacteria engineered to lack RapA experienced genetic instability when stressed.

The findings suggest that RapA is a key safeguard against transcription-induced genome instability, and Darst suspects a similar mechanism may exist in all bacteria—and possibly across species.

"This work not only clarifies RapA's role," he says, "but also opens up broader questions about how all cells prevent transcription from becoming a genomic liability." ◎



IMMUNOTHERAPY

How cancer can use lipids to hide

SOME CANCER CELLS are loud and proud, announcing their presence with chemical markers that allow the body's immune system to find and destroy them. But others learn to hide, and a recent study from Kivanç Birsoy's lab reveals that certain tumors rely on the fatty molecules known as lipids to do it.

One class of lipids stood out in particular: sphingolipids, which are named after the enigmatic Sphinx of Greek lore due to their initially puzzling structure and function. Scientists eventually came to view sphingolipids as important components of cell membranes—and useful fuel for hungry cancer cells. But Birsoy's study, which was carried out in collaboration with Gabriel D. Victora's lab, suggests that sphingolipids also play an active role in shielding cancer from immune detection.

"We believe modulating dietary lipids may be an interesting avenue to target cancer cells' ability to evade immune cells."

Cancer cells seemed to manipulate these lipids to distort the "eat me" signals that normally flag them for destruction. To test whether glycosphingolipids were essential for this deception, the researchers used an FDA-approved drug for Gaucher disease, a disorder in which lipids accumulate in certain organs, to block their synthesis. Sure enough, the drug dramatically slowed tumor growth in pancreatic, lung, and colorectal cancer models.

While more research is needed, the treatment appears to have worked by leaving the cancer cells exposed, suggesting that targeting sphingolipid production—through drugs or even lipids acquired through diet—could make cancers more vulnerable to immunotherapy.

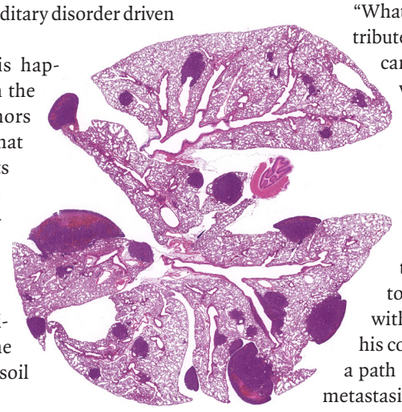
"We believe modulating dietary lipids may be an interesting avenue to target cancer cells' ability to evade immune cells," Birsoy says. ◎

RISK ASSESSMENT

Is metastasis a hereditary disorder?

THE VAST MAJORITY of cancer deaths are caused by metastasis, or the spread of cancer cells from tumors to other parts of the body. Scientists long thought this was caused by mutations in the tumors themselves. Recent research by Sohail Tavazoie, however, indicates that metastasis is in part a hereditary disorder driven by our own DNA.

"We always thought that metastasis happens because people get a mutation in the tumor itself. But after searching tumors for decades, looking for a mutation that can explain metastasis, cancer biologists came up empty-handed. No one has ever found a real causal human mutation that promotes metastasis in the tumor," Tavazoie says. "We've been so focused on the cancer cells, the 'seeds,' that we've ignored inherited genetic variations in otherwise healthy tissue—the 'soil.' It's now clear that focusing on the soil is critical."



LABORATORY OF METABOLIC REGULATION AND GENETICS; ELIZABETH AND VINCENT MEYER LABORATORY OF SYSTEMS CANCER BIOLOGY

Tavazoie's team focused on *PCSK9*, a gene variant carried by roughly 70 percent of white women. Analyzing patient data from international cohorts and experimental data from mice, the team found that *PCSK9* significantly increased the risk of metastasis within 15 years, raising it from 2 to 22 percent.

The work built on the lab's previous research into skin cancer, which showed that variants of a gene called APOE caused metastasis by acting on a particular receptor. Interestingly, the *PCSK9* variant appears to degrade that same receptor in breast cancer, triggering molecular changes that favor metastasis.

"What we're seeing is that inherited genetics contribute to cancer metastasis by these two different cancer types," Tavazoie says. "This makes me wonder whether the same pathway is related to the spread of other cancers as well."

The results also point toward potential therapies. The team found preliminary evidence that an FDA-approved antibody that blocks *PCSK9* and is currently prescribed for high cholesterol can suppress metastasis in lab models. In addition to seeking to test therapeutic targeting of this pathway with collaborators in the clinic, Tavazoie and his colleagues hope that future work will provide a path toward identifying those at highest risk of metastasis. ◎

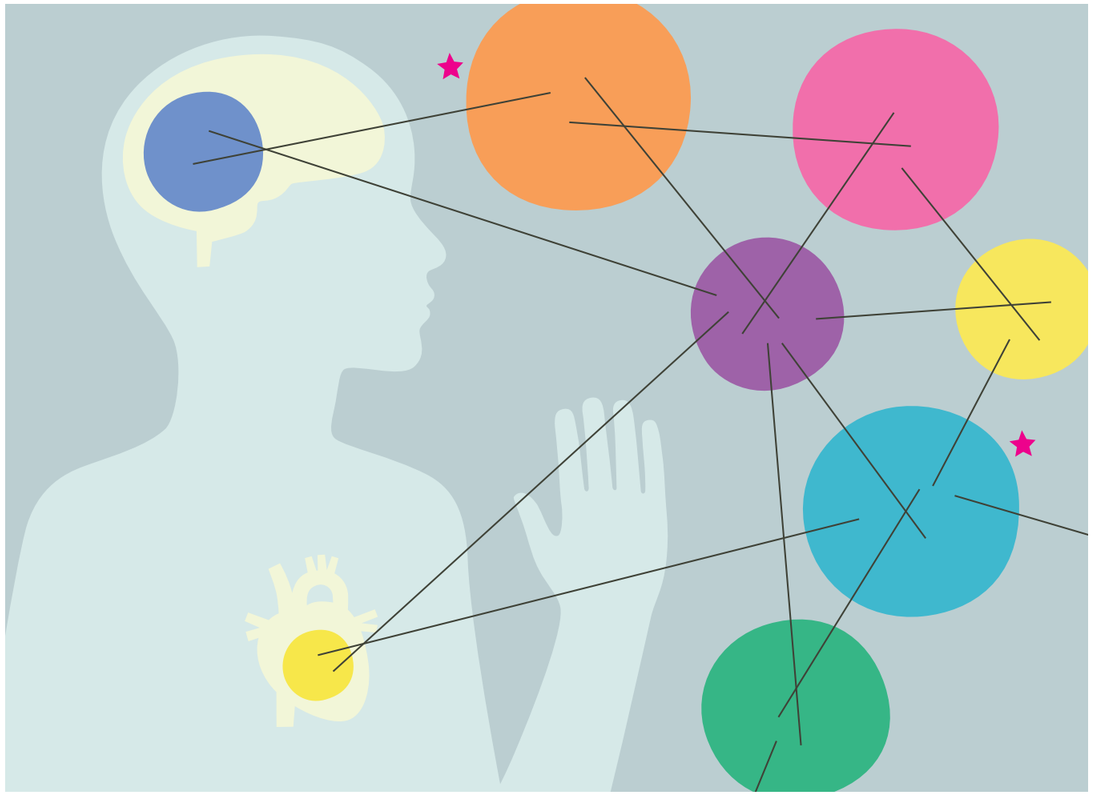


Illustration by Kari Modén

SYNDROMES

Mutations in 60 genes implicated in congenital heart disease

SCREENING KIDS FOR the genes that cause congenital heart disease (CHD)—one of the most common birth defects and a leading cause of infant mortality—would be a game changer. But what if those same genes could tell you something about a child's risk of neurodevelopmental problems as well?

That's precisely what a sweeping study from the laboratory of Richard P. Lifton, who is Rockefeller's president, promises to make possible. The study examined the genes of more than 11,000 children and identified mutations in 60 genes that are implicated in CHD, many of which are also linked to neurodevelopmental conditions such as autism. The results lend new insight into the biology of heart development and offer guidance for screening and early intervention across a wide array of disorders.

Although many of the mutations were spontaneous, the researchers were surprised to find that nearly half were inherited from parents who often showed no symptoms themselves. And while mutations in 33 genes were strongly associated with specific forms of CHD, others spanned a wide spectrum, producing narrow or broad cardiac outcomes depending on their exact nature. More than half of the implicated genes were also associated with neurodevelopmental disorders.

The findings have immediate clinical implications. Genetic screening may catch syndromes that would otherwise go undiagnosed, and early detection of neurodevelopmental risk could improve outcomes. Although every child in the study had already been diagnosed with congenital heart disease, genetic analysis revealed that nearly one third carried mutations linked to broader syndromes, many of which had gone unrecognized. In the absence of telltale symptoms, these additional conditions often escaped clinical detection, leaving associated cardiac or neurodevelopmental risks hidden in plain sight.

"This study sheds light on the complex architecture of CHD," Lifton says. "With this information, physicians can better clarify diagnoses, anticipate outcomes, and assess the risk of CHD in future children." ◎

NEURAL CIRCUITS

Balancing cooperation and competition

IF YOU THOUGHT courtship was tricky for humans, consider the games that fruit flies play.

Male fruit flies woo prospective mates by vibrating their tiny wings to produce high-frequency mating songs. But recent research from Vanessa Ruta's lab reveals that competing males can "borrow" their rivals' songs to win a female's affections—or jam them with noise to spoil their chances.

Ruta's team looked at what happened when two males competed for the attention of a single female. When one of the males was wingless and therefore incapable of singing—usually a recipe for courtship disaster—they found that it could sometimes sneak in a mating while its winged rival was singing, stealing his thunder and his mate.

Meanwhile, when both suitors had wings, they often tried to drown out one another's songs with buzzy, high-pitched wing flicks. Further experiments confirmed that these flicks were indeed acts of sabotage that interfered with the female's perception of courtship songs, activating brain pathways that blocked mating behavior.

"It turns out that mating success is not just about whether a male fly is the most vigorous in his courtship."

The team also made neural recordings that revealed how male flies manage to balance this aggressive behavior with courtship.

Visual cues activate neurons associated with courtship, while the sound of a rival's song switches on aggression-promoting neurons. Both neural systems can be co-activated, allowing rapid shifts between mating and aggressive interference. Genetically silencing aggression-related neurons eliminated the interfering wing flicks while leaving courtship behaviors intact, providing evidence of separate, interacting brain circuits.

The team's findings highlight just how fluid and context-dependent fly behavior can be, while also underscoring the growing recognition in neuroscience that complex social behaviors, such as balancing competition and cooperation, don't require complex brains—just precise, well-tuned neural circuits evolved for social survival.

"It turns out that mating success is not just about whether a male fly is the most vigorous in his courtship," Ruta says. "It is also about whether he can successfully interweave courtship and aggression from moment to moment." ◎

Illustration by Federica Bordoni

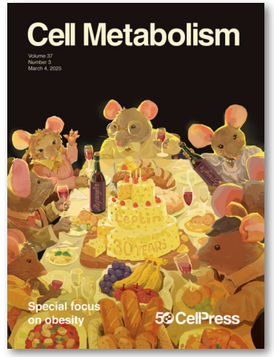
OBESITY

New hope for reversing leptin resistance

THE MODERN WEIGHT-LOSS drugs known as GLP-1 agonists (think: Ozempic) have dramatically improved the health of millions. Yet we still haven't solved the obesity crisis. Nor do we fully understand the one characteristic that 90 percent of obesity cases share: resistance to the hormone leptin. Recently, however, the lab of Jeffrey M. Friedman, who discovered leptin in the 1990s, revealed some of its molecular underpinnings—and a deeper understanding of this hormone which regulates eating.

Leptin is produced by fat cells and suppresses appetite in lean individuals. But in most obese individuals, this appetite-suppressing signal fails to register in the brain.

Earlier this year, Bowen Tan, Kristina Hedbacker, and other researchers in



Friedman's lab discovered a neural mechanism underlying leptin resistance: increased activity by a signaling molecule called mTOR in a particular population of neurons in the brain.

Intrigued, the researchers tested the effects of rapamycin, a drug that inhibits mTOR, on mice with diet-induced leptin resistance. The results were striking: "Obese mice fed a high-fat diet and treated with rapamycin lost significant amounts of weight," says Tan.

"It essentially resensitized the animals to leptin," Hedbacker adds. "Moreover, it was mostly fat that disappeared. That's a significant difference from the effect of GLP-1 agonists, which cause the loss of both fat and muscle."

In another study, Friedman's lab identified a neural circuit that connects leptin to the jaw to stimulate chewing movements, suggesting that the impulse to eat may be more reflexive than previously thought. Inhibiting a specific group of neurons in the circuit led mice to consume more food and to make chewing motions even when food wasn't nearby. Stimulating the same neurons, meanwhile, reduced both chewing motions and food intake, demonstrating an effective curb against hunger.

Together, these findings also bolster the idea that obesity is a far more complex condition than the old saying "calories in, calories out" might suggest.

"The available evidence tells us that obesity is an endocrine disorder, not a personal failing," Friedman says. "It's time for the stigma associated with obesity to end." ◎

FOOD ALLERGIES

What the gut tolerates

THE GUT IS a gatekeeper, trained to recognize what belongs inside of us—and what doesn't. But how does the intestinal immune system learn to distinguish friend from foe? And why does it sometimes make the wrong call, triggering a potentially dangerous allergic response to something as innocuous as a peanut or an egg?

"The big question is how we survive eating," says Maria C.C. Canesso, a postdoc in the laboratory of Daniel Mucida. "Why do our bodies normally tolerate food, and what goes awry when we develop food allergies?"

A recent study led by Canesso and carried out in collaboration with the laboratory of Gabriel D. Victora offers clues. The researchers used new technology known as LIPSTIC, which catalogues cell-to-cell interactions, to identify how the intestinal lining teaches the immune system to tolerate dietary antigens, or the components of food molecules that immune cells recognize. Their findings reveal that two different intestinal immune cells capture food antigens and signal the immune system to stand down, preventing allergic reactions.

"Why do our bodies normally tolerate food, and what goes awry when we develop food allergies?"

The findings illuminate how the immune system maintains food tolerance. And while the scientists have not quite drawn a straight line from molecular mechanisms to food allergies, their work throws light on an intriguing path forward. If food allergies arise when intestinal cells lose their grip on immune balance, the authors suspect that we could one day fine-tune those cells to orchestrate tolerance rather than cause chaos. ◎

SAI LAUNG LINN; LORI CHERTOFF

FLOPPY FILAMENTS

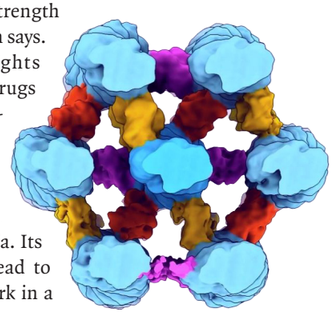
Solving a 40-year-old puzzle

A CELL'S ABILITY to move from place to place can be crucial. But that mobility can be a double-edged sword: The same mechanisms that allow an immune cell to rush to the site of an infection can also help metastatic cancer cells spread throughout the body. As such, new research from the lab of Gregory M. Alushin that reveals how cells get around could help improve cancer treatments—and even inspire new ones.

Many cell types have sensitive, finger-like protrusions called filopodia that help them move. But while filopodia require a certain amount of structural strength to enable locomotion, they are composed of highly floppy strands of protein known as actin filaments. These, in turn, must be bundled together by a protein called fascin in order to do anything useful.

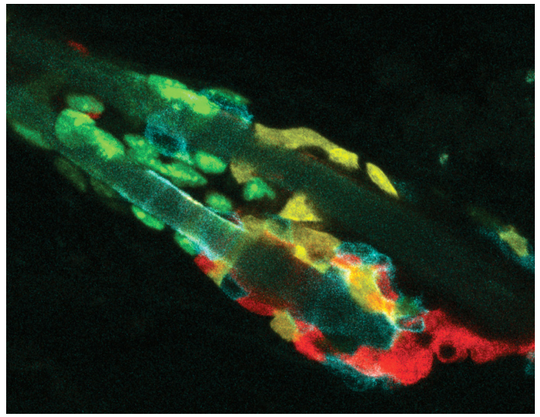
How fascin puts these bundles together has been a puzzle for more than 40 years—one Alushin's team solved by developing advanced imaging technology that revealed the first clear three-dimensional images of fascin proteins binding actin filaments to form structures that "hit a sweet spot between strength and flexibility," Alushin says.

