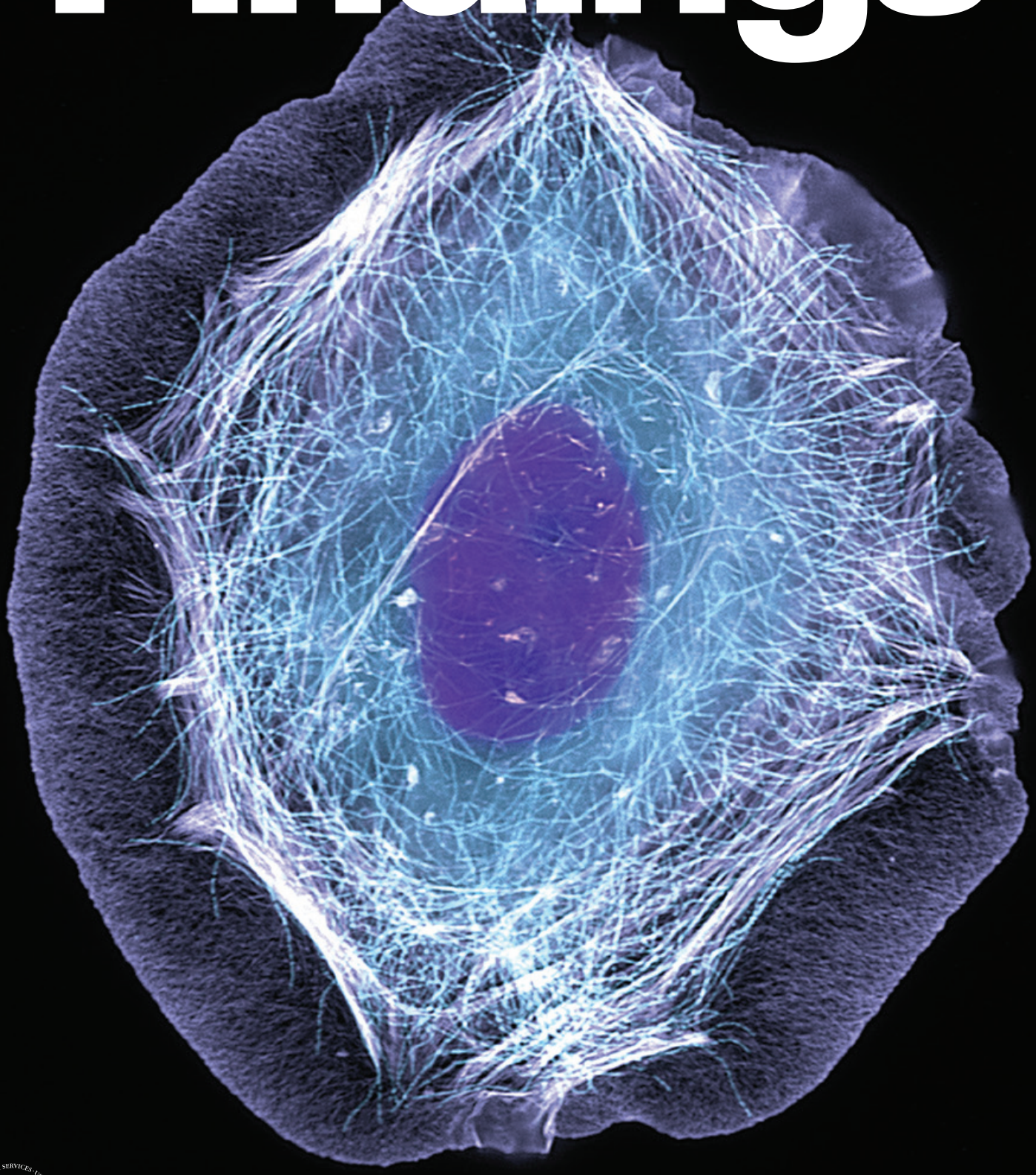
Findings

FALL 2017



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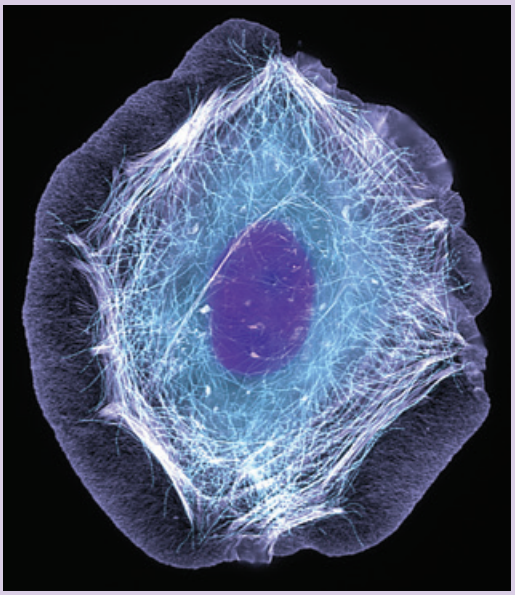

—TORSTEN WITTMANN,
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

ON THE COVER This human skin cell was bathed in a liquid containing a growth factor. The procedure triggered the formation of specialized protein structures that enable the cell to move. We depend on our cells being able to move for basic functions such as the healing of wounds and the launch of immune responses.