"We've been able to detail essential design principles for the bundles."



The team's insights could help improve drugs currently in development that stop cancer cells in their tracks by preventing fascin from bundling actin filaments into filopodia. Its findings could also lead to new therapies that work in a similar fashion.

"We've been able to detail essential design principles for the bundles, which could be really helpful information for finding new ways to interfere with their construction," Alushin says.



LABORATORY OF STRUCTURAL BIOPHYSICS AND MECHANOBIOLOGY; ROBIN CHEMERS NEUSTEIN LABORATORY OF MAMMALIAN CELL BIOLOGY AND DEVELOPMENT

PART-TIME PHAGOCYTES

Why cells sometimes eat their neighbors

EVERY DAY, BILLIONS of our cells die and are swept away to make room for new ones. Some of these expired cells are literally devoured by specialized immune cells called phagocytes, which take their name from the Greek for "cell eater." But others are consumed by their neighbors: non-phagocytes that normally do other jobs. So, how do these ordinary cells know when it's time to suit up as temporary sanitation workers?

A recent study by Elaine Fuchs and her team provides answers. The researchers examined mouse hair follicles, which have relatively few phagocytes but still need to clear away dead cells to prevent unwanted inflammatory responses from occurring. They found that a pair of molecular sensors within follicle stem cells fuel the cyclical bouts of follicle and hair regeneration that (if you're lucky) naturally occur throughout life. The sensors also pick up signals from their dying neighbors. In turn, this triggers living cells to eat the decaying ones, in turn extinguishing the signals and terminating the disposal operation before healthy cells get gobbled up too.

One of these sensors, called RXRα, detects the lipids secreted by dying cells, while the other, RARγ, picks up the retinoic acid secreted by healthy cells. Dying cells trigger the cleanup process by releasing lipids, and once all the dead cells have been eliminated, only the retinoic acid signal from the healthy cells remains, shutting the program down because the two work together to unleash the phagocytic process. "It's a really beautiful way to keep the area clean," says Katherine Stewart, a former research associate in Fuchs's lab.

The team's findings have implications that go far beyond hair follicles, however. For example, stem cells in parts of the brain, breasts, and lungs also moonlight as ersatz phagocytes, keeping their own neighborhoods free from unwanted debris.

"For our body's stem cells, this may be their way of keeping tissues fit by clearing out naturally dying cells and guarding against inflammation," Fuchs says.

New antiretroviral treatment puts HIV remission on the table—and the possibility of an eventual cure more likely.

The beginning of the end of HIV?

By Sarah C.P. Williams

FOR DECADES, TREATING HIV has meant a daily battle against a virus that never truly leaves the body. Antiretroviral drugs can suppress HIV to undetectable levels, but a missed dose or loss of access to care can make the virus come roaring back.

But recent clinical trial results are finding something extraordinary: an HIV treatment that could keep the virus at bay for six months with a single injection.

At the heart of this research are broadly neutralizing antibodies (bNAbs), proteins that bind to HIV, blocking infection and enhancing the immune system's attack on the virus. Unlike typical antibodies, bNAbs can target many different HIV strains, making them especially valuable against the rapidly mutating virus.

The antibodies were first discovered, and fine-tuned for clinical use, in the lab of Michel C. Nussenzweig and Marina Caskey. Now, biopharmaceutical company Gilead Sciences—which has licensed the antibodies from Rockefeller—is carrying out Phase 2 trials, testing their safety and efficacy in patients with HIV.

In March, Gilead presented data showing that a combination of bNAbs—along with the long-acting antiretroviral drug lenacapavir—given every six months led to undetectable levels of virus in 96 percent of study participants, numbers comparable to standard daily treatment regimens.

"To be able to switch patients from daily pills, or injections every two months, to a treatment just twice a year would be a huge advance to the field."

Marina Caskey

"Seeing that data from Gilead was incredibly exciting and reassuring," says Nussenzweig, the Zanvil A. Cohn and Ralph M. Steinman Professor and an investigator at the Howard Hughes Medical Institute. "This is what we thought would happen, but having it validated is just amazing."

Nussenzweig first identified the antibodies, known as 3BNC117 and 10-1074, while studying "elite controllers"—individuals living with HIV whose immune systems have a powerful ability to neutralize the virus, preventing them from developing symptoms of disease.

Isolating and studying the antibodies was only possible because of a method Nussenzweig pioneered in 2009 to find immune cells that make desired antibodies and manufacture those cells in the lab. He and Caskey have used the same approach to develop antibodies against diseases, including malaria, Zika, and COVID-19. Now, they are also using it to tackle hepatitis B.

In the case of HIV, bNAbs work by recognizing and binding to specific proteins on the surface of the virus that are essential for it to infect cells. The antibodies directly block HIV from infecting cells and also recruit the immune system to find and destroy already-infected cells.

"These two antibodies showed really strong activity against the virus and had a number of other qualities that told us they might work in patients," says Caskey, a professor of clinical investigation.

Early trials led by Nussenzweig and Caskey showed that single infusions of the antibodies sharply reduced viral levels, and combining them made the effects even longer lasting. Moreover, giving multiple treatments together makes it harder for the virus to mutate resistance.

In 2020, Gilead licensed long-acting versions of 3BNC117 (now teropavimab) and 10-1074 (now zinlirvimab) from Rockefeller, which retained rights for early-stage research aimed at improving the antibodies' effectiveness.

Since then, the work has progressed into a promising new phase. In 2023, Gilead's Phase 1b trial showed that combining teropavimab, zinlirvimab, and the long-acting drug lenacapavir suppressed the virus in 90 percent of participants for six months. The more recent Phase 2 results, on a larger patient population, showed even more encouraging data. Those results came on the heels of a January decision by the FDA to grant the drug combination Breakthrough Therapy designation, which is given to treatments that show

early promise of being significantly more effective than existing options.

"To be able to switch patients from daily pills, or injections every two months, to a treatment just twice a year would be a huge advance to the field," says Caskey. "For a significant number of people with HIV, it's challenging to take daily medication."

Although Gilead is focusing on refining these antibodies as a viable treatment, Nussenzweig and Caskey are still pursuing broader questions through exploratory research funded by the Stavros Niarchos Foundation Institute for Global Infectious Disease Research, the Gates Foundation, and the National Institutes of Health. Their goal is to use bNAbs to achieve remission—control of HIV without ongoing therapy.

Caskey's recent studies suggest that when the antibodies are given at the same time as standard HIV drugs, they seem to boost certain immune cells that are particularly good at recognizing and attacking the virus. In a few cases, this improved immune response has allowed individuals to maintain undetectable or very low levels of the virus for years without daily medication. Caskey is also investigating whether the antibodies can target "hidden reservoirs" of HIV that allow the virus to rebound when treatment stops.

"The exciting thing in this field right now is that we have a much better understanding than ever before of what holds people back from being cured," says Nussenzweig. "The basic science progress over the last five years has been huge, and we now have an inkling of how to change the course of disease in a rational way."

The latest results out of Gilead, he says, may be just the beginning of how bNAbs could revolutionize the treatment of HIV.

"The exciting thing in this field right now is that we have a much better understanding than ever before of what holds people back from being cured."

Michel Nussenzweig

Zalunfiban, a cutting-edge injectable that inhibits platelet clumping, represents the culmination of decades of life-saving research.

A faster clot-buster for heart attacks

By Sarah C.P. Williams

PICTURE THIS: A man in his 60s is mowing his lawn when a sudden, crushing pain rips through his chest. His arm feels heavy, his breathing labored. Panicked, his wife calls 911.

Within minutes, paramedics arrive and realize the man is having a heart attack; a clot in a major artery is blocking the flow of blood to his heart. Immediately, they pull out a small injector containing zalunfiban—an experimental new medication developed by Barry S. Coller, who heads the Allen and Frances Adler Laboratory of Blood and Vascular Biology and is the physician-in-chief at the Rockefeller University Hospital. Unlike heart attack treatments that require injection directly into a vein, zalunfiban can be injected just under the skin, like an at-home insulin shot or EpiPen.

Within 15 minutes, the drug has stopped blood platelets from clumping together, preventing the formation of additional clots and giving the blocked artery a chance to reopen. Because it acts so fast, the medication buys him time, keeping blood flowing through the heart rather than letting tissue become permanently damaged en route to the hospital.

For years, doctors have performed life-saving procedures to open closed arteries once patients arrive at the hospital. But the real danger often happens before they get there. Half of all heart attack deaths occur before a patient reaches the emergency room; the further someone lives from a hospital, the worse they tend to fare. Zalunfiban, currently in Phase 3 clinical trials running on two continents, aims to change that.

"We hope that zalunfiban will save lives," says Coller, who is also The David Rockefeller Professor and vice president for medical affairs. "If successful, it could eventually be in every ambulance, and someday, even in medicine chests of people at high risk of having a heart attack."

Coller has spent more than five decades studying how platelets clump to form clots—a process essential to stop bleeding but dangerous when it occurs in the heart or brain. His first breakthrough came with abciximab, an antibody targeting the platelet receptor that binds fibrinogen, a protein that supports clumping by bridging between platelets.

Abciximab was approved by the FDA in 1994 and given to millions of patients undergoing artery-opening procedures. But it had one big drawback: It had to be given intraveniously through an IV controlled by an electric pump, limiting its use primarily to hospitalized patients.

"With abciximab, it became really clear that the people who were treated earlier were the ones who got the greatest benefit," says Coller. "So the question for me became: How do we get a drug that potently and predictably inhibits platelet clumping to patients even earlier?"

In 2001, Coller joined Rockefeller, where he worked with the university's cutting-edge drug screening facility to search for chemical compounds—small molecules instead of antibodies—that could block the interaction between platelets and fibrinogen. The first hit was dubbed Rockefeller University Compound 1, or RUC-1. With colleagues at the Mount Sinai Icahn School of Medicine and the National Institutes of Health, Coller refined that molecule so that it locked platelet receptors into an inactive state, leading to RUC-2 and ultimately RUC-4.

RUC-4 acts within minutes after injection, eliminating the need for controlled intravenous delivery. Importantly, its effect wears off in about two hours—which complements treatments that take longer to take effect and diminishes the risk of excess bleeding if surgery needs to be performed.

In 2017, Rockefeller licensed RUC-4 to CeleCor Therapeutics. Coller became its chief scientific advisor, continuing to advance RUC-4 (now zalunfiban). Initial testing in healthy volunteers and patients on daily aspirin went well, leading to a small Phase 2 trial in the Netherlands. There, 27 patients treated in the hospital for heart attacks were given varying doses of zalunfiban to test its effect on their arteries in just the brief time period in which they were being prepared for artery-opening procedures.

"This study was not designed to directly assess whether zalunfiban opens arteries, but it was gratifying to see that the higher doses were associated with a strikingly higher percentage of open arteries with good blood flow," Coller says.

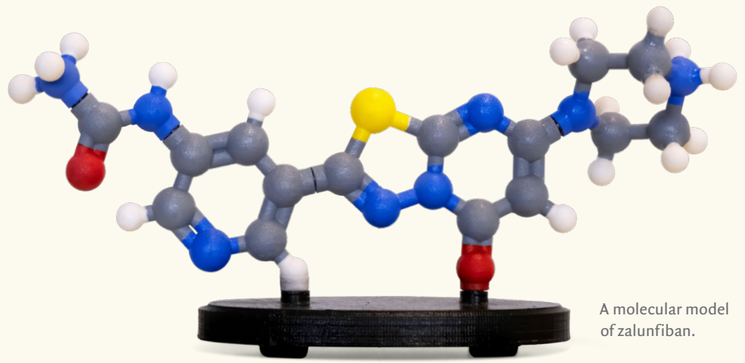
In 2021, CeleCor began a Phase 2b trial to study zalunfiban in ambulances—finally using the drug as an early intervention, exactly what Coller had been aiming for when he set out to develop it almost 20 years before. After consulting with the FDA, CeleCor converted the trial to a Phase 3 trial aiming to assess the drug's safety and efficacy.

Today, that trial is ongoing at dozens of hospital systems in Europe, Canada, the U.S., and Mexico. In some locations, prefilled syringes of zalunfiban are stored in ambulances associated with these hospitals, ready to be injected into patients as soon as a heart attack is suspected. At others, zalunfiban is administered as soon as a patient arrives. Data on the patients—so far, more than 2,350 of them—is being collected for one year after their treatment. CeleCor is aiming to present and publish the first results in late 2025.

The hard work to reach this moment has been well worth it, Coller says: "I saw that there were people dying who I thought didn't need to die. I had to try to help."

Barry Coller

"We hope that zalunfiban will save lives. If successful, it could eventually be in every ambulance, and someday, even in medicine chests of people at high risk of having a heart attack."

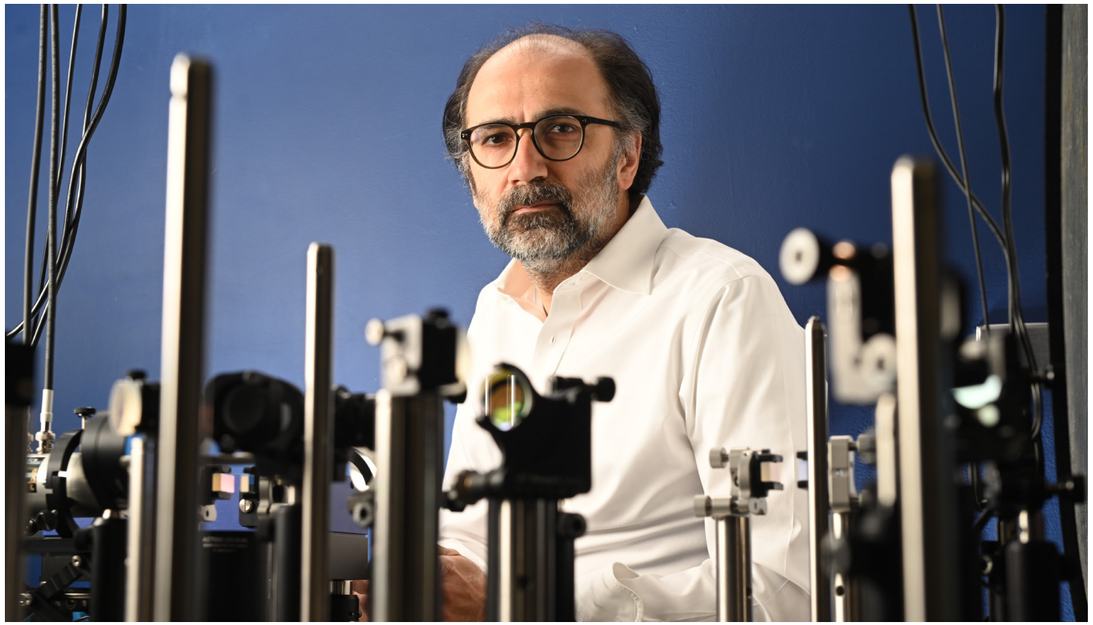


CHRIS TAGGART; LORI CHERTOFF

A molecular model of zalunfiban.

A new way to look at neurons

Alipasha Vaziri



CHRIS TAGGART

Vaziri's technological breakthroughs allow researchers to observe large swaths of the brain and draw new connections between brain activity and animal behavior.

EVERYTHING WE SEE, feel, and remember—every surprise, habit, joy, decision, and memory—emerges from bursts of electricity pulsing through the brain. Yet scientists have long struggled to track these patterns at the scale, resolution, and speed at which they happen. Only recently have new technologies made it possible to observe brain-wide neural activity at the cellular scale in real time. Some of the most powerful of these tools have emerged from the lab of Alipasha Vaziri.

A physicist turned neuroscientist, Vaziri leads Rockefeller's Laboratory of Neurotechnology and Biophysics, where he develops cutting-edge imaging systems capable of simultaneously recording activity from large populations of neurons at the cellular scale across the brain.

His inventions include Light Beads Microscopy (LBM), which can capture the activity of up to a million neurons at once while spatially resolving individual cells, and penny-sized microscopes that can be worn by freely moving rodents, among others. These technologies allow researchers to watch the brain in action as animals move, learn, and react to their environment, leading to a new understanding of how brain cells and the connections between them are reorganized in real time as an animal practices a skill, makes decisions, or carries out a behavior.

That these capabilities far surpass those of any currently available commercial technologies has drawn many neuroscientists to collaborate with Vaziri's lab. And as director of the Elizabeth R. Miller Brain Observatory, he and his team there, headed by Raghav Chhetri, support ambitious, long-term research projects by Rockefeller scientists right on campus.

Ultimately, Vaziri hopes that his science and the technologies he develops can answer big, existential questions—what is the computational and neuronal circuit level basis of intelligence? What is the neuronal basis of consciousness and our subjective experience?—but his work also holds promise for transforming how we diagnose and treat brain disorders, develop targeted therapies, and understand the roots of conditions like addiction and dementia.

What made you become a neuroscientist?

I was always interested in philosophy and fundamental questions, like what's the relationship between what is objectively out there in the world and what's going on in our brains? But I realized that philosophy didn't really allow for ways to empirically advance our understanding of those questions. This drew me to study physics for my Ph.D. I focused on the foundations of quantum physics, which—to my astonishment—seemed to offer opportunities to experimentally advance philosophical questions such as the nature of reality.

As a postdoc, I continued working on quantum optics, but I realized the field was increasingly directed towards quantum technologies, which weren't my main interests. I had always been interested in neuroscience because it has a fundamental quality yet is experimentally accessible. Our entire notion of the existence of oneself and the world—what we call reality—is ultimately confined to a specific piece of matter. In that sense, I felt questions that have puzzled us for hundreds and even thousands of years ought to be answerable by studying the brain.

But the more I read and thought about this, the more I realized that the lack of appropriate tools and technologies was the key impediment here. It's like attempting to study distant galaxies and the laws that govern the evolution of the universe by observing it through a pair of binoculars.

So you decided to develop those tools. What was one of your first breakthroughs?

That would be the first application of a technology called temporal focusing, which we and many others still use today. It is a two-photon excitation technique that, unlike conventional two-photon methods, does not require mechanical scanning while maintaining high resolution. This was around the time when optogenetics was starting to find broad applications in neuroscience. But a major limitation until then was that it was not technically possible to optically activate an individual neuron within a pool of genetically identical neurons. I realized that by using temporal focusing, we could simultaneously recruit a sufficiently large number of channels to fire a neuron while maintaining the spatial confinement of excitation to a single neuron.

Later, while running a lab in Vienna, I became interested in how to image the activity of large neural populations at cellular resolution in living animals. Neuroscientists were trying to figure out how sensory inputs like sights or sounds are represented as patterns of activity across large groups of neurons and how these are turned into patterns related to an animal's behavior. So I developed a microscope based on a new version of temporal focusing; a colleague and I then used it to record the neuron activity across the entire brain of *C. elegans* simultaneously while exposing it to different sensory inputs. Prior to our work, researchers had been able to record only four neurons in *C. elegans*, so that was a nice advance.

"We often take for granted just how much information the brain processes—it's an enormous amount—yet the underlying computational principles remain largely unknown."

Why is it so important to study entire populations of neurons?

Neurons in the brain show a tremendous density of recurrent interconnectedness. As a result, at each moment, a large number of neurons distributed across different brain regions are active at once. But in many cases, the recurrent nature of the connectivity makes it difficult to "follow" how signals propagate through the system, especially by just observing a few neurons. Such systems are better described as dynamical systems.

You've developed numerous bioimaging technologies at Rockefeller. Which are you currently most excited about?

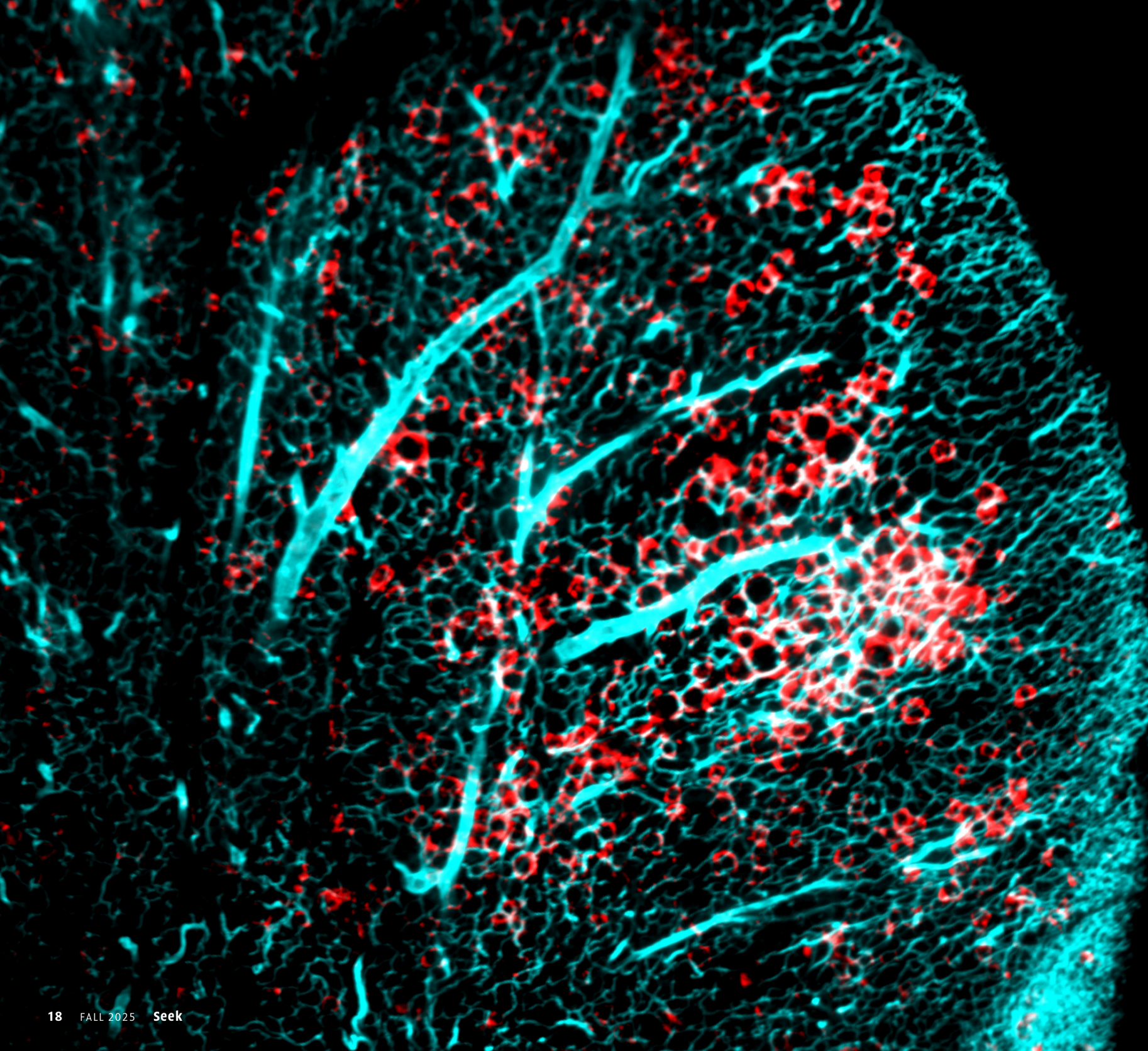
LBM in its different variations, and our efforts to combine it with optogenetics. It's capable of recording up to a million neurons across the entire mouse cortex at once. Using LBM, we have recently shown how widespread brain activity is across different time and spatial scales. We have also found that a significant portion of the observed neuroactivity embedded within a brain-wide distributed network is neither related to an animal's movements nor to sensory inputs. That raises fascinating questions about what our brains are doing in the background, when they appear to be at rest. We're now using LBM to investigate how changes in brain states affect decision making. And in a collaboration with a lab at UCLA, we've used it to explain why practice makes perfect at a neurocircuitry level.

We also developed a microscope that's as light as a penny, so we can mount it on a mouse's head while it freely moves about. Despite its tiny size, the microscope captures broad swaths of activity within a large brain volume. Another attractive aspect of these miniaturized microscopes is that they are relatively cheap, and most of their parts can be 3D printed.

Where are you hoping your technology can ultimately lead us?

We often take for granted just how much information the brain processes—it's an enormous amount—yet the underlying computational principles remain largely unknown. For example, how are brain functions such as abstraction or generalization realized on the level of neuronal circuits?

Take an object like a car. We know how certain of its visual features—such as contours, texture, or color—are individually represented in states of neural activity in specific brain regions and groups of neurons. But if I look at a car with a different shape, size, or color, or a car that has been completely deformed in a crash, I still know it's a car. So how is car encoded in the brain? What makes the carness of a car? The field is still in the process of finding the answers. In this regard, the most exciting thing I could imagine is if some of what we are developing would allow us to come a step closer to understanding the relationship between the physical matter under our skulls, the structure of information represented by it, and our inner experience.



SNAPSHOT

Metabolic havoc

AS BODY WEIGHT fluctuates, fat cells—collectively known as adipose tissue—wax and wane. This oscillation can wreak havoc on the body's metabolism, especially in the case of yo-yo dieting, a phenomenon that's been tied to a higher risk of developing diabetes, fatty liver disease, and hypertension.

Mascha Koenen, a postdoc in Paul Cohen's lab, suspects that's largely a consequence of how yo-yo dieting feeds chronic inflammation simmering in visceral adipose tissue, a type of fat stored deep in our abdomen that contains a complex web of blood vessels and immune cells.

To probe deeper, Koenen took tissue samples from obese mice that went through a round of extreme weight loss, and stained their white blood cells—known as macrophages—red. The tiny crimson, crown-like structures that emerged revealed an unexpected pattern of sustained inflammation after weight loss. Koenen is now tracking how these immune cells interact with other cell types—whether they are essential to resetting the fat tissue to a normal state, or, alternatively, if they play a role in the detrimental outcomes associated with weight cycling. She hopes her research will inspire new efforts to treat the comorbidities that can linger long after the dieting is over. ◎

WESLIE R. AND WILLIAM H. JANEWAY LABORATORY OF MOLECULAR METABOLISM

When The Rockefeller University was founded in 1901, the average life expectancy in the U.S. was less than 50 years. A century of scientific advancements later, that average lifespan has increased by more than three decades.

This dramatic shift is due in no small part to the enormous progress scientists have made in the fight against infectious diseases. And at every point in the past 125 years, Rockefeller has played a pivotal role in that fight. Our labs discovered the first clinically tested antibiotic (launching the golden age of antibiotics—and a robust line of research at Rockefeller to this day), the first vaccine against deadly yellow fever (winning the first Nobel ever given for a viral vaccine), and the hepatitis C virus, leading to the first, and so far only, cure of a chronic viral disease (and another Nobel Prize). And that names but a few of our accomplishments, as scientists here continue to study infectious disease from a myriad of angles.

They are also confronting a changing landscape—global factors that spread pathogens more quickly, foster the emergence of new diseases, and drive a resurgence of old foes—and are responding with ever more creativity and innovation. Now, some of this work holds the promise to tamp down pandemics, tame the threat of vector-borne diseases, and generate novel methods that translate into extraordinary breakthroughs.

"Fundamental research is transforming our understanding of infectious diseases," says Charles M. Rice, a Nobel laureate and head of the Stavros Niarchos Foundation Institute for Global Infectious Disease Research at Rockefeller. "We have never had better tools to identify and study disease agents, which will continue to accelerate our ability to prevent and treat infectious disease."

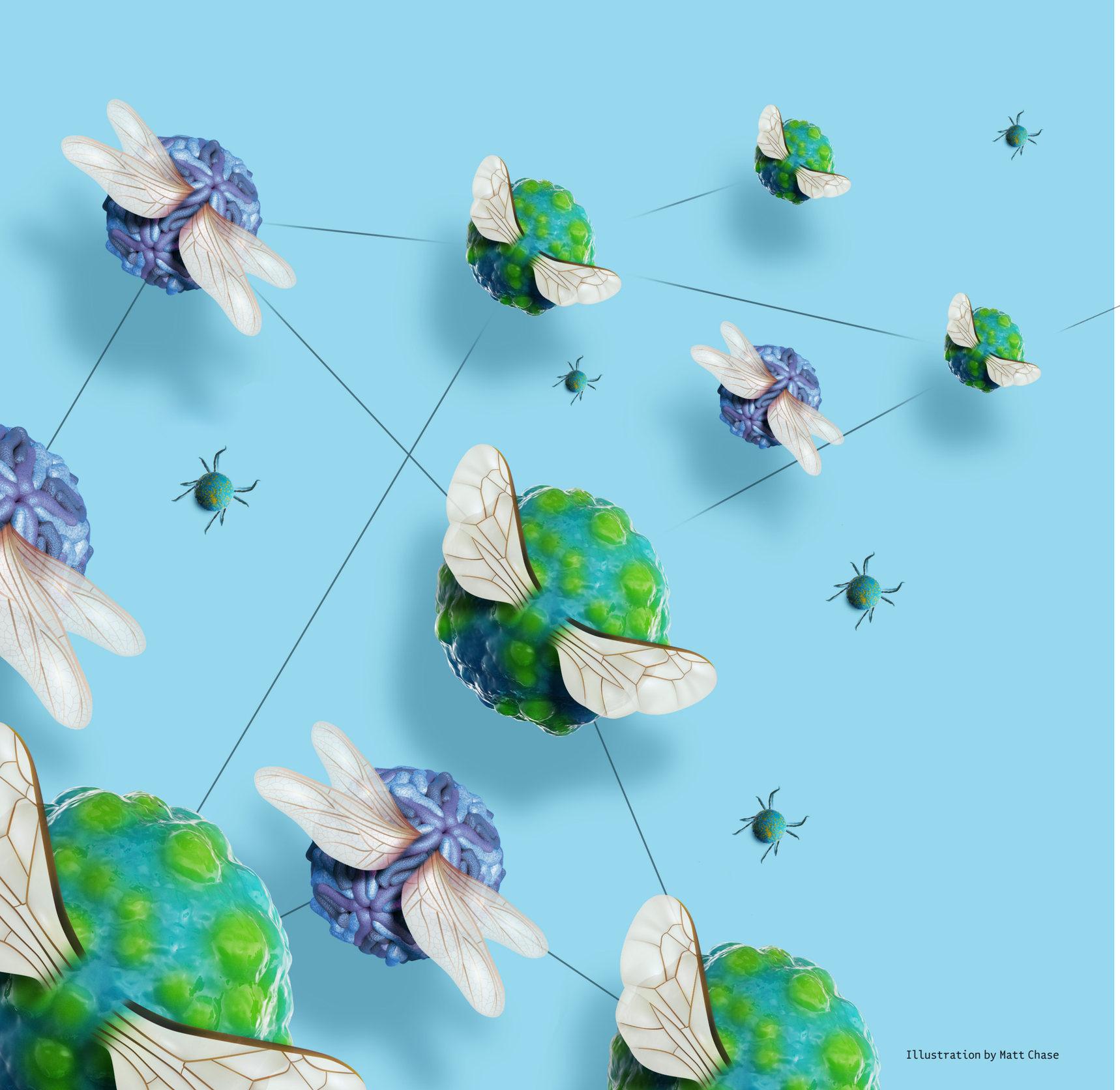


Illustration by Matt Chase

Taming the threat

Vector-borne diseases are on the rise. But new treatments wait in the wings.

By Alexander Gelfand

MOSQUITOES, FLEAS, TICKS, LICE: Such humble creatures have played an outsized role in human history. During the Middle Ages, fleas carrying the bacterium that causes plague wiped out a third of Europe's population. The *Anopheles* mosquito helped shape the course of the Revolutionary War, laying waste to British troops with its malarial payload. Overall, vector-borne diseases—those passed through living organisms acting as middlemen on behalf of germs and parasites—accounted for more illness and death from the 1600s to the early 1900s than all other causes combined.