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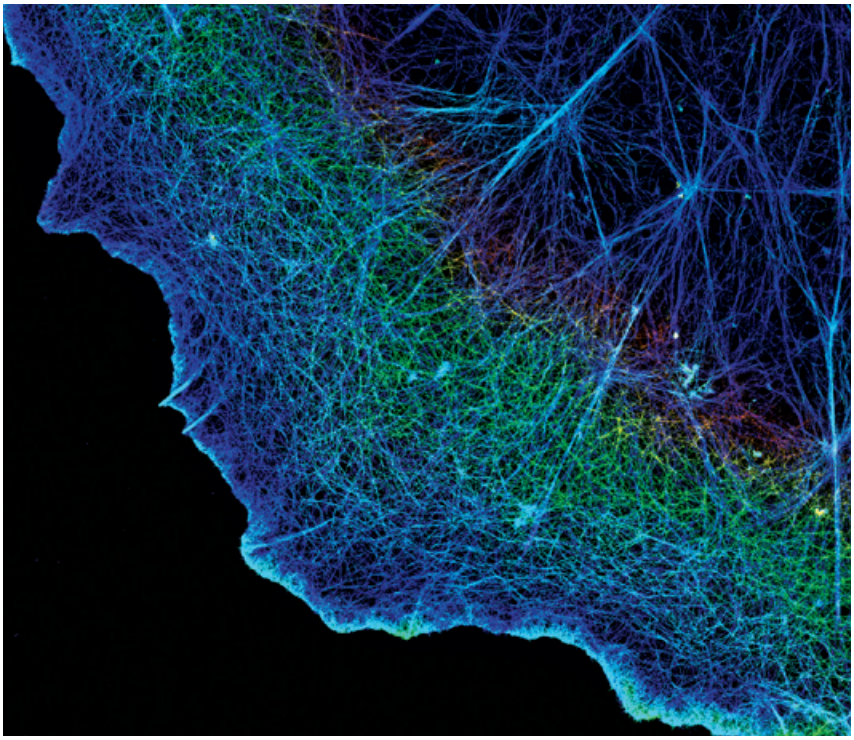
Protein Paradox:

Enrique De La Cruz Aims to Understand Actin

BY EMILY CARLSON



—XIAOWEI ZHUANG, HARVARD UNIVERSITY, AND NATURE PUBLISHING GROUP

Actin (blue) and other proteins support a cell's structure similar to the way bones support our bodies.

Enrique De La Cruz stood off to the side in a packed room. As he waited for his turn to speak, he stroked the beads of a necklace. Was he nervous? Quietly praying? When he took center stage, the purpose of the strand became clear.

Like a magician—and dressed all in black—De La Cruz held up the necklace with two hands so everyone, even those sitting in the back, could see it. It was made of snap-together beads. De La Cruz waved the strand. It wiggled in different directions. Then, with no sleight of hand, he popped off one of the beads. The necklace broke in two.

For the next hour, De La Cruz pulled out one prop after another: a piece of rope from his pocket, a pencil tucked behind his ear and even a fresh spear of asparagus stuffed in his backpack. At one point, De La Cruz assembled a conga line with people in the front row.

But De La Cruz isn't a professional performer. He's a molecular biophysicist at Yale University. The show-and-tell performance was part of a scientific lecture on a paradox De La Cruz has studied for more than 10 years—how a chain of molecules, called actin, that is strong enough to support a cell can break so easily.

"I benefit from seeing and holding things as much as anyone else," he says, explaining that the props help people—even scientists—understand his research.

By his own account, De La Cruz is an unlikely scientist. A first-generation Cuban-American, he grew up in and around Newark, New Jersey. Few of his friends earned more than a high school diploma. De La Cruz never thought he'd end up running his own lab at an Ivy League research university.

As a young adult, he recalls, "It wasn't even on my radar as a possibility."

Although discovering new details about biology keeps his job exciting, he said sharing lessons he's learned with students and other aspiring scientists makes it truly rewarding.

Inner City to Ivy League

De La Cruz's first taste of research came during his senior year of high school, when he participated in a work-study program at a nearby pharmaceutical company. He tested chemical compounds for their

Instead of feeling like he didn't belong, he felt empowered to seek out the knowledge and guidance he needed to succeed.

RESEARCHER

Enrique M. De La Cruz

JEFF FOLEY, AMER CAN HEART ASSOCIATION

GREW UP IN
Newark and Kearny, New Jersey

JOB SITE
Yale University

FAVORITE FOOD
His mom s Spanish style polenta (harina de maíz)

IF I WASN T A SCIENTIST I WOULD BE
Managing a vinyl record shop

FAVORITE SONG
Do Anything You Wanna Do by Eddie & the Hot Rods

effects on cholesterol in the bloodstream. Although the project was unrelated to what he studies now, De La Cruz said the experience made science tangible, partly by putting people and faces to the process.

Because his parents—a welder and a hospital pharmacist—instilled in De La Cruz and his siblings the importance of education, he headed to college. But he stayed close to home. He applied only to Rutgers University. Interested in both medicine and teaching, De La Cruz ultimately decided to pursue a career doing research on basic life processes in an academic setting.

But his path to becoming a scientist almost hit a dead end when De La Cruz started graduate school at Johns Hopkins University in Baltimore, Maryland.

"On my first exam—in a subject I wasn't very familiar with—I scored an 18.5," he says. "The mean of the class was an 88! I thought, 'That's it. I had my chance. This experiment is over.'"

His course instructor told him not to stress about the score and to work harder at the things he didn't know. De La Cruz knew this was true: He had aced an exam in biophysical chemistry, a subject he was interested in and already knew a lot about.

Instead of feeling like he didn't belong, he felt empowered to seek out the knowledge and guidance he needed to succeed.

Actin Action

Much of De La Cruz's career has focused on studying actin, one of the most prevalent proteins on the planet. Actin molecules form long, thin chains that grow and shrink from the ends. These chains, or filaments, allow cells to move and contract, and they help cells keep their shapes. The filaments also play a central role in muscle contraction. Because of these tasks, the filaments must be strong.

Yet, the filaments can break. In many cases, they must break to carry out their functions. To assemble new chains, the filaments recycle their parts. Numerous proteins facilitate this process in cells. Some of the proteins break the filament chains to make more ends, which allows the chains to shrink more rapidly and recycle parts faster.

To investigate how actin filaments break, De La Cruz has relied heavily on techniques, expertise and published papers from other fields.