As the 20th century progressed, however, the situation began to improve. In 1936, scientists at the Rockefeller Institute developed an effective vaccine against yellow fever, one of the world's most dangerous mosquito-borne illnesses. Further advances in prevention, treatment, and vector control—including insecticides, drugs, and more vaccines—meant that by the 1960s, vector-borne diseases looked a lot more manageable.

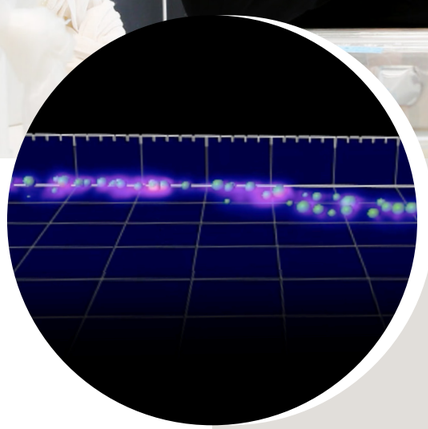
And then something unsettling began to happen.

"The risk of catching a known vector-borne disease has been steadily going up. And new ones are surfacing all the time," says Jean-Laurent Casanova, who has been investigating immune-system defects related to viruses spread by mosquitoes and ticks—aka arthropod-borne viruses, or "arboviruses."

Indeed, relative newcomers such as West Nile virus and eastern equine encephalitis, and longstanding foes such as dengue and chikungunya, are all on the rise. (Instances of dengue alone have increased as much as tenfold since 2000, while West Nile is now the most common mosquito-borne illness in the United States.) Currently, these diseases kill more than 700,000 people annually, and leave many survivors with chronic disabilities.

Global travel, widespread deforestation, and rapid urban expansion are all partly to blame for this new reality. But a host of factors are at play. "Much has changed in recent

The *Aedes aegypti* mosquito lives only three weeks yet is nonetheless the most dangerous animal on earth. "As the globe warms, many more places in the United States and South America will become hospitable to these critters."
VOSSHALL



Leslie Vosshall (left) and Laura Duvall (right) identified a molecule that could reduce a mosquito's appetite for blood.

Inset: 2D image of neurons in the leg of the yellow fever mosquito.

JOHN ABBOTT; LABORATORY OF NEUROGENETICS AND BEHAVIOR

years," says James Logan, a medical entomologist at the London School of Hygiene & Tropical Medicine who runs the Global Vector Hub, an open-access resource for vector research and vector-control programs. "Climate change is driving the spread of vectors and the pathogens they transmit, without a doubt. Resistance to insecticides and drugs is also fueling the fire."

Unfortunately, innovations in vaccines and treatments have not kept pace. At the heart of the problem lies a biological conundrum: Most vector-borne diseases are caused by viruses and parasites, which present extremely slippery targets. "Many of these pathogens have evolved to be super-variable to avoid being eliminated by the host immune system," says Douglas Norris, an expert in vector and pathogen biology at Johns Hopkins University. As a result, until we can unpack the basic biology of these microscopic invaders—and our own immune responses to them—we have little hope of developing the necessary tools to ward them off.

But Rockefeller scientists have long been studying these essential mechanisms. And many are leveraging the insights they've gained to inform novel ways of preventing and treating vector-borne diseases. Some, like Leslie Vosshall, concentrate on the organisms that spread these global threats. Others, like Charles M. Rice, focus on the pathogens that cause them. And still others, including Casanova, Jeffrey Ravetch, and Michel Nussenzweig, study the defenses our bodies mount against them, and how they sometimes go awry.

New discoveries in each of these areas will be crucial to tackling this large and growing list of diseases that, if left unchecked, could do even more harm in the future than they have in the past.

WILY ADVERSARIES

THE VERY THING THAT gives vector-borne diseases their name—the organisms or "vectors" that spread them—also makes them particularly difficult to stamp out. For in addition to adding a layer of complexity to the chain of transmission, these tiny adversaries can be incredibly resourceful.

No one knows this better than Vosshall, head of the Laboratory of Neurogenetics and Behavior.

Vosshall began her career investigating olfaction in the fruit fly, as harmless an arthropod as one could encounter. But her fascination with how insects are led to their next meal by their sense of smell led her to *Aedes aegypti*, an elegant mosquito with white polka-dot markings that lives only a few weeks yet nonetheless manages to spread illnesses like dengue, Zika, yellow fever, and chikungunya with ruthless efficiency. Dengue alone menaces an estimated 4 billion people around the world, and while *Aedes* does not like the cold, that could soon prove much less of a deterrent. "As the globe warms, many more places in the United States and South America will become hospitable to these critters," Vosshall says.

Vosshall uses genetic and behavioral experiments to examine everything from *Aedes*' feeding behavior to its sex life. (Only female mosquitoes feed on blood, which they need to produce their eggs.) She's revealing the animal's basic biology in order to discover ways of rendering it harmless—for example, by interfering with its ability to perceive the cues it uses to hunt us, like the carbon dioxide we exhale and the heat we emit.

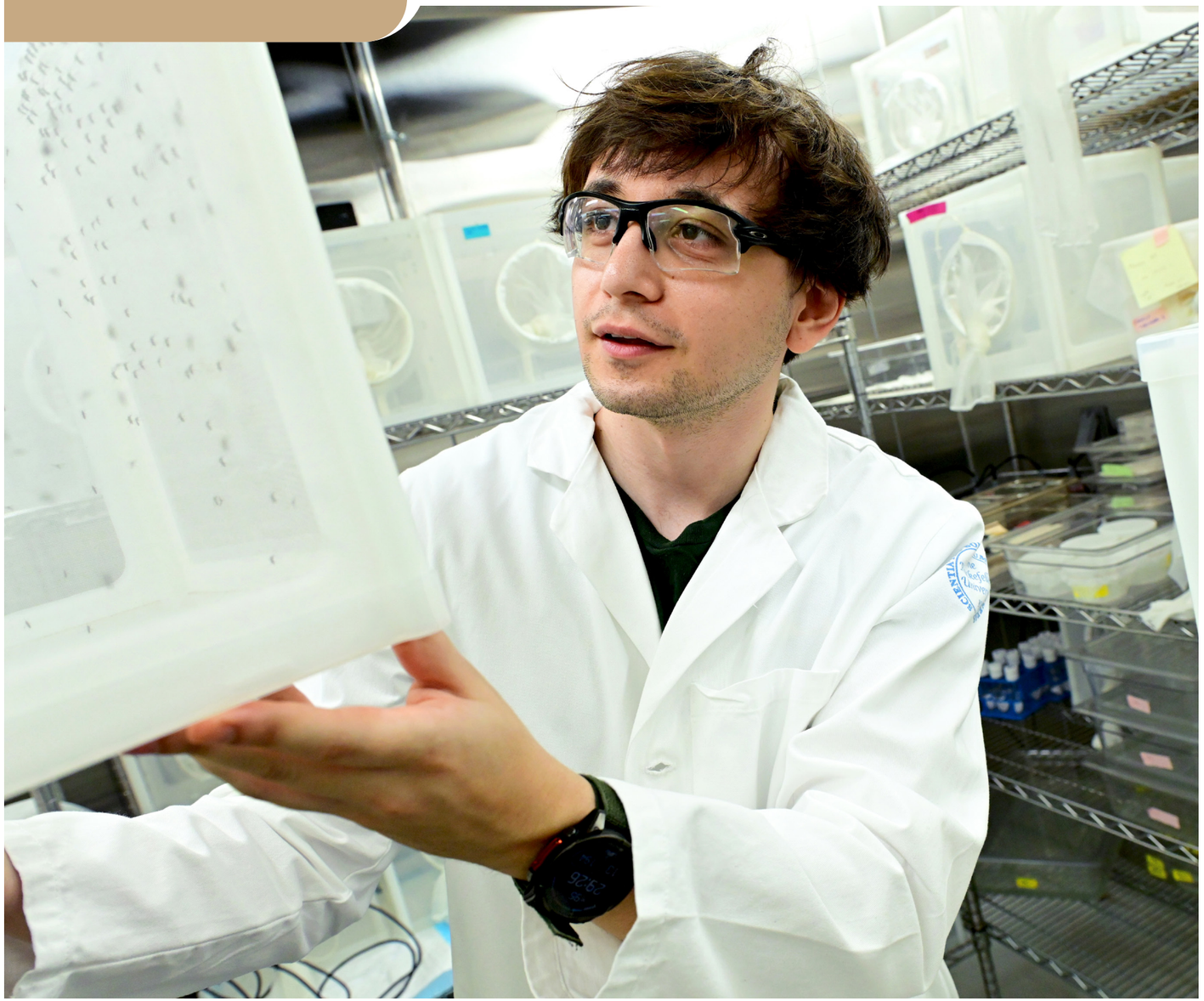
Numerous studies from Vosshall's lab have repeatedly confirmed what a wily adversary *Aedes* is. More than a decade ago, she and her colleagues engineered a mutant version of the insect that could not sense carbon dioxide. It was, Vosshall says, one of the earliest efforts "to break the mosquito." But while these mutants seemed innocuous when confined to the lab, they had no trouble locating human prey when released into more naturalistic environments. That finding was partially explained by a 2025 study, which revealed that mosquitoes became more sensitive to body heat after their olfactory sensors were knocked out, much as people develop more acute hearing after losing their sight. "These kinds of studies show that we're dealing with a very, very formidable foe," she says.

But that hasn't stopped Vosshall and her team from dreaming up ever more creative ways of stymying *Aedes*.

Together with Laura Duvall, a former postdoc who is now on faculty at Columbia University, Vosshall identified a molecule called compound 18 that reduced *Aedes*' appetite for blood. "It's like Ozempic for mosquitoes," Vosshall says.

Razzauti has developed a machine learning algorithm that can track every single mosquito in HOSTel as it approaches and ultimately recoils from the repellents.

Jacopo Razzauti, a Ph.D. student in the Vosshall lab, is trying to understand how insect repellents work so that scientists can improve them.



CHRIS TAGGART

When first discovered, large quantities of compound 18 were needed to kill a mosquito's appetite, rendering it too costly for commercial use. But Vosshall and Duvall recently managed to increase the drug's potency by a hundredfold, thereby also increasing the likelihood that a mosquito appetite suppressant might someday hit the market. Outdoor feeders filled with the compound could serve as mosquito snack bars, leaving the tiny bloodsuckers feeling too stuffed to pursue human beings.

Ph.D. student Jacopo Razzauti is taking a different tack, going back to the basics to improve one of the most effective tools we already have for deterring *Aedes*: insect repellents.

The two most popular, DEET and picaridin, have been around since the 1940s and 1980s, respectively. Yet we still don't really understand how they work. And without knowing the precise mechanisms at play, scientists cannot rationally design better alternatives. (Neither repellent is 100 percent effective, and DEET, the gold standard, is stinky, greasy, and melts plastic.)

Razzauti is trying to solve the puzzle of repellency by capturing the precise moment when *Aedes* bounce off the invisible force field created by DEET and picaridin. Once that's done, he plans to replicate the experience while imaging *Aedes*' neuronal system.

Razzauti has built a special chamber, dubbed the HOSTel, that can house multiple mosquitoes while administering all the things that make a host attractive: carbon dioxide, body odor, and heat. The chamber is equipped with a sliding door behind which Razzauti can position his bare arm—an enticing target for any female *Aedes*—protected by a bit of mesh. And because mosquitoes are too small and fast for the human eye to follow, it is also equipped with a high-speed camera that can record up to 500 frames per second. With help from data scientists at Rockefeller, Razzauti has developed a machine learning algorithm that can track every single mosquito in the HOSTel as it approaches and ultimately recoils from the repellents, capturing the precise instant when attraction turns to disgust.

Preliminary data suggest that the mosquito's legs play an important role in sensing the repellents, so Razzauti has made custom-tailored cover slips that slide over *Aedes*' delicate limbs like fingerless gloves. He plans to expose the tips of the animal's legs to the repellents while imaging its neurons to determine exactly which cells respond and at what distance. Such data might finally answer the fundamental question of how repellents work, while also pointing the way toward more effective ones.

INBORN ERRORS

EIGHTY PERCENT OF PEOPLE infected with West Nile show no symptoms, and 19 percent experience mild ones like fever and joint pain. But 1 percent wind up in the hospital with encephalitis or meningitis—and 20 percent of those with encephalitis die.

West Nile is far from the only infection to provoke such wildly different outcomes; COVID, for instance, offered a stark illustration of another. Yet why and how such variability emerges has baffled doctors for decades.

Casanova, head of the St. Giles Laboratory of Human Genetics of Infectious Diseases, has spent 30 years seeking answers to those questions. Since the 1990s, he has discovered hundreds of inborn errors of immunity, holes in our bodies' defenses that make certain people particularly vulnerable to infection. He's learned that some of these errors are genetic mutations that directly impair immune responses, while others manifest as autoantibodies that attack the very proteins we rely upon to repel viral and bacterial invaders.

In the depths of the pandemic, Casanova and his colleagues showed that 20 percent of COVID deaths were caused by autoantibodies that neutralize a group of immune system proteins called type I interferons. (He and others have found that the same autoantibodies cause 15 percent of critical MERS cases and 5 percent of critical flu cases.) Casanova estimates that up to 1 percent of people below the age of 65 produce such autoantibodies, a number that jumps to 5 percent after age 70, translating to 100 million people worldwide. And the older a person gets, the more potent the autoantibodies become. "Once the autoantibodies appear, it only gets worse," he says.

Now Casanova has shown that these very same autoantibodies can have an even more significant impact on the severity of vector-borne diseases.

In 2019, Casanova and Rice, head of the Laboratory of Virology and Infectious Diseases, identified a genetic mutation that could provoke a life-threatening reaction to the yellow fever vaccine, a live vaccine that contains weakened yellow fever virus. Soon after, they demonstrated that a third of all such adverse reactions were caused by type I interferon autoantibodies.

Reasoning that a virus injected through a needle is not so different from one injected through the proboscis of a live animal—"in essence, you could think of a mosquito or a tick as a kind of syringe," Casanova says—he wondered whether the same autoantibodies might cause severe disease in other arboviral infections.

Casanova first turned his attention to West Nile, which is spread by *Culex* mosquitoes that have in turn acquired it from birds. There is no vaccine or targeted antiviral treatment for the virus, and since arriving in the United States in 1999 (it was first isolated in Uganda in 1937), it has become the leading cause of mosquito-borne disease and epidemic encephalitis in the country.

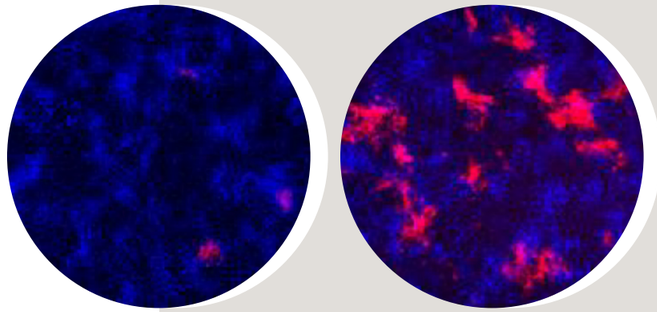
In 2023, Casanova and an international team of collaborators published a study analyzing hundreds of patients hospitalized with West Nile in Italy, Hungary, and the U.S. Shockingly, they found that 35 percent of them—and a whopping 40 percent of patients with encephalitis—had type I interferon autoantibodies.

A follow-up study showed that the same autoantibodies cropped up in 10 percent of patients hospitalized with tick-borne encephalitis (TBE), an emerging health threat in Europe and Asia. Like West Nile, TBE also severely sickens a relatively small number of infected patients, but it leaves 10 to 20 percent of survivors with lasting neurological problems such as paralysis and cognitive impairment.

"It's really devastating," says Nussenzweig, who works on TBE with collaborators in Switzerland, where the disease is endemic.

A third study by the Casanova lab, published earlier this year, once again found high concentrations of type I interferon autoantibodies among severely ill patients infected with three emerging arboviruses: Powassan, a tick-borne illness found in North America; Ross River, which is spread by ticks in Australia and other parts of the South Pacific; and Usutu, which is transmitted by mosquitoes in parts of Europe, Africa, and the Middle East.

Casanova continues to work his way through the list of arboviruses, looking for the same autoimmune culprits. But he already thinks that elderly people should be routinely screened for them. Should they test positive, they can take steps to avoid both arboviruses and respiratory viruses and make sure to get any available vaccines—though not live ones.



(Left) infected cells given an +IFN-α treatment along with healthy plasma from a healthy donor. (Right) infected cells given an +IFN-α treatment and plasma from a patient with autoantibodies against +IFN-α. The red indicates the presence of the virus.

A virus injected through a needle is not so different from one injected through the proboscis of a biting vector. "In essence, you could think of a mosquito or a tick as a kind of syringe."
CASANOVA

Jean-Laurent Casanova has identified inborn errors of immunity that make some people more vulnerable to vector-borne diseases than others.

CHRIS TAGGART; ST. GILES LABORATORY OF HUMAN GENETICS OF INFECTIOUS DISEASES

PREDICTIVE BIOMARKERS

If such wildly different outcomes weren't perplexing enough, one mosquito-borne illness is associated with an even more curious phenomenon: People who contract dengue, a disease so painful that it's known as "breakbone fever," are at far higher risk of developing a life-threatening case specifically if they've had the virus before.

For many years, the prevailing theory was that leftover antibodies from prior infections somehow increased viral uptake, a phenomenon known as

antibody-dependent enhancement, or ADE. But that never made much sense to Ravetch.

Ravetch, who heads the Leonard Wagner Laboratory of Molecular Genetics and Immunology, knew that people with mild and severe disease had the same levels of virus in their blood. He had other reasons for suspecting that something else might be going on: For decades, Ravetch has studied a structural component of antibodies known as the Fc region that can both promote and inhibit inflammation. Over time, he has shown that subtle molecular changes to the Fc and its corresponding receptors can turn otherwise protective antibodies pathogenic and vice versa. Ravetch therefore wondered if such modifications might underlie ADE, which can lead to deadly conditions such as hemorrhagic fever and septic shock.

The first evidence this might be true came in 2017, when Ravetch and his colleagues discovered that patients with severe dengue had antibodies whose Fc lacked a particular sugar, a chemical alteration known as afucosylation. In a subsequent study conducted with the help of researchers at the Pasteur Institute in Cambodia, the Ravetch lab demonstrated that afucosylated antibodies could serve as a predictive biomarker for people at risk of developing severe disease, a finding that could allow clinicians in the developing countries where dengue is most common to concentrate their resources on the highest-risk patients.

"In settings like field hospitals in resource-limited countries, this is a big deal," says Stylianos Bournazos, a research associate professor in the Ravetch lab who led the Cambodian study.

Testing people for afucosylated antibodies, however, is a slow and expensive process. So the lab developed a synthetic antibody, known as a nanobody, that could be used to screen for afucosylation quickly and cheaply. As a bonus, in 2023, Ravetch and his colleagues showed that the same nanobody could also block the activity of afucosylated antibodies in mice, raising the possibility of a dual-purpose tool that could serve not only as a rapid diagnostic for severe dengue, but also as a treatment. With help from the Rice lab, Ravetch also developed a mouse model that allowed him to trace the specific mechanism whereby afucosylated antibodies cause life-threatening complications.

More recently, the Ravetch lab teamed up with collaborators at Emory University to isolate an enzyme that can also prevent severe dengue in mice, suggesting another potential treatment—one that shows promise for a variety of other inflammatory and autoimmune conditions as well. And Ravetch is currently collaborating with Casanova to see if afucosylation might drive other instances of severe arboviral disease, and to explore the possible interplay between Fc modifications and type I interferon autoantibodies.

Bournazos, meanwhile, is taking a deep dive into a different arbovirus: chikungunya, which has spread to more than 60 countries on the wings of *Aedes aegypti*. Unlike dengue, chikungunya causes symptoms in nearly everyone who contracts it, and in almost 50 percent of patients, some of those symptoms, such as disabling joint pain, can persist for months or even years.

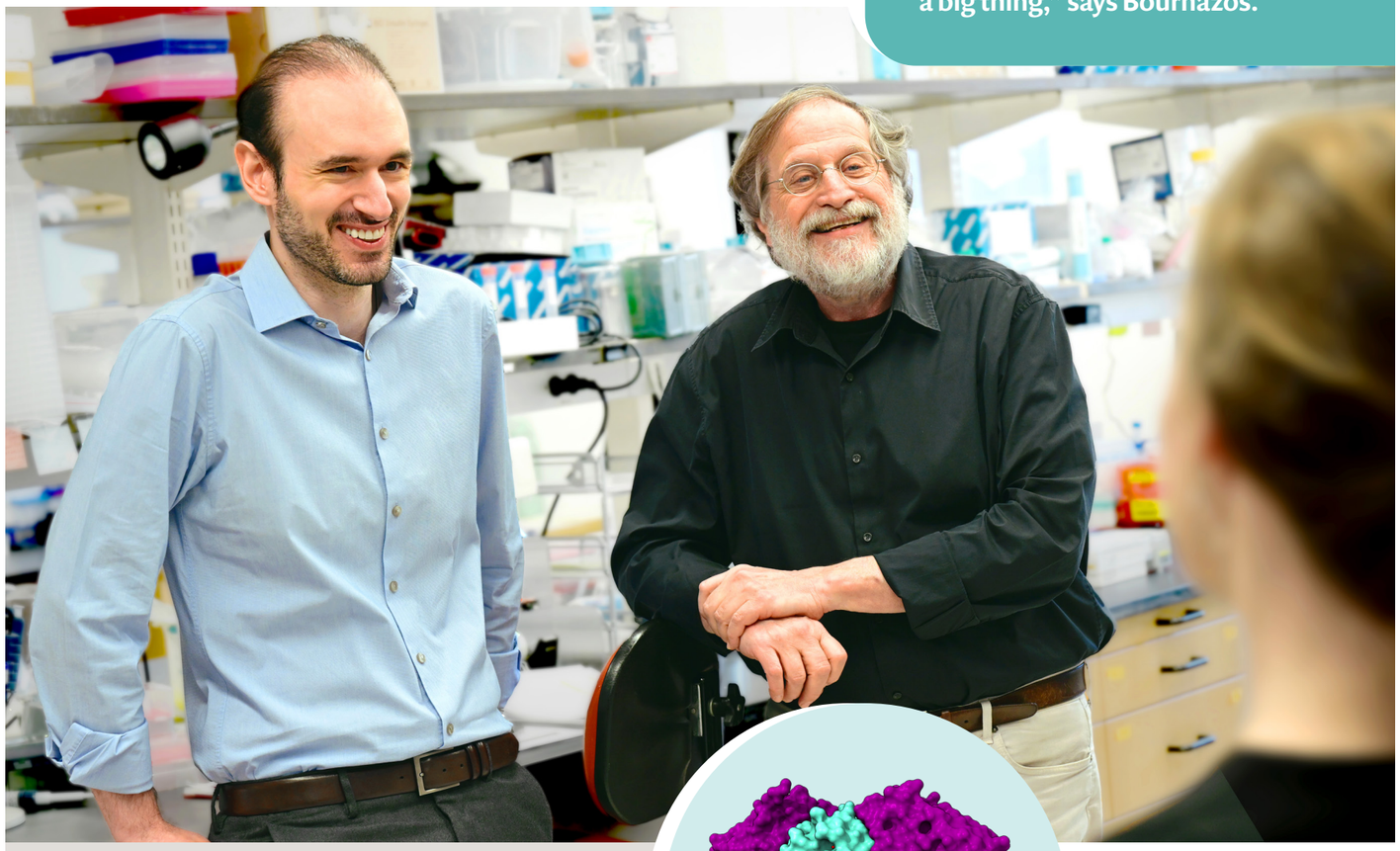
Again, with assistance from the Rice lab and his Cambodian collaborators, Bournazos aims to learn whether an abnormal antibody response is to blame for chronic chikungunya, and, if so, whether changes to the Fc can once again serve as a predictive biomarker. In this case, however, the goal would be to improve care by identifying—and perhaps, someday, even treating—patients at risk of chronic, rather than severe vector-borne disease.

ENHANCING DEFENSES

IF RAVETCH AND CASANOVA are interested in those cases where the immune system fails to defend against vector-borne diseases, Nussenzweig is interested in the ones where it succeeds.

Nussenzweig has spent decades studying antibodies and the immune cells that produce them. Along the way, he has established a track record of finding and enhancing highly potent human antibodies to treat and prevent viral diseases. He and his close collaborator Marina Caskey, a professor of clinical investigation, honed this approach to antibody therapy against HIV and have since applied it to SARS-CoV-2 and hepatitis B. The duo first turned their attention to vector-borne diseases during the 2015-2016 Zika epidemic, which had its epicenter in Brazil—the same country where both happen to have been born.

The Ravetch lab showed that certain antibodies could serve as a predictive biomarker for people at risk of developing severe disease. "In settings like field hospitals in resource-limited countries, this is a big thing," says Bournazos.



CHRIS TAGGART; LEONARD WAGNER LABORATORY OF MOLECULAR GENETICS AND IMMUNOLOGY

Having figured out what makes dengue so deadly, Jeff Ravetch (right) and his team, including Stylianos Bournazos (left), are exploring potential treatments and looking at other vector-borne illnesses.

Inset: the crystal structure of a potential nanobody treatment for dengue.

As with dengue, most Zika infections are mild or asymptomatic. When the virus infects pregnant women, however, it can have catastrophic consequences for their babies. During the Brazil outbreak, thousands of children born to infected mothers developed microcephaly and other serious neurological problems.

"Zika was a terrible tragedy for Brazil, so we were both interested in seeing if we could learn something about human immunity to the virus—and find some potent antibodies that would be protective against infection," Nussenzweig says.

Together with Davide Robbiani, a former lab member who now directs the Institute for Research in Biomedicine in Switzerland, Nussenzweig and Caskey isolated potent anti-Zika antibodies from the blood of infected patients. By modifying the Fc of the most effective one, they managed to increase its half-life to the point where it could potentially protect a pregnant woman's embryo throughout the period when the virus is most likely to do serious damage.

The Butantan Institute, a state-run biomedical research institution in Brazil, is currently gearing up to produce this engineered antibody for clinical use in hopes of preventing infection in women who are pregnant or wish to be. "You could offer it to people that are about to be or are already pregnant to bridge them safely through the pregnancy," Caskey says.

Now the team is looking to repeat that success with another vector-borne disease that can have devastating effects: TBE.

There are several effective vaccines against TBE. But uptake has been low for reasons including cost, access, and vaccine hesitancy, and there are no targeted therapies for people who contract the illness. As a result, while severe cases remain relatively rare, "it's a bad disease without any options," Nussenzweig says.

That may soon change. With support from the Stavros Niarchos Foundation Institute for Global Infectious Disease Research, Nussenzweig, Caskey, and Robbiani have developed a potent antibody against the TBE virus. They have already demonstrated that the antibody can treat and prevent TBE in mice and plan to begin testing it in Swiss volunteers this fall. (Two other Swiss research groups are also involved, as is the Swiss National Reference Center for tick-borne diseases, which will help recruit participants.)

Marina Caskey and Michel Nussenzweig have identified powerful antibodies that can be used to treat and prevent diseases such as Zika and tick-borne encephalitis.

CHRIS TAGGART

"Zika was a terrible tragedy for Brazil, so we were both interested in seeing if we could learn something about human immunity to the virus—and find some potent antibodies that would be protective against infection."
NUSSENZWEIG

As with the work being done by his colleagues in labs across campus, Nussenzweig's research could have broader implications. For example, the anti-TBE antibodies that he identified showed activity against other tick-borne viruses, including Powassan, which can also leave survivors with lasting neurological problems. And Nussenzweig is looking into possible collaborations with researchers in Australia, home to a variety of arboviruses, on other vector-borne diseases.

A UNITED FRONT

THE PACE AT WHICH these scientists are producing new ways of managing vectors and the diseases they transmit may seem astonishing. After all, each has turned out studies in the past few years that could revolutionize the way we treat and prevent everything from West Nile virus to TBE and beyond.

Yet all these successes were built on decades of painstaking research. Vosshall's work on *Aedes aegypti* grew out of an insatiable curiosity about the mechanisms underlying olfaction in insects and humans. Casanova's work on arboviruses sprang from his larger quest to understand why some people become deathly ill from infections while most do not. Ravetch's work on dengue and now chikungunya emerged from his desire to understand how antibodies can have both destructive and protective effects. And Nussenzweig came to antibody therapy through his fascination with the fundamental building blocks of the immune system.

All hoped that their research would help improve health and alleviate suffering. But none could have envisioned exactly where it might lead. Such is the power of practicing science even when the practical benefits may be decades away—and all but impossible to predict in precise detail.

"It does come full circle," says Ravetch. "But it takes a lot of long-term thinking."

Illustration by Matt Chase

The key to better antivirals

Medicine has long been stymied by unique challenges inherent to developing antiviral drugs. But the rush to take down one virus may have unlocked new methods to knock out multiple viral foes.

By Bethany Brookshire

In the early days of 2020, Rockefeller buzzed with its usual quiet intensity. Graduate students hunched over benches and racks of tubes. Postdocs scribbled diagrams onto glass whiteboards. And in his spartan office at the back of a sprawling lab, Thomas Tuschl was preoccupied with molecules that much of the world had barely heard of—proteins that guide RNA as it shuttles genetic material around cells.

Then everything changed. While many began sheltering at home during the COVID-19 pandemic, researchers at Rockefeller quickly began working to try to understand SARS-CoV-2, a virus that stores its genetic instructions in strands of RNA. "As an RNA scientist, I wanted to contribute," recalls Tuschl. So his lab pivoted, searching for drugs that would shut down the virus's genetic apparatus. At the same time, a few floors below, Rockefeller virologists Theodora Hatziioannou and Paul Bieniasz had also seized on the idea of developing antivirals, testing how SARS-CoV-2 dodged antibodies—and how to coax immune molecules to launch an attack on the virus.

Both labs had spent decades studying how viruses replicate and how the immune system fights back. "It's hard to overstate the amount of adrenaline that was flowing," says Bieniasz, who is the Purnell W. Choppin Professor, as well an investigator at the Howard Hughes Medical Institute.

Five years later, that adrenaline has diminished for most people; much of the world has moved past COVID-19. Pandemic-related scientific funding has expired or been withdrawn, and most labs have shifted their research back to other topics. But the virus hasn't disappeared—in fact, it continues to mutate, even as related threats may already be evolving somewhere out of sight.

"There's a whole collection of coronaviruses circulating in bats," notes Hatziioannou. "Their introductions into the human population are getting more and more frequent."

So, at Rockefeller, the work continues, and it's been revealing insights that may have implications far beyond COVID-19. The same viral tricks used by SARS-CoV-2 are employed by viruses like dengue, MERS, and even the common cold. By investigating COVID-19's weak points, Rockefeller's researchers may find themselves laying the groundwork for a new generation of antivirals.

"This is not just about one pathogen," says Nobel laureate Charles M. Rice, who leads the Stavros Niarchos Foundation Institute for Global Infectious Disease Research at Rockefeller. "If we create a drug that protects against a whole family of viruses, it could head off the next pandemic."

It may even do more than that.

AN EVASIVE ENEMY

VIRUSES ARE, IN a sense, the ultimate minimalists. Unlike bacteria, which have their own cellular machinery and numerous components scientists can target, viruses are little more than genetic material wrapped in protein. They don't grow or divide. They don't even metabolize. Instead, they invade a host cell and hijack its inner workings, transforming it into a virus-making factory. That parasitic simplicity makes them difficult to kill without harming the host in the process.