"An hour in the library can save a week in the lab," De La Cruz says. "There's a lot of information already out there, and it's always useful to look at others' studies."

Over the years, he and his team have pieced together many details on how actin filaments form and break.

"Curiosity is what gets you into science and what keeps it fun," he says. "You're going to know something in a few months that you don't know today."

Individual actin molecules, like the pop-beads of the necklace, string together with the help of salt. The salt helps "glue" the chain links together, De La Cruz explains.

By integrating computer models with biochemical and biophysical experiments, the De La Cruz team learned where the salt connects to actin molecules. Each salt-actin joint is tight, making the chain stiff, like the pencil prop De La Cruz showed the crowd. But a protein called cofilin can push off the salt, weakening the joint so it becomes wiggly—De La Cruz demonstrated this with the rope—and more likely to come apart.

Filament breaks occur where different sections meet, similar to the way an asparagus spear snaps where the hard part meets the soft, fleshy part.

Because a filament has thousands of actin molecules and joints, some sections can be weak and wiggly, while others are stiff. Filament breaks occur where different sections meet, similar to the way an asparagus spear snaps where the hard, woody part meets the soft, fleshy part.

"This explanation sounds like it was simple to figure out, but it was really difficult," says De La Cruz, adding that the team worked on this study for several years.

"I'm an example of what can happen when good people take a genuine interest and care about you as a person."

The research team is now planning to use computer modeling to better understand the specific roles of the wiggly and stiff filament sections during the breaking process. They'll test the modeling results with carefully designed lab experiments.

Paying It Forward

De La Cruz credits his success as a scientist to the mentors he's had since his very first research experience in high school. "I'm an example of what can happen when good people take a genuine interest and care about you as a person."

For the students and aspiring scientists working in his lab today, De La Cruz tries to do the same. He considers scientists' most important job to be stimulating great minds to think independently and continue to grow, even if it's sometimes through failure.

He tells them, "The future is in your hands more than you know." ■

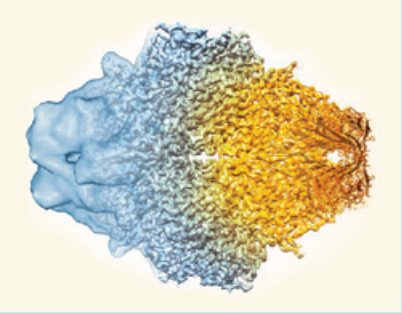
cool tools

High-Resolution Microscopy—in Living Color

BY ALISA ZAPP MACHALEK

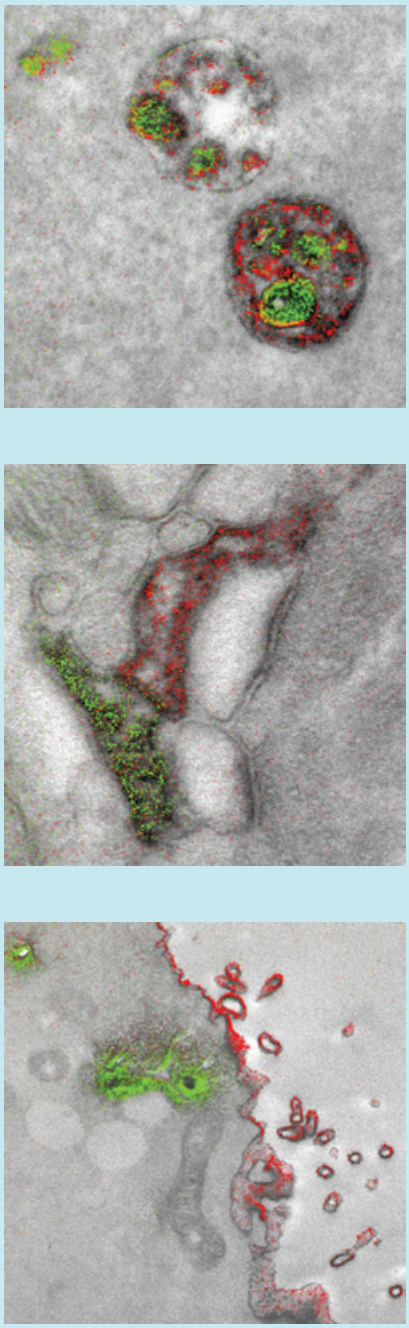
Cell biologists would love to shrink themselves down and actually see, touch and hear cells' inner workings. Because that's impossible, they have developed an ever-growing collection of microscopes to study cellular innards from the outside. Using these powerful tools, researchers can exhaustively inventory the molecular bits and pieces that make up cells, eavesdrop on cellular communication and spy on cells as they adapt to changing environments.

In recent years, scientists have developed new cellular imaging techniques that allow them to visualize cells' contents in ways and at levels of detail never before possible. Many of these techniques



—VERONICA FALCONIERI, SUBRAMANIAM LAB, NATIONAL CANCER INSTITUTE

This image, showing a single protein molecule, is a montage. It was created to demonstrate how dramatically cryo-EM has improved in recent years. In the past, cryo-EM was only able to obtain a blobby approximation of a molecule's shape, such as that shown on the far left. Now, the technique yields exquisitely detailed images in which individual atoms are nearly visible (far right). Color is artificially applied.



—ADAMS ET AL./CELL CHEMICAL BIOLOGY 2016

After decades of black-and-white electron microscopy images, scientists now have a way to incorporate color.

build upon the power of electron microscopy (EM) to see ever smaller aspects.

Unlike traditional light microscopy, EM uses electrons, not light, to create an image. To do so, EM accelerates electrons in a vacuum, shoots them out of an electron gun and focuses them with doughnut-shaped magnets onto a sample. When electrons bombard the sample, some pass though without being absorbed while others are scattered. The transmitted electrons land on a detector and produce an image, just as light strikes a detector (or film) in a camera to create a photograph.

Transmission electron microscopes (TEM), the most powerful EMs, can magnify objects more than 10 million times, enabling scientists to see the outline and some details of cells, viruses and even some large molecules. A relatively new form of transmission electron microscopy called cryo-EM enables scientists to view specimens in their natural or near-natural state without the need for dyes or stains.

In cryo-EM—the prefix *cry-*, from the Greek *cryos*, means "cold" or "freezing"—scientists freeze a biological sample so rapidly that water molecules do not have time to form ice crystals, which could shove cellular materials out of their normal place. Cold samples are more stable and can be imaged many times over, allowing researchers to refine the image, remove artifacts and produce even sharper images than ever before.

Thanks to a new generation of detectors and improved image-processing software, cryo-EM enables extremely high magnification. The level of detail, or resolution, of cryo-EM imagery now rivals that obtained with x-ray crystallography, a technique in which scientists shoot x-rays at a structure and use the patterns with which the rays bounce off the object to indicate the exact location in space of every atom in a molecule.

Some scientists are using cryo-EM to create 3-D models, or maps, of molecular complexes. To make these models, scientists record thousands of 2-D images of a single sample, or a set of identical samples, viewed from many angles. Then, they use specialized computer programs to combine these snapshots into extremely detailed 3-D models. This technique is yielding new information on biological molecule structures and on how these molecules function and interact.

Historically, TEM images have only been in black and white. In late 2016, a group of researchers that included the late Roger Tsien—who won a Nobel Prize for bringing color to *light* microscopy using green fluorescent protein—published the first ever color TEM images. The technique uses rare earth metals called lanthanides to label different biomolecules. This multicolor TEM is already providing scientists with previously unobtainable information about cell structure, protein movements within and between cells, and views of cell components at a level of detail not possible with light microscopy. ■

A World Without Pain

BY CHRIS PALMER

You glide across an icy canyon where you meet smiling snowmen, view waddling penguins and see a glistening river that winds forever. You toss snowballs, hear them smash against igloos, then watch them explode in vibrant colors.

Back in the real world, a dentist digs around your mouth to remove an impacted tooth, a procedure that really, really hurts. Could experiencing a "virtual" world distract you from the pain? Scientists David Patterson and Hunter Hoffman show it's a real possibility.

Patterson, a psychologist at the University of Washington (UW) in Seattle, and Hoffman, a UW cognitive psychologist, helped create the virtual reality program "Snow World" in an effort to reduce excessive pain experienced by people suffering from burns. However, the researchers expect "Snow World" to help alleviate all kinds of pain, including the pain people experience during dental procedures. Because our minds can focus on just a few things at once, the researchers say, if we're busy building igloos and making friends with snowmen, we have less brainpower available to register the heat on our bodies or the twang in our tooth.

To find out if life in "Snow World" really is painless, the scientists worked with healthy undergraduate student volunteers. One group of students received immersive virtual reality (VR) glasses and a wireless mouse that they used to directly interact with the wintry environment. A second group of students received a passive VR system that included glasses but no wireless mouse. This group saw the snowy world as if they were watching a movie, unable to go ice skating, make a snowball or pat a penguin. The researchers exposed each group of students to brief periods of painful, but tolerable, heat both before and during their virtual reality experiences, and then they measured students' perception of pain.

—ARI HOLLANDER AND HOWARD ROSE, COPYRIGHT HUNTER HOFFMAN, UNIVERSITY OF WASHINGTON

In an immersive virtual reality environment called "Snow World," people with burns distract themselves from their pain by tossing snow balls, building snowmen and interacting with penguins.

The result? Even though all the students were exposed to an identical amount of heat, the ones fully immersed in the interactive virtual reality world reported 75 percent less pain than those in the noninteractive world.

Patterson and his team also have encouraging results using next-generation VR goggles to reduce pain in pediatric burn patients.

In addition, the team recently began testing augmented reality to prompt children with leg and foot burns to move around. Movement facilitates skin healing, prevents muscle atrophy and promotes mental health. Specifically, the researchers are using the mobile device game "Pokémon GO" to motivate young people with burns to walk around the hospital (with close supervision) and capture Pokémon characters. The team is pursuing formal clinical trials.

Although virtual environments can have drawbacks—such as giving users motion sickness—they offer a promising new way to manage pain during medical or dental procedures. And, as recent research shows, reducing pain can speed recovery. Now that's a relief! ■

Demystifying General Anesthetics

BY CAROLYN BEANS

Anesthetics usually induce unconsciousness in about 2 minutes.

When Margaret Sedensky, now of Seattle Children's Research Institute, started as an anesthesiology resident, she wasn't entirely clear on how anesthetics—drugs given during surgery to prevent pain—worked. "I didn't know, but I figured someone did," she says. "I asked the senior resident. I asked the attending. I asked the chair. Nobody knew."

For decades, doctors called general anesthetics a "modern mystery." Even though they safely administered anesthetics to millions of Americans every year, they didn't know exactly how the drugs produced the different states of general anesthesia. These states include unconsciousness, immobility, analgesia (lack of pain) and amnesia (lack of memory).

Understanding anesthetics has been challenging for several reasons. Unlike many drugs that act on a limited number of proteins in the body, anesthetics interact with seemingly countless proteins and other molecules. Additionally, some anesthesiologists believe that anesthetics may work through many different molecular pathways. This means no single molecular target may be required for an anesthetic to work, or no single molecular target can do the job without the help of others.

"It's like a symphony," says Roderic Eckenhoff of the University of Pennsylvania Perelman School of Medicine, who has studied anesthesia for decades. "Each molecular target is an instrument, and you need all of them to produce Beethoven's 5th."