Adding to the challenges, viruses mutate incessantly. Each time a virus copies itself, it makes tiny mistakes. Most of those mutations go nowhere, but the rare ones that offer an advantage, like escaping the immune system or resisting drugs, can take over in a matter of days.

"Viruses are not smart," Hatziioannou explains, but with how fast they seem to evolve to evade scientists' best efforts, you'd be forgiven for thinking they are. "It's like the virus is trying every possible move simultaneously in chess matches against you," she says. "In most of the games it's going to lose, and those are the variants that you're never going to see. But in one it's going to win, and that's the game that counts. That's all it needs."

It's no surprise, then, that while we have hundreds of antibiotics to treat bacterial infections, we have relatively few antiviral drugs, and even fewer that combat multiple viruses.

Scientists have long dreamed of something analgous: a powerful broad-spectrum antiviral that could work across many viruses, perhaps even an entire family like coronaviruses or flaviviruses. Something like the way amoxicillin works on a range of bacterial infections—simple to administer, widely effective, and, importantly, resistant to resistance.

The urgency of COVID-19 prompted labs to begin putting more resources than ever toward this goal. How could scientists stop playing catch-up and develop a drug that would protect against both currently circulating strains of COVID-19 and any future variants? Could such a drug also combat viruses beyond COVID-19?

"It's a tall order," Rice says. "How do you come up with an approach that gives good protection against a founding virus, and then all of the variants that it could generate?"

STRIPPING AWAY A VIRAL DISGUISE

WHEN SARS-COV-2 BURST onto the global stage, most scientists turned their attention to the spike protein—the now-infamous protrusion that allows the virus to enter human cells. But Tuschl, after years of studying RNA molecules, was looking elsewhere. He had his eye on an enzyme called NSP14, which modifies a protective cap on SARS-CoV-2's RNA. The cap convinces human cells that the viral RNA is "self" and should be translated into proteins rather than be destroyed. Without the modified cap, the virus's genetic material would be unmasked, exposed to the human immune system as foreign.

SARS-CoV-2 and related viruses must use NSP14 rather than human proteins to attach this genetic cap, and that made it enticing: It's a viral enzyme that's essential, unique to the virus, and different enough from anything in human cells that a drug could block it without harming us. "If you're looking for a target, any viral enzyme that makes its own RNA look like it belongs to the host is a good one," Tuschl says. "In this case, disabling the virus's capping mechanism stops the virus from replicating and spreading out from the host cell."

So Tuschl's lab got to work. They isolated NSP14, studied its activity, and began searching for ways to thwart it. In collaboration with Rockefeller's Fisher Drug Discovery Resource Center, the team threw the pharmaceutical kitchen sink at it, testing more than 430,000 compounds to see if any would block the enzyme's function.

The effort paid off. They identified a molecule that bound tightly to NSP14's active site. Then, they made chemical tweaks to the molecule to make it even more potent. The final product, dubbed TDI-015051, acted like a molecular wrench, jamming the enzyme and preventing the virus from accessing its own RNA. When tested in cultured human cells, the drug stopped SARS-CoV-2 from multiplying. When tested in mice, it inhibited virus reproduction just as

"Our work not only establishes NSP14 as a therapeutic target, it also opens the door to many more antiviral developments against pathogens that until now we've had only limited tools to fight."
TUSCHL

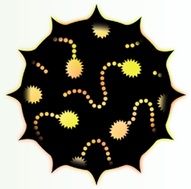
Thomas Tuschl is using his knowledge of RNA to disrupt the molecular machinery that viruses rely upon to infect us.

CHRIS TAGGART

KNEE CAPPING THE VIRUS

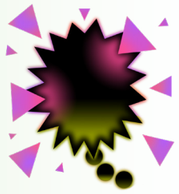
One reason viral infections are so difficult to treat is because of how they coopt the cellular machinery of the host, making viruses hard to kill without harming the host in the process.

In studying SARS-CoV-2, researchers found an intriguing drug target: an enzyme essential and unique to the virus, but different from anything in human cells.

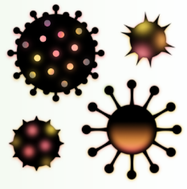


This enzyme adds a "cap modification" to the end of viral RNA, preventing the host cell from recognizing the genetic matter as foreign and enabling viral protein synthesis by the host.

The team developed a compound capable of jamming this enzyme, preventing the virus from accessing its own RNA.



The same approach can be applied to some other coronaviruses as well as RNA viruses like dengue, Zika, mpox, RSV, and Ebola.



effectively as nirmatrelvir, the active ingredient in the COVID-19 antiviral Paxlovid.

"Our work not only establishes it as a therapeutic target," says Tuschl of TDI-015051, "but it also opens the door to many more antiviral developments against pathogens that until now we've had only limited tools to fight."

All coronaviruses—from SARS to some common cold strains—use similar proteins to modify their RNA caps, suggesting that this compound or its successors might someday work against all of them. Even more tantalizing: Other RNA viruses, such as dengue and Ebola, also rely on their own unique capping proteins to disguise their RNA. "This is a new entry on the list of viable viral targets," Rice says. "This kind of work could potentially lead to a whole new class of antiviral drugs." More pre-clinical work is needed to solidify TDI-015051 as a potential drug for humans, but Tuschl says his lab is continuing on the case, testing how to shut down other similar proteins.

Rice, who has seen the slow, discouraging pace of efforts to fight viruses like Ebola and influenza, was stunned by the speed and success of Tuschl's work. "In hepatitis C, it took decades to go from identifying the virus to having an effective drug," he says. "Tom's lab did it in under three years. That's extraordinary."

FIGHTING ON MULTIPLE FRONTS

TUSCHL'S STRATEGY AIMED squarely at SARS-CoV-2's internal machinery. Meanwhile, another Rockefeller team was tackling the same enemy from a different angle: not by disrupting the virus's tools, but by rearming the human immune system. For Hatziioannou and Bieniasz, the central question wasn't how to break the virus—it was how to make our bodies better at recognizing and neutralizing it, even as it changed.

Their lab focused on a simple idea: Rather than generating a single, specialized antibody, what if they could coax the immune system into simultaneously producing a diverse arsenal of antibodies, each targeting a different part of the viral spike protein? This protein, which allows the virus to enter cells and initiate infection, was the main target of prophylactic vaccines and therapeutic antibodies during the pandemic. Traditionally, antibody therapies have relied on monoclonal antibodies—laboratory-produced molecules that precisely target one single vulnerable spot on a virus. This approach can be highly effective, but only until the virus mutates that one spot—something that SARS-CoV-2 proved more than capable of doing. A polyclonal response, by contrast, involves many antibodies at once, making it harder for the virus to mutate its way out of detection. If a virus changes one lock, the immune system still has plenty of keys.

Initial experiments by Hatziioannou and Bieniasz, in close collaboration with Rockefeller colleagues in Michel Nussenweig's lab, analyzed the blood of people who had recovered from COVID-19. People had many different antibodies to the virus, proving that there were multiple spots that could be recognized by antibodies.

Next, the researchers built pseudoviruses—lab-designed viruses that mimic SARS-CoV-2 but lack any ability to cause disease. The pseudoviruses allowed the team to study infection and immunity with greater speed and flexibility, free from the constraints of high-containment labs. "You take one piece of one virus and put it together with another piece of a different virus to make a virus that has useful properties," Bieniasz explains.

Based on the antibody responses, and how those drove virus evolution, the researchers then designed protein immunogens to persuade immune cells to produce a variety of antibodies at once. If B cells—the immune cells that make antibodies—were exposed to two different versions of a virus positioned very close together, could they produce antibodies that recognized both?

"When that B cell receives a stronger signal from two related viral proteins simultaneously," Bieniasz explains, "it's more likely to generate antibodies that are capable of binding to multiple targets."

This research reveals much about what will—and won't—work to train the immune system to deploy a broader attack against a virus. After all, B cells are a central component of the human immune system, and learning how to make them better at recognizing divergent antigens could help fight off many types of viruses.

CLOSING A DOOR

AT THE SAME time, Hatziioannou and Bieniasz also delved into the idea of making antibodies that bind to human cells, blocking the molecular door that the virus uses to gain entry.

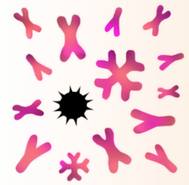
"If the virus is mutating so rapidly, why not target something that's more difficult to mutate?" says Hatziioannou. "That, of course, is the host."

Many coronaviruses sneak into human cells through the same receptor, known as ACE2. But slamming shut

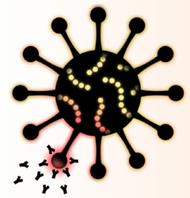
FORTIFYING THE HOST

The rapid rate at which viruses mutate and diversify poses another major obstacle to developing potent, durable, and broadly acting antivirals.

GENERATING POLYCLONAL ANTIBODIES

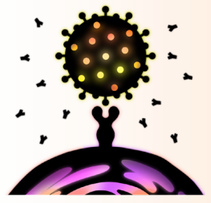


Rather than generating a narrowly focused, specialized antibody, researchers asked: What if the immune system could be coaxed into simultaneously producing a diverse arsenal of antibodies?

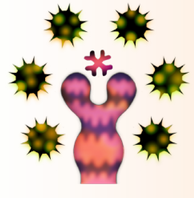


In the example of SARS-CoV-2, each could target a slightly different part of the viral spike protein, or variant spike proteins, thus requiring numerous mutations to reduce efficacy.

BLOCKING HUMAN RECEPTORS



On the other hand, a single antibody only needs one unchanging target: such as the human cell receptor known as ACE2.



Many coronaviruses sneak into human cells using ACE2, thus closing this one door could shut out multiple viruses.

Illustration by JR Bee

> **If the virus is mutating so rapidly, why not target something that's more difficult to mutate? That, of course, is the host."**
> **HATZIIOANNOU**

Paul Bieniasz and Theodora Hatziioannou are honing the immune system's ability to recognize and neutralize viral invaders.

CHRIS TAGGART

Miranda Aldis is a research assistant in the Laboratory of Retrovirology.

ACE2 throughout the human body could have dire consequences because the protein also helps regulate blood pressure. In the past, this conflict would have been a death knell for a drug targeting ACE2. But in recent years, scientists have developed new tools to precisely control proteins' functions, targeting one role without impacting their other jobs. As such, the number of antibody-based medicines has also been rapidly growing. Hatziioannou and Bieniasz saw a path forward.

The researchers isolated dozens of antibodies that mice generated and compared them against the human ACE2 protein. From there, they identified six antibodies that could successfully block viral infection without interfering with ACE2's other biological activities. "It's an incredibly clever approach to block the receptor, or to interfere with the ability of the virus to bind to the receptor," says Rice.

The strategy worked even better than expected: The ACE2 antibodies prevented every tested strain of the COVID-19 virus, including tough-to-target Delta and Omicron variants, from entering human cells. It even prevented the first SARS virus, which caused an epidemic in the early 2000s. In mice, the antibodies protected against SARS-CoV-2 infection. "If this antibody had been developed early on, we think it would still be in use," says Bieniasz.

The antibodies that Hatziioannou and Bieniasz created could be given prophylactically to people who are at high risk of serious disease, or as a treatment after infection. That kind of forward-looking strategy could be key if another coronavirus jumps from animals to humans, as SARS and SARS-CoV-2 once did. And it could potentially protect against another virus that binds to ACE2 that may still be waiting in the wings.

"If SARS-CoV-3 comes along tomorrow, then millions of people could benefit from this drug," says Bieniasz.

LESSONS FROM AN INVISIBLE WAR

WHEN THE COVID-19 pandemic spurred labs across Rockefeller into action, they began with the basics: Know your enemy. Over the first months of exploration, they learned how SARS-CoV-2 infects, spreads, and kills. Then they began to learn the tricks that the virus uses to avoid immune recognition and treatment, which are shared across other types of viruses.

Ultimately, the best tactic to prevent the next pandemic from spinning out of control may be for scientists to have multiple tricks up their sleeves, ready and waiting.

"If we've learned one thing about developing antiviral drugs, it's that you don't want to go in with just one of them," Rice adds.

That is why Rockefeller scientists haven't stopped using SARS-CoV-2 as a test case—dismantling the machinery it relies on, enhancing the immune system's memory, and locking the doors before the next virus can walk through. They're playing the long game, looking not just for treatments that work today, but for approaches that can survive the viral evolution of tomorrow.

"Right now, there's not a lot of incentive for a company to invest in a COVID-19 drug when there aren't patients dying in the hospital," says Tuschl. "So we could say, 'Let's just stop here.' But then, when the next viral pandemic comes up, nobody wants to lock everybody up for the few years it takes to make a drug."

Nothing about getting to this point has been easy. Each breakthrough—each antibody, each compound—is the result of years of molecular sleuthing and trial and error. But the momentum is real. And the payoff, if it comes, won't just be another COVID drug. It will be a new way of fighting viruses—broad, durable, and ready before the next outbreak begins.

"We can't predict what the next biggest viral threat will be," says Rice. "But we can acquire the fundamental knowledge and prepare the tools that will help us fight it."

Breaking ground often means not just dreaming up new ideas, but also devising the technology to pursue them.

Transformative Tools

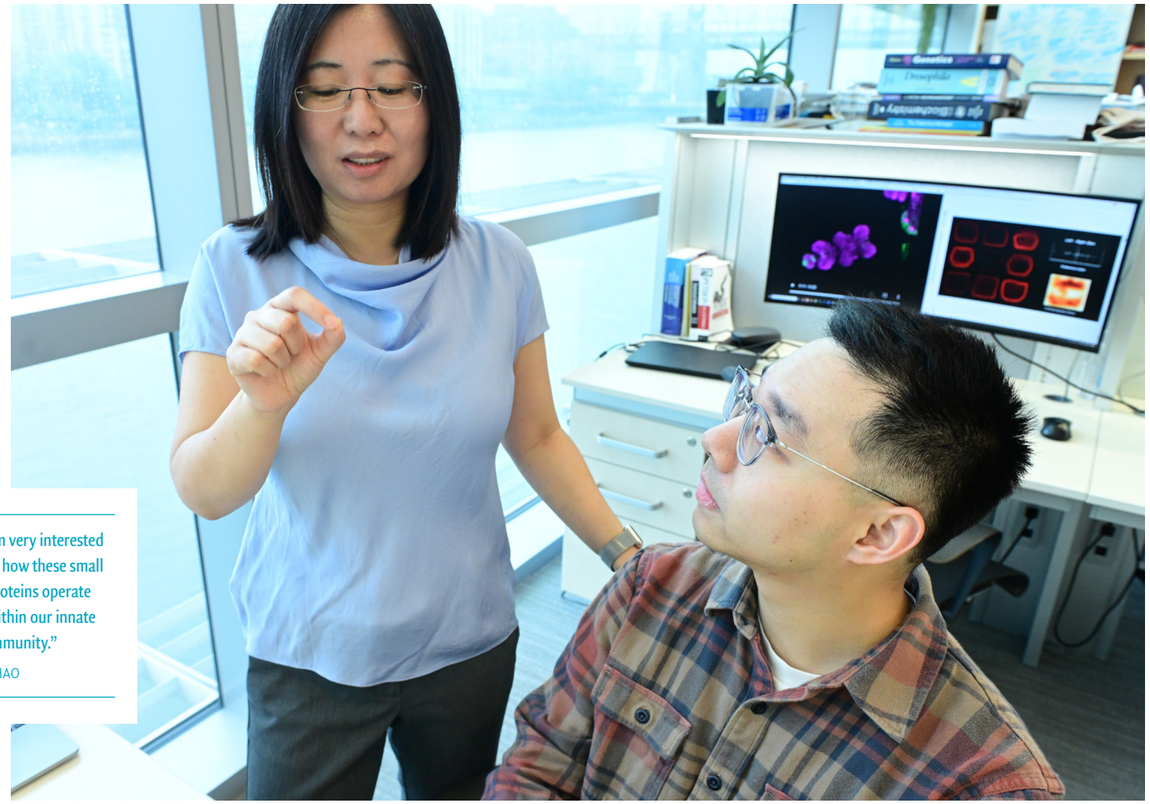
CHARTING THE UNCHARTED

How an atlas of unconventional peptides could help spur treatments for novel virus strains and hard-to-treat infections

WHEN A VIRUS, bacteria, fungus, or other pathogen enters a person's body, the immune system mobilizes in two phases. The body's first line of defense is innate immunity, a general and rapid response present from birth. Its second line of defense, adaptive immunity, is a slower but more precise response targeting a specific antigen, which develops throughout a person's life—either through infections or vaccinations. Together, these complementary mechanisms help clear out infections.