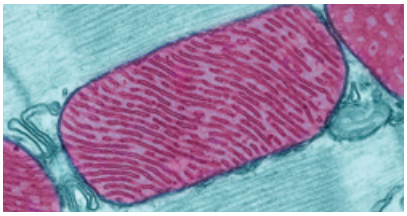
Another challenge is that general anesthetics function, in part, by halting something else scientists don't fully comprehend: consciousness.

But in recent years, researchers have been making steady progress toward understanding anesthetics.

Cell's Energy Factories Play a Role

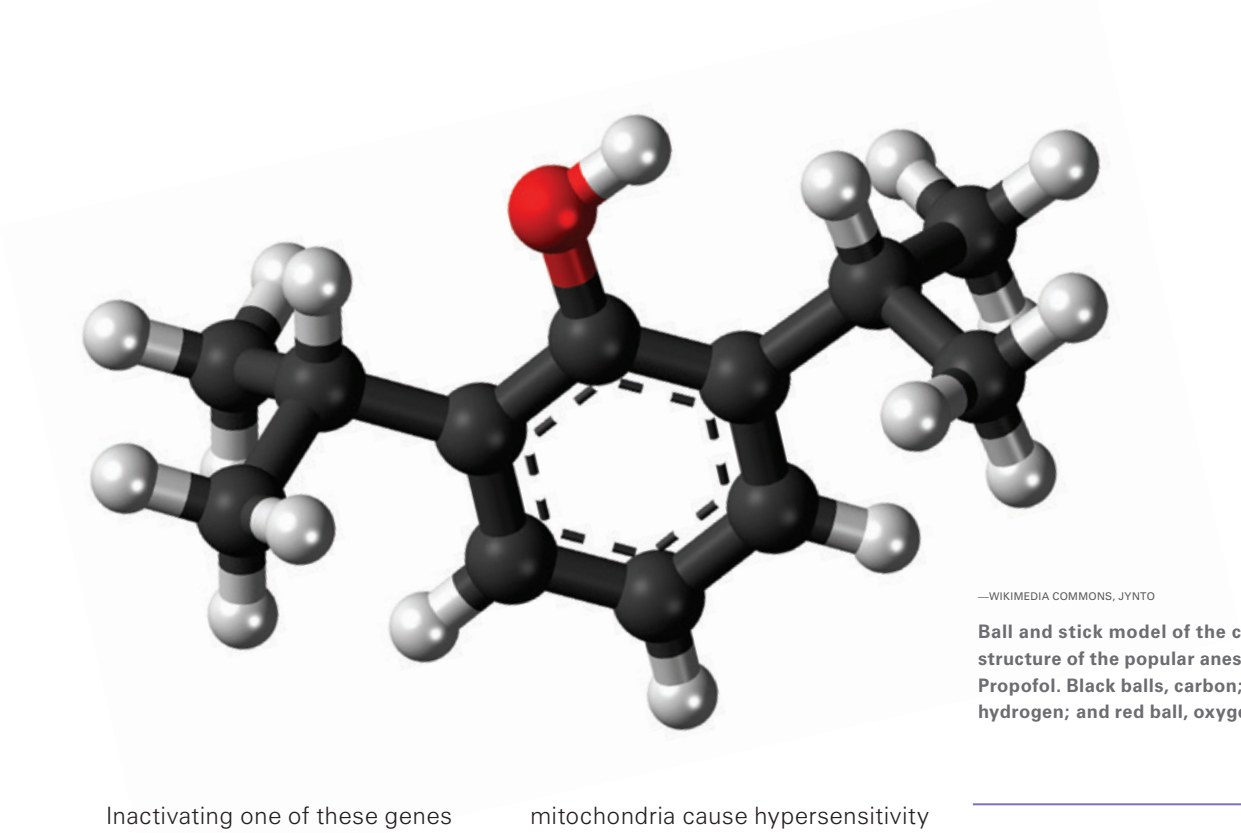
When Sedensky set out to reveal how general anesthetics work on a molecular level, she didn't want to focus on any single anesthetic target because she recognized that many targets could be important. She and Phil Morgan, also of Seattle Children's Research Institute and Sedensky's husband, decided to instead test anesthetics' effects on a wide range of molecular targets by shutting down the genes that code for the targets one by one and in various combinations. Working with a tiny worm called *C. elegans*, which is an organism commonly used to study health and disease, they found that shutting down multiple genes affected the worm's response to anesthetics.

The roundworm *C. elegans* is a widely studied research organism.



—THOMAS DEERINCK, NATIONAL CENTER FOR MICROSCOPY AND IMAGING RESEARCH

Anesthetics may work in part by limiting energy production in cellular structures called mitochondria, shown here in pink.



—WIKIMEDIA COMMONS, JYNTO

Ball and stick model of the chemical structure of the popular anesthetic Propofol. Black balls, carbon; silver balls, hydrogen; and red ball, oxygen.

Inactivating one of these genes made the worm hypersensitive to every anesthetic the scientists tested. It turns out that this gene, called *gas-1*, codes for a protein that controls a key component of mitochondria, the cell's energy factories.

This finding was interesting to Sedensky and Morgan because organs such as the brain and heart require a lot of energy—and anesthetics have a major effect on them. If anesthetics work by limiting energy production in the mitochondria of *C. elegans*, their impact could produce a double whammy in organisms (such as the *gas-1* mutants and people with a condition called "mitochondrial disease") whose mitochondria are already functioning at a lower capacity.

Morgan thought the children he and Sedensky treat at Seattle Children's Research Institute who are hypersensitive to anesthetics might have alterations in their mitochondria as well. This proved to be true: The children had decreased function in the key mitochondrial component involved in energy production.

Sedensky and her team are now using mice to study how altered mitochondria cause hypersensitivity to anesthetics at a molecular level.

"The molecular mechanisms are going to be not so simple to figure out," says Sedensky.

Probing for Anesthetic Targets

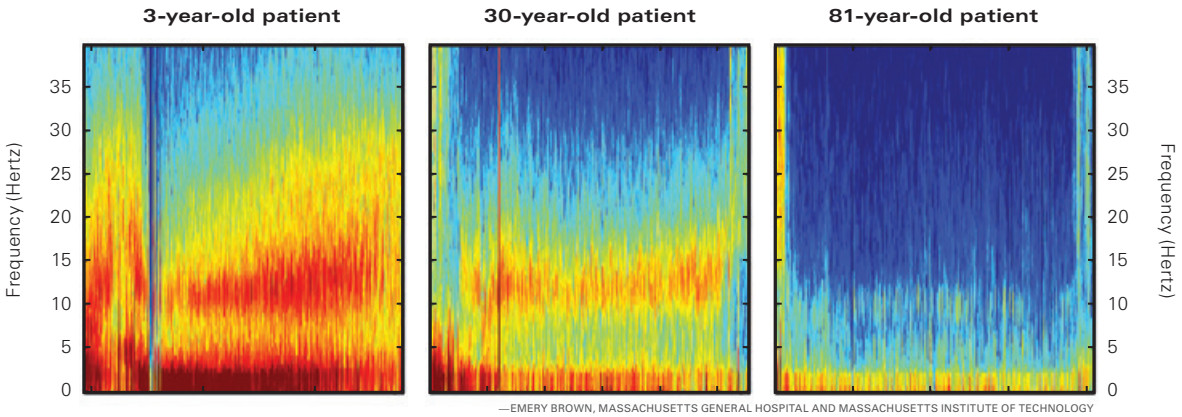
Eckenhoff and his team work with colleagues in the University of Pennsylvania's chemistry department to create chemical probes that identify the targets of anesthetic drugs. These probes are molecules shaped like anesthetics. The probes include additional features that allow them to bind tightly to target molecules whenever scientists shine light of a certain wavelength on them.

The researchers place their probes in complex mixtures of brain, spinal cord and heart cells. The probes then show which molecules interact with anesthetics in these organs. The anesthetic Propofol, for example, interacts with hundreds of different molecules.

The researchers then use structural biology methods to get a better look at the exact shapes of the target molecules' binding sites that the anesthetics interact with. Understanding the structures and other features of the binding sites could help scientists design new anesthetics.

> "It's like a symphony, … Each molecular target is an instrument, and you need all of them to produce Beethoven's 5th."

Eckenhoff has already used what he's learned about the structures of anesthetic targets to identify what he hopes are the first entirely new anesthetics developed since



The brain waves induced by a widely used anesthetic differ among age groups.

the 1970s. He and his team screened about half a million compounds and found that 1 percent of these drugs targeted a molecule that was shaped similarly to the ones anesthetics typically target. Further testing is needed, but Eckenhoff hopes that at least one of these drugs will prove to be an anesthetic with fewer side effects (e.g., nausea and vomiting) than those currently available.

How does a change at the level of a single molecule affect consciousness?

Brain Waves, General Anesthesia and Unconsciousness

Emery Brown of the Massachusetts General Hospital and Massachusetts Institute of Technology is studying how anesthetics act on the brain to create a state of unconsciousness. He uses an electroencephalogram (EEG) to record the brain's electrical activity while patients are under anesthesia.

According to Brown, the anesthetics generate electrical waves that impair the brain's ability to transmit information. "If you do that in the circuits that are responsible for arousal and cognition," he says, "then you're going to cause unconsciousness." The anesthetic-induced brain waves are highly organized and larger than the brain's natural waves. Brown's research suggests they occur when the drugs bind to their molecular targets in the brain.

Brown's research also provides insight into why the doses required to achieve an anesthetic state differ among age groups. In one study, the anesthetic-induced brain waves of older adults were two to three times smaller than those of younger adults. As we age, Brown explains, brain cells function at a lower level, so weaker brain waves can disrupt their activity and cause unconsciousness.

Now Brown is using animal models to understand in greater detail how anesthetics control specific brain circuits. His research group is also developing strategies for turning the brain back on after general anesthesia as a way to lessen the brain dysfunction that can follow general anesthesia, particularly in elderly people.

Connecting the Pieces

"How do you connect an effect at a single molecular target to an end point like consciousness?" asks Eckenhoff of the notion that anesthetics generally change the function of a single kind of molecule on the surface of neurons. That question presents perhaps the biggest challenge facing anesthesiology research today. Answering it, Eckenhoff, Sedensky and Brown all agree, will require collaborations across disciplines and research spanning all levels of biological organization—from the molecule to the whole being. And the answer could eventually mean safer use of anesthetics. ■

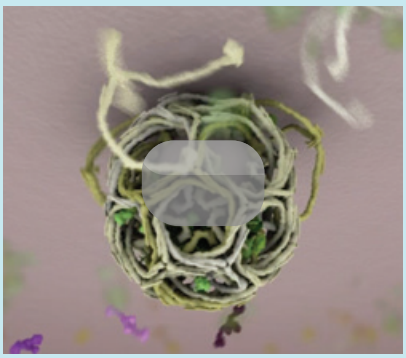
Scientists in Action

BY CHRIS PALMER AND ERIN ROSS

spotlight on videos

— CHRIS PALMER AND ERIN ROSS

Janet Iwasa, Molecular Animator



— TOMAS KIRCHHAUSEN, HARVARD MEDICAL SCHOOL, AND JANET IWASA

Cells form small intracellular bubbles, called vesicles, to package extracellular materials that will be brought into the cell—a process called endocytosis.

The world beneath our skin is full of movement. Hemoglobin in our blood grabs oxygen and delivers it throughout the body. Molecular motors in cells chug along tiny tubes, hauling cargo with them. Biological invaders such as viruses enter our bodies, hijack our cells and reproduce wildly before bursting out to infect other cells.