But between these two primary components of the immune system lie many unanswered questions about the types and functions of molecules involved: While scientists understand the roles of many traditionally defined antimicrobial proteins—called peptides—involved in immune responses, a specific class of recently discovered unidentified ones are playing roles that scientists can only conjecture.

"I'm very interested in how these small proteins operate within our innate immunity," says Li Zhao, associate professor and head of Rockefeller's Laboratory of Evolutionary Genetics and Genomics. Zhao studies how new genes can suddenly emerge from noncoding sequences of DNA and how that helps drive evolution. Recently, researchers were surprised to find that some of these mysterious young genes are subsequently conserved across species, leading them to suspect they may in fact serve a widely useful function: protection from pathogens. To find out, Zhao is homing in on tiny chains of amino acids—known as micropeptides—that lurk within this dark matter.



"I'm very interested in how these small proteins operate within our innate immunity."
ZHAO

Li Zhao is creating an atlas of the types and functions of novel micropeptides, which have been dramatically undercounted and largely unannotated.

CHRIS TAGGART

This much scientists know: Once a pathogen infects a person, certain very short antimicrobial peptides rush to the infection site to help clear a pathogen and related infection.

Consisting of a chain of less than 100 acids, classic antimicrobial micropeptides detect features, such as negative charges on the membrane of the pathogen, to kill them. Others located on the membranes of host cells serve as scaffolds for immune signaling. But how many immune-related peptides remain unidentified? And do these previously unidentified micropeptides contribute to innate immunity in the same way as known ones, or do they behave differently? Could some of these novel peptides function outside of well-understood pathways, potentially revealing new mechanisms or alternative biological processes? To answer these questions, Zhao has set out to create an atlas of the types and functions of these novel micropeptides, which have been dramatically undercounted and largely unannotated.

Zhao is developing theories about how some such micropeptides come to be, but, "from a very simple perspective we still don't know how many exist, what they mean in terms of biological response, and what kind of pathways they are regulating, especially in non-model species," she says. The reasons are threefold.

First, these short proteins are so small that they often escape detection in mass spectrometers that more easily spot their larger cousins, macropeptides. Second, micropeptides evolve very rapidly, so their possible functions and roles in biology are often overlooked. Lastly, they aren't transcribed or translated when there is no infection. So, in order to detect them, scientists need to infect cells or an organism to determine which proteins play a role in defense.

To create the atlas, Zhao and her team are studying a number of species belonging to the common fruit fly, or *Drosophila*, whose only defense against pathogens is innate immunity. Insects also represent a huge proportion of the planet's animal species—about 80 percent—and are exposed to a plethora of pathogens. Because a human body's first line of defense is similar, researchers can use what they learn from flies to better understand the mechanism in people.

With a combination of lab experiments, such as RNA sequencing infected flies and computational work, including machine learning, Zhao and three members of her lab have thus far identified hundreds of new antimicrobial and immune-related micropeptides. They're currently working on a manuscript to describe these findings

From there, says Zhao, her team will move on to looking at genes in the adaptive response, which can illuminate the role of micropeptides in human health even more. That knowledge, along with the newly identified peptides, will be valuable in devising preventative measures and treatments for ailments ranging from those caused by novel virus strains, like bird flu, to difficult-to-treat infections, such as methicillin-resistant Staphylococcus aureus, or MRSA. Their research may also provide new insights into why some individuals are more susceptible to infections.

By Sara Goudarzi

MAKING MAGIC WITH CRYO-EM

A new method offers a clearer picture of viral infections

FOR MORE THAN two decades, Hironori Funabiki's Laboratory of Chromosome and Cell Biology has studied the way chromosomes are partitioned during cell division and the genetic changes this process creates, or what he calls "the evolution of the living system." This work has greatly contributed to our understanding of genetic disorders, birth defects, and tumor progression.

But recently, he's expanded his repertoire in a new direction. Because when a few researchers in his lab started discussing ways to improve the cryo-electron microscopy (cryo-EM) technique they were using to create 3D models of molecules' structures, they ended up creating a method with major implications for studying not only chromosomes but also other small, complex molecules—especially viruses.

Their novel technique, called magnetic isolation and concentration cryo-EM (or MagIC-cryo-EM), improves the technology dramatically, allowing scientists to analyze highly diluted samples. This enables structural studies for biomolecules that are difficult to produce in their natural environments, offering a real boon to scientists investigating infectious diseases.

Cryo-EM has been a game-changer for those studying biological structures in recent decades, but the issue of sample loss has limited its use, says Yasuhiro

Arimura, a former research associate at Funabiki's lab and first author on an eLife study about the new technology. In the typical cryo-EM process, a filter is used to blot away excess liquid before imaging takes place, and much of the sample sticks to that filter, leaving only small amounts for the electron camera to capture.

Previously, this loss meant researchers had to either find molecules that were already abundant or reassemble an abundance of molecules in an artificial setting. With viruses, this compromise is particularly tricky because if researchers are studying a viral protein in a test tube, it may act differently than it would when attacking a human cell, making it difficult to predict the virus's real-world behavior.

The goal, says Arimura, was to find a new method that would allow researchers to analyze tiny samples so they can focus in on their target protein interacting with another cell. "What we envision is to capture a cell invaded by a virus, and then catch the moment that the viral or host protein binds to viral DNA or RNA," he says.

Mapping the 3D structure of a viral protein complex precisely as it enters a cell suddenly opens a door to devising new therapies or fresh strategies for preventing infection, Arimura says. Cryo-EM has been used to study the structure of viruses including Zika, SARS, influenza, and SARS-CoV-2, the virus that causes COVID-19. But studying the infection process is often difficult, and developing a much clearer picture of the host-virus interaction is urgently needed.

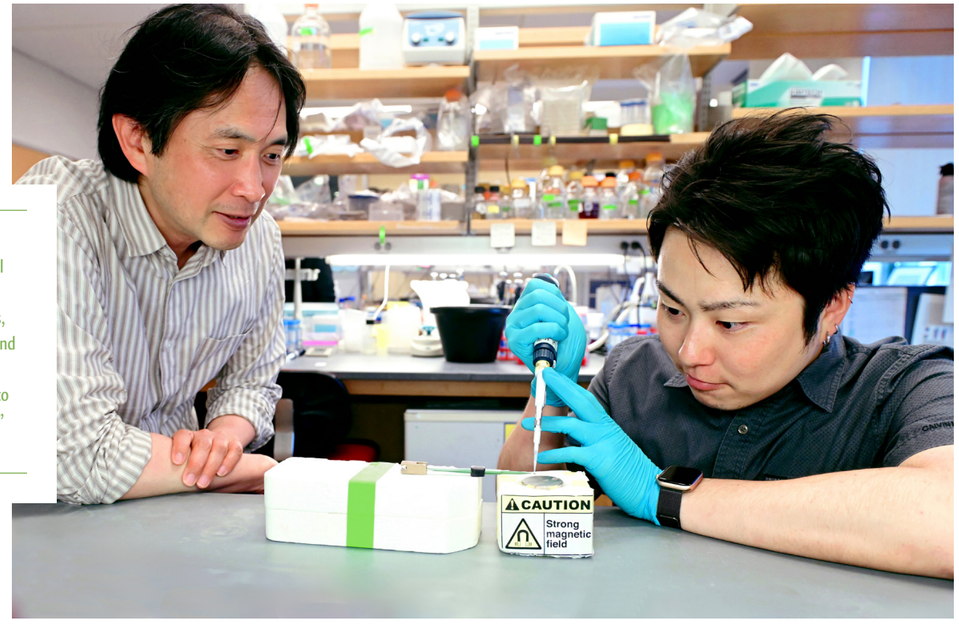
Arimura, now an assistant professor leading his own lab at the Fred Hutchinson Cancer Center in Seattle, came up with the idea for MagIC-cryo-EM while at Rockefeller. Along with his fellow postdoc Hide Konishi and Funabiki, Arimura was determined to clear roadblocks hindering their research.

Cryo-EM's need for large sample sizes meant that researchers often used the eggs of the African clawed frog, which are big enough to facilitate the study of cell division. Interestingly, Funabiki notes, frog sperm entering an egg represents a rare example of a cell naturally acquiring DNA from outside its system, similar to a virus entering a human cell—exactly the kind of action during which traditional cryo-EM routinely failed to capture the desired molecular structures.

Arimura says he and Konishi tweaked their cryo-EM process repeatedly before their 15th version succeeded. Now, Funabiki says, researchers can use it to study a host of biological processes. For his part, Funabiki plans to leverage the group's vast experience in chromosome inheritance in the study of how cells respond to foreign DNA.

"This method will be very useful for infectious disease biologists, immunologists, and other structural biologists trying to solve a structure," Funabiki says. "We've already gotten lots of requests for collaboration." ◎ *By Abigail Abrams*

"This method will be very useful for infectious disease biologists, immunologists, and other structural biologists trying to solve a structure."
FUNABIKI



CHRIS TAGGART; MATTHEW SEPTIMUS

Hironori Funabiki worked with his team, including Hide Konishi, to develop a method for capturing the moment foreign DNA enters a cell.

Junyue Cao's technology allows researchers to identify which genes are activating in up to 20 million cells at a time.

"If you can identify a virus's targets, then you can design targeted approaches to block it from infecting those specific cell types."
CAO

EVERY GENE EVERYWHERE ALL AT ONCE

Tracking gene expression across millions of cells could lead to new ways to fight infections—and more effective gene therapy.

EVER TRIED TO do 20 million things at once?

For a team of scientists studying cell behavior at Rockefeller, that's just a day at the office. Using a technology known as EasySci, the researchers have unlocked a method to study which genes are activating at any given moment in more than 20 million cells at a time. The team previously harnessed the technology to radically revise our understanding of the aging process. Now, its inventor, Junyue Cao, who is the Fisher Center Foundation Assistant Professor and head of the Laboratory of Single-Cell Genomics and Population Dynamics, is adapting this powerful tool to the study of infectious diseases.

What a cell actually does within the body is determined by which parts of its DNA instruction manual are opened, read, and converted into the proteins that carry out its functions. If a cell is producing antibodies, interferons, interleukins, histamines, or any other proteins known for fighting infection, EasySci can now detect it. If a cell has been infected by a virus, EasySci can show the viral proteins replicating inside the cell. While the technology doesn't offer a way to address those infections, it can tell researchers exactly where to start hunting for therapeutic targets.

This knowledge is crucial, as viruses are famously picky about which cells they infect. HIV, for example, only infects white blood cells with a specific protein, known as CD4, on their surface. COVID-19, on the other hand, is less selective but prefers cells in the respiratory system that express ACE2. Even within a population of a single virus, there are subtypes that differ slightly. These small distinctions can make a major difference in which host cells are ultimately infected. Thus, "If you can identify a virus's targets, then you can design targeted approaches to block it from infecting those specific cell types," Cao explains.

This ability to recognize compromised cells has already sparked a range of inventive uses. Rockefeller colleague Alexander Tarakhovsky, in collaboration with Anne Schaefer, a director at the Max Planck Institute for Biology of Ageing in Germany, is employing it to probe a vital question: Why do disease-induced cellular and organismal phenotypic states linger long after the body has cleared an infection? Tarakhovsky, a pioneer in the study of how viruses mimic our epigenomic gene regulation, now wants to understand how virus-induced modulators might be reprogramming the brain's immune cells. Doing so could identify mechanisms driving neuronal changes supporting sickness behavior that persists beyond the original illness, as with long COVID.

In this way, EasySci may yield fundamentally new insights into the damaging consequences of viral infections as well as ideas for how to treat infections themselves. But Cao is also excited about a flip side: using the technology to help viruses infect cells. While it may sound counterintuitive, gene therapies use nonpathogenic viruses as a vector to deliver genes into cells to change the way they operate. In these techniques, a modified virus is loaded with the desired gene and injected into the body. The virus then enters the target cell and tricks its host into producing the desired protein. This technique can be used to replace faulty genes, like in sickle cell anemia, or even to train immune cells to attack cancers and other diseases.

The promise of this strategy is enormous, but attempts thus far have been underwhelming due to a central difficulty that Cao's technology is well-tailored to tackle: delivering the right gene to exactly the right place at the right time. ◎ *By David Schultz*

INTERVIEW

With supercomputers, algorithms, and troves of big data, the AI revolution is sparking new opportunities—and some challenges.

Biomedical science in the age of AI

By Megan Scudellari

One of the greatest achievements in AI was inspired by the human brain itself. Starting in the 1980s, computer scientist Geoffrey Hinton and physicist John Hopfield developed artificial neural networks by training machines to process data using principles discovered in the visual system of the brain.

That work, for which Hinton and Hopfield received the 2024 Nobel Prize in Physics, set the foundation for today's powerful machine learning, including AlphaFold, an artificial intelligence program that predicts 3D structures of proteins from their amino acid sequences. For creating such a transformative tool, AlphaFold's developers, Demis Hassabis and John Jumper of Google DeepMind, also received Nobel Prizes in 2024, theirs in chemistry.

And so, from serving as biological inspiration to dramatically advancing the biomedical sciences, AI is coming full circle. With its rapidly improving ability to collect, classify, organize, and rationalize information, computers in some ways now surpass what people can do: identifying patterns, relating concepts, and drawing conclusions from massive amounts of data that human brains simply cannot process.

With these capabilities, the technology has begun transforming workflows and speeding discovery in biomedical labs, which constantly generate vast troves of scientific data through whole genome sequencing, digital imaging, single-cell genomics, and more. Researchers are now exploring the use of AI to generate hypotheses, automate experiments, and develop computational models.

In fact, academic research may be the ideal playground for AI tools, researchers suggest, since results are repeatedly tested and analyzed. So, AI in the lab may be less prone to errors or so-called hallucinations than other tools such as chatbots.

At Rockefeller, researchers are applying machine learning and signal processing to their projects in new ways while exploring questions about data quality, the limits of AI, and trustworthiness. We delved into conversation around these topics and more with three Rockefeller scientists currently employing AI in their work: neuroscientists Cori Bargmann and Nathaniel Heintz and biochemist Jiankun Lyu.

Illustration by Chad Hagen

Bargmann is the Torsten N. Wiesel Professor and head of the Lulu and Anthony Wang Laboratory of Neural Circuits and Behavior at Rockefeller and the former head of science at the Chan Zuckerberg Initiative. She studies the neuronal basis of behavior in *C. elegans*. Heintz is Rockefeller's James and Marilyn Simons Professor and director of the university's Zachary and Elizabeth M. Fisher Center for Research on Alzheimer's Disease. His work explores the genes, circuits, and cells that contribute to mammalian brain function and dysfunction. Lyu is an assistant professor and head of the Evnin Family Laboratory of Computational Molecular Discovery, where he develops computational methods to screen ultra-large digital libraries for small molecules that can help interrogate biological targets.

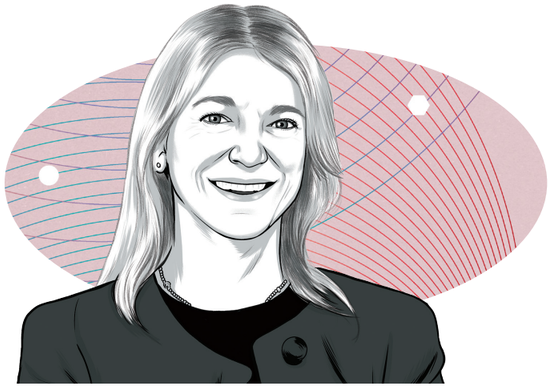
Give us the big picture. How is AI changing research in the life sciences?