To make sense of the subcutaneous world, Janet Iwasa, a molecular animator at the University of Utah, creates "visual hypotheses"—detailed animations that convey the latest thinking of how biological molecules interact.

"It's really building the animated model that brings insights," Iwasa says. "When you're creating an animation, you're really grappling with a lot of issues that don't necessarily come up by any other means. In some cases, it might raise more questions and make people go back and do some more experiments when they realize there might be something missing."

As she discusses in a video interview, Iwasa collaborates with numerous scientists to develop animations of a range of biological processes and structures. Recently, she's undertaken an ambitious, multiyear project to animate HIV reproduction.

https://biobeat.nigms.nih.gov/2016/08/interview-with-a-scientist-janet-iwasa-molecular-animator

— CHRIS PALMER

Laura Kiessling, Carbohydrate Scientist

Streptococcus pneumoniae

The outside of every cell on Earth—from the cells in your body to single-celled microorganisms—is blanketed with a coat of carbohydrates, or sugar molecules, that extend from the cell surface, branching off and bending as they interface with the extra-cellular space. The specific patterns in which these carbohydrates are arranged serve as an ID code that helps cells recognize each other. For example, human liver cells have one pattern, and human red blood cells have another. Certain diseases can even alter the pattern of surface carbohydrates, which is one way the body can recognize damaged cells. On foreign cells, including invading bacteria such as *Streptococcus pneumoniae*, the carbohydrate coat is even more distinct.

In a video interview, Laura Kiessling, a professor of chemistry at the University of Wisconsin-Madison, discusses how carbohydrate coats are assembled and how cells use these coats to tell friend from foe. The implications of her research suggest strategies for targeting tumors, fighting diseases of inflammation and developing new classes of antibiotics.

https://biobeat.nigms.nih.gov/2016/10/interview-with-a-scientist-laura-kiessling-carbohydrate-scientist

There's an "Ome" for That

BY CHRIS PALMER

Have you ever collected coins, cards, toy trains, stuffed animals? Did you feel the need to obtain every item in the set? If so, then you may be a completist, someone who goes to great lengths to acquire a complete set of something.

Scientists can also be completists, inspired to identify and catalog every object in a particular field to further our understanding of it. For example, a comprehensive parts list of the human body could aid researchers in developing novel treatments for diseases in the same way that a parts list for a car enables auto mechanics to build or repair it.

More than 15 years ago, scientists figured out how to catalog every gene in the human body. In the years since, rapid advances in technology and computational tools have allowed researchers to begin to categorize numerous aspects of the biological world. There's actually a special way to name these collections: Add "ome" to the end of the class of objects being compiled. So following this naming scheme, the complete set of genes in the body is called the "genome"; the complete set of proteins is called the "proteome."

Here are three omes and descriptions of how they can be useful for understanding human health (see more examples, below).

Genome

The genome is the original ome. In 1976, Belgium scientists identified all 3,569 DNA bases—the A's, C's, G's and T's that make up DNA's code—in the genes of *bacteriophage MS2*, immortalizing this bacteria-infecting virus as possessing the first fully sequenced genome.

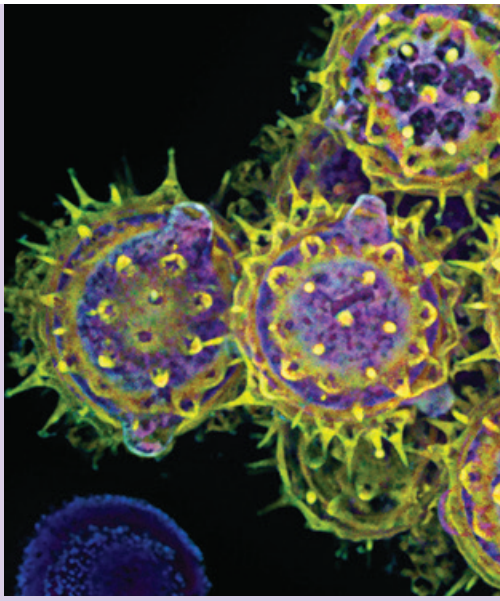
Over the next two decades, a small handful of additional genomes from other microorganisms followed. The first animal genome was completed in 1998. Just 5 years later, scientists identified all 3.2 billion DNA bases in the human genome, representing the work of more than 1,000 researchers from six countries over a period of 13 years.

As more individuals' genomes have been sequenced, scientists have found that humans share 99.5 percent of their genome with

Since the completion of the human genome more than 10 years ago, scientists continue to suggest new omes. Here's a partial list (sorry, completists!).

▶ Allergenome

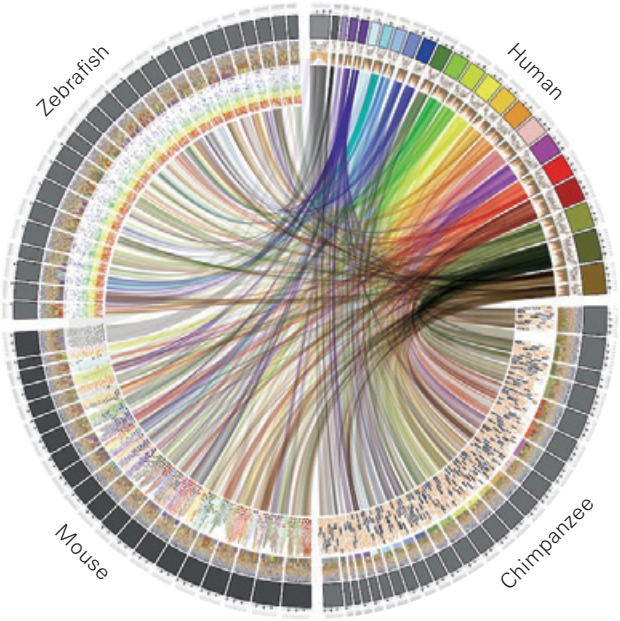
All of the proteins found in allergens, substances capable of causing an allergic reaction, such as pollen, grass and dust mites.