CB: There are two major ways in which AI is making things possible at Rockefeller that were extremely difficult before. One is the ability to bring data together at scale. AI has the ability to analyze and find patterns in very large, very complex multimodal datasets. As biologists, we've been very good at studying one molecule at a time, but AI methods enable us to look at complex biological systems and pull out all kinds of information flowing through those systems. For example, in neuroscience this gives us the ability to examine the dynamics and interactions of many cells in the brain.

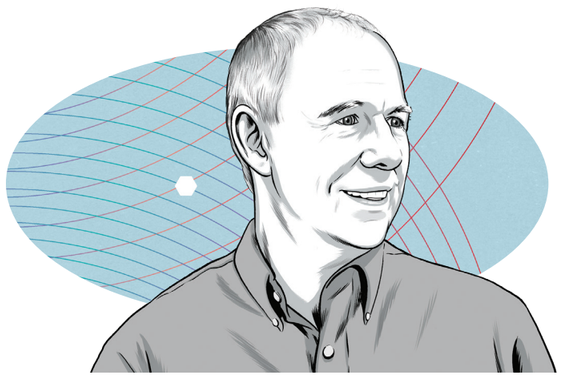
The second advance is in the area of machine vision, which is image processing to identify objects and follow them over time. Whenever you are looking at a complex image, a highly trained individual might find things one at a time. Machine learning models can do it much faster, as they can quickly process a lot more information. These methods are being applied to everything from finding specific proteins in complex electron micrographs to tracking fast-moving mosquitoes when they find a host.

JL: AI is changing work in many ways, even in small things. For instance, chatbots are becoming competent at programming, so if a researcher wants to write a simple script, these chatbots can quickly do it well. For scientists who used to spend a lot of time writing programs, especially experimentalists without a lot of experience programming, these tools can really expedite their work.

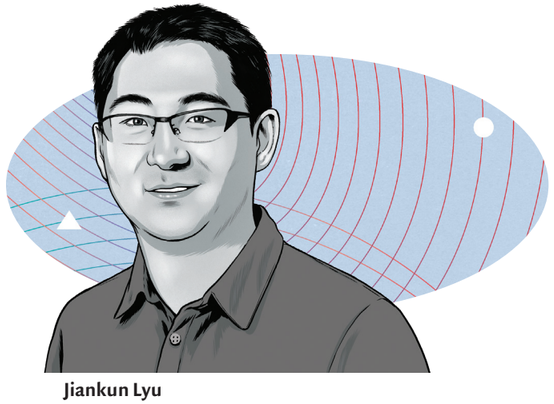
For example, a machine-learning-based protein structure search tool called Foldseek can cluster the entire known protein universe of over 214 million sequences by structural homology, generating functional hypotheses for previously unannotated proteins.



Cori Bargmann



Nathaniel Heintz



Jiankun Lyu

NH: In my laboratory, we study the human brain, which has over 100 billion cells and over 10,000 genes expressed in each cell type. The data we generate is massive; we already use machine learning methods all the time, but we're hoping newer AI-based methods will help us even more. In my experience as a scientist, methodological breakthroughs are extremely important, and the advent of AI is a big one.

However, people are rightly concerned about how accurate new AI tools will be and whether their conclusions will be valid. We have to work through this phase. We certainly wouldn't want to not apply AI to modern, available datasets. I'm excited about the possibilities.

Will AI replace some of the roles or tasks of technicians or academic scientists?

JL: I'm not concerned about that at the current stage. These general foundational AI models have made substantial progress, but in biomedical research it is still hard to replace academic scientists and skilled technicians for two big reasons. One, foundation models are usually good at summarizing published literature but lack scientific insights and vision. And, two, AI methods give predictions, not results. And it still requires benchwork to validate predictions.

NH: AI will be one of many methods required to do effective science, so I don't think it replaces anything. It updates efforts, such as bioinformatics and machine learning, to understand our data, but it still takes the same teams of people doing bench science to generate the data.

CB: At this point, a skilled person is still better than a machine at generating high-level analyses. Our goal for the future should be to find the right partnership between the human expert and the machine.

"AI methods enable us to look at complex biological systems and pull out all kinds of information flowing through those systems."

There's a term—human-in-the-loop—that emphasizes the need for human input and expertise to improve a machine's data analysis. You start by giving the machine annotated information and asking it to sort it out. It can do that—data comes back from the machine—but the experts then look more closely at what the machine has done. What did it do well? What did it miss? How did it sort the information? You can use that information to ask better questions, so that the machine can get better at providing valuable answers. That back and forth between skilled scientists and the machine enables the refinement of data into useful tools and understanding.

Can you give us an example of AI use in your laboratory?

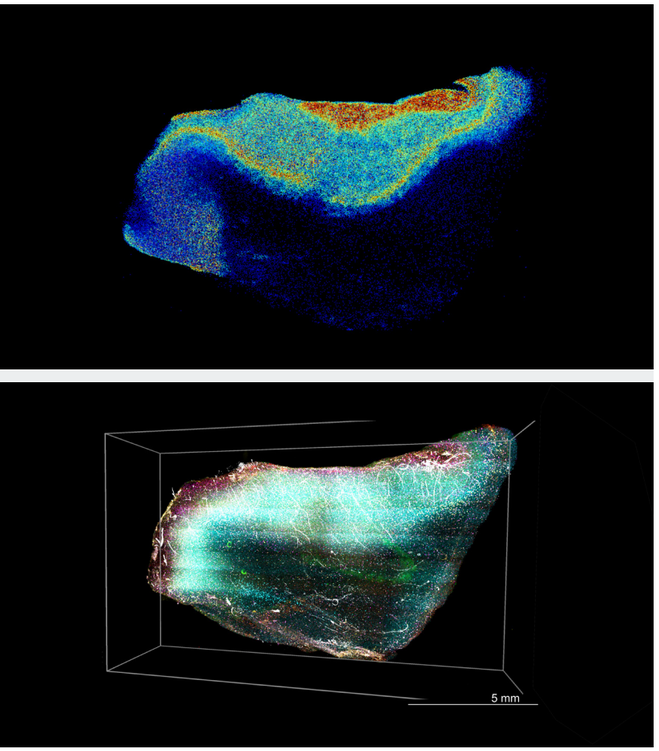
CB: We are one of a number of labs now using AI methods to track animals at high-resolution in complex environments. We study tiny, low-contrast, fast-moving animals in noisy backgrounds. They have quite complex behaviors and are hard to follow. You could track them by hand, but it is so tedious. Our work utilizing AI now enables us to track many of them at once and gather high-quality data about their behavior. With the machine doing the tracking for us, the speed at which we can make discoveries is many times faster.

NH: When we are studying neurodegenerative diseases, it's very important to know which cell types are being lost in any region of the brain. If I take a small 3D piece of the human brain, just two millimeters by one millimeter in size, there are many millions of neurons in there. We have generated methodologies in our lab for visualizing and labeling all those neurons, but counting them by eye or any other methodology is really challenging.

In collaboration with AI experts, we've developed the initial ability to count individual neurons. It is ongoing work that needs to be further refined, but it's exciting because we should be able to detect even small changes in the occurrence of cell types very early in Huntington's or Alzheimer's disease brains.

We're also using AI for the analysis of molecular data. To study a certain type of neuron, we'll profile 20,000 cells of the same type, which means we have tens of thousands of bits of information. Analyzing these datasets, each of which has megabytes of data on thousands of genes, is taxing and difficult. We're now trying to apply AI to those datasets to find out if they will actually reveal more than we're able to discern using current methodologies.

Illustration by Joel Kimmel



Scientists in the Heintz lab are combining traditional light sheet microscopy (bottom) with AI analysis (top) to better predict where different cell types are located in brain tissue samples.

a protein in mind as a therapeutic target, you want to quickly know what potential compounds from this library can effectively bind to that target. AI, especially deep learning methods, can help us speed up that search process.

As AI use has expanded, researchers have documented biased results from some algorithms based on the data fed into them. How can we maintain research integrity and reliability when using these models?

CB: You have to put good data in to get good information out. The primary reason AlphaFold was so successful was that it was trained on a very high-quality dataset, the protein structure information in the Protein Data Bank. The second reason was that there were competitions to validate early models and determine which were the best at prediction, and the field could then build on the most successful models. Based on that experience, scientific AI is currently laser-focused on two things: what the training data is going to be and how we validate the results.

JL: This is a challenge we are facing in biomedical research. To train an AI model, our field has low amounts of high-quality data available, compared to fields such as image recognition and natural language processing. Deep learning methods are data-hungry algorithms, so you need to feed a lot of data into them to have a reliable model. This is an area of ongoing research for computer science teams: how to make relatively accurate predictions with a smaller amount of data and how to gauge the model's confidence in its prediction. The deep learning field is already building these sorts of tools.

NH: I'm a particular stickler about data quality because I think if the quality of a complex dataset isn't high enough, you can easily be misled. We have pretty good methods for telling which of the actual datasets we collect are of high quality and which aren't. For now, if we limit the analysis to our own high-quality laboratory data, then AI can help us analyze that data.

To non-experts, AI can seem like a black box. A lot of data goes in, then, through some magic, an answer comes out. Do AI models in biomedical sciences lack transparency? Can we verify and trust the results?

NH: I don't really believe results unless they can be validated. If the AI program gives us some strange result which we have no way of validating, I think it will be of limited use for us. On the other hand, scientists know a lot about their topics. I've been studying the brain for 30 years, so I think my sense of what can be validated should be pretty good once we start to get results. Of course, every scientist has built-in ideas about what they think should happen, and we have to be careful about these biases as well. Maybe AI will help root out our own biases toward the data. That kind of cautious openness is a hallmark of great science.

CB: Ten years ago, when people started using machine learning models in a large-scale way, they might put things in, get things out, and see that it looked pretty good, but they couldn't figure out what the models were doing. A big advance in science occurred when we started to be able to crack open the hood. We can now look at intermediate steps and see what features the models pulled out, not just the end results. That is one aspect of trustworthiness, and that's important from a scientific perspective: As a scientist, you can't have a black box.

An even more basic aspect of trustworthiness is validation. In the lab, we might do experiments and use them to train a model. But we don't use the same experiments to determine if the model is good. Instead, we use brand new, validated data that was gathered independently. Then we put that data in, knowing what results should come out of the model. You give the model a test.

JL: There are many ways to validate predictions from AI models, but it is hard to validate all of them, as they can throw out a lot of predictions. Even newly published models, some of which are trained in commercial companies and well-known labs, will still require quite a long period of time to realize their potential because experimental validation takes much longer than the predictions. My greatest fear for AI is that we may end up with a bunch of published AI models that will give you lots of predictions, but without any validation. People should consider these predictions carefully.

> "Scientific AI is currently laser-focused on two things: what the training data is going to be and how we validate the results."

What's your greatest hope for AI in the life sciences?

NH: Right now, we only have probes to detect signals in the brain that indicate the final stages of neurodegeneration. Ideally, we could use AI-based drug design to create probes that could be used in living human beings to access the earliest stages of neurodegeneration and substance abuse, and watch them progress in precise detail.

I can imagine a world where AI generates enough information to create a whole new panoply of different probes and methodologies that would enable scientists to really tell us precisely what is happening in the brain during illness, so we can learn to design new interventions.

CB: There is a lot of excitement around the idea of using AI methods to decode complex relationships in medicine and neuroscience. In translational neuroscience, there are some astonishing uses of AI, like reading brain signals from paralyzed patients with ALS, transforming those signals into speech, and allowing them to talk. These are still rare examples that require invasive brain surgery and massive resources, but they show the promise of AI to alleviate human suffering. Ideally, I can imagine AI methods putting together many complex pieces of information from a patient someday. We could see not just symptoms, but also a long-term view of the individual that includes the person's genome and environmental exposures, the trajectory of their blood markers (not just "normal" or "abnormal"), and their past medical history—and come to a diagnosis and treatment plan. For psychiatric disorders, for example, we are treating very complicated aspects of an individual, and we need to have the individual in mind. There is exciting potential in the future to work with the complexity and heterogeneity of human data to inform medicine.

JL: After the Nobel Prizes for AI last year, I'm optimistic that a lot of young scientists will go into this area and develop new architectures for the application of AI to the sciences. Additionally, as people start to consider what is needed to get the most out of AI models, bench scientists are thinking about how to generate more high-quality data for these data-hungry algorithms, so that area is flourishing. There are so many reasons to have great hope for the use of AI in the biomedical sciences.

LABORATORY OF MOLECULAR BIOLOGY

Listening in

Say you're standing in a loud, crowded cocktail party: Somehow, you find yourself effortlessly concentrating on the one conversation you're participating in. For this deceptively mundane feat, you can thank your cochlear amplifier—rows of sensory hair cells deep within the inner ear that create tiny bursts of mechanical energy to strengthen faint sounds and sharpen tones before they reach the brain.

When this amplifier fails—whether through aging or noise exposure, for example—clarity fades and hearing loss begins. This tiny piece of biology has been maddeningly hard to study: The cochlea sits behind one of the densest bones in the body and is far too delicate to withstand probing in vitro. And until scientists can see the cochlear amplifier's cellular gears in action, they can't fully grasp how we process sound, why the system breaks down, or how to build hearing aids that might rival the ear's natural finesse.

That's why Rodrigo Alonso and Francesco Gianoli from the Hudspeth lab, working with instrumentation engineer Nicholas Belenko from Rockefeller's Gruss Lipper Precision Instrumentation Technologies Center, created a way to keep cochlear amplifiers alive and functioning outside the body. By meticulously controlling ion balance, oxygen, temperature, and pressure, they can preserve the amplifier's native environment, giving scientists unprecendented experimental access to its cellular components.

Researchers are now using this new system to study how mammalian inner ear cells behave across the full range of audible frequencies, measuring motions smaller than a billionth of a meter.

"For the first time, we can keep a tiny slice of the inner ear alive in the lab and watch the ear's built-in amplifier at work under controlled conditions," says Gianoli. "By pinpointing the key elements that give this system its sensitivity, we can see exactly where mutations, diseases, noise, and aging start to erode it."

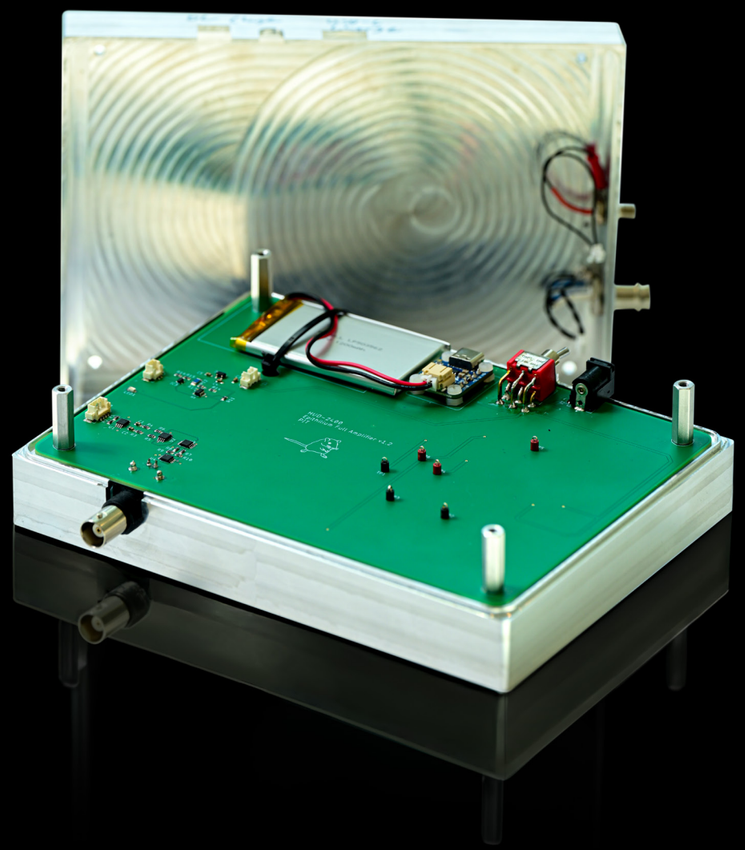


Photo by Chris Taggart

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