Pollen grains, like the ones shown here, can cause seasonal allergies.

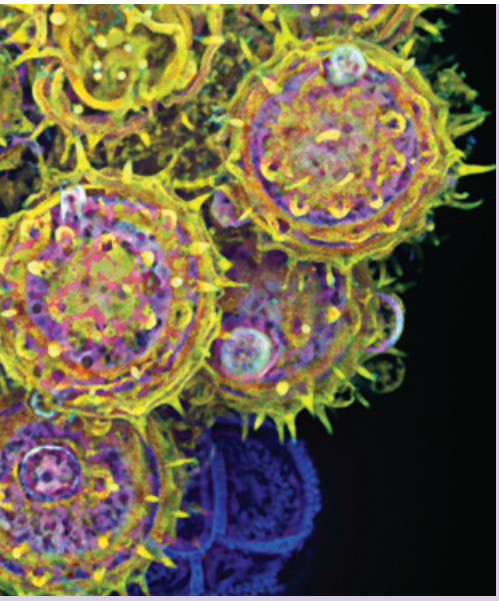
each other. However, small differences can be quite important. As the cost of sequencing genomes has plummeted from an initial $3 billion to the current $1,000, scientists are sequencing the genomes of people as well as those of other types of organisms used to investigate biological questions.

And all the effort is paying off. Genomics—the study of genes and their function—is beginning to reveal many of the basic components of cells and their interactions. Already, researchers are linking the presence of certain genes in the genome to specific diseases. Furthering our understanding of the genome could have a profound impact on the diagnosis and treatment of disease. Also, comparing the genomes of related and disparate species can shed light on how species evolve over time.

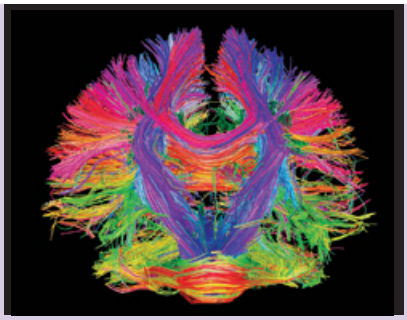


—MARTIN KRZYWINSKI, CANADA'S MICHEL SMITH GENOME SCIENCES CENTRE

Clockwise from top right, the genomes of a human, chimpanzee, mouse and zebrafish are arranged in a circle. Each colored square at the outside of the circle corresponds to a pair of chromosomes, the threadlike packages of double helical DNA (inset) stored in the nucleus. Lines connect similar DNA sequences, visually emphasizing just how much DNA humans share with other species. The density of the connections indicates that humans have more in common with chimpanzees than zebrafish.



—EDNA, GIL AND AMIT CUKIERMAN, FOX CHASE CANCER CENTER



—THE HUMAN CONNECTOME PROJECT

Wiring diagram of the major connections within the human brain.

▲ Connectome

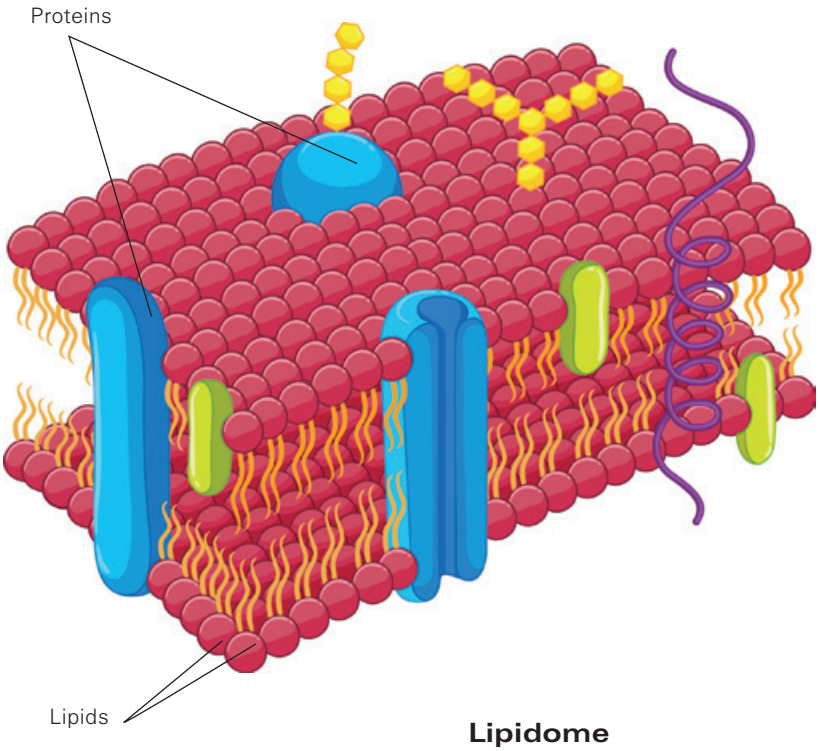
All of the connections among neurons in the brain. The human brain has 86 billion neurons with an estimated 1 trillion total connections among them.

Epigenome

The collection of chemical compounds that attach themselves to the genome as a way to regulate the activity, or expression, of all the genes within the genome.

Metabolome

All of the small molecules, known as metabolites, produced by cells, tissues or whole organisms.



Composed of two layers of lipids (small red spheres) studded with proteins (elongated blue shapes), cell membranes form a barrier around cells.

Lipidome

The lipidome is the collection of all the lipids, or fat molecules, within a cell. Cells use lipids to form a continuous membrane around themselves and to separate their inner organelles (specialized cellular structures such as the nucleus) from each other. These cellular membranes aren't simply for protection. They're also highly organized and dynamic work zones, seeded with proteins that help regulate the way cells attach to other cells, talk to each other, collect nutrients and grow.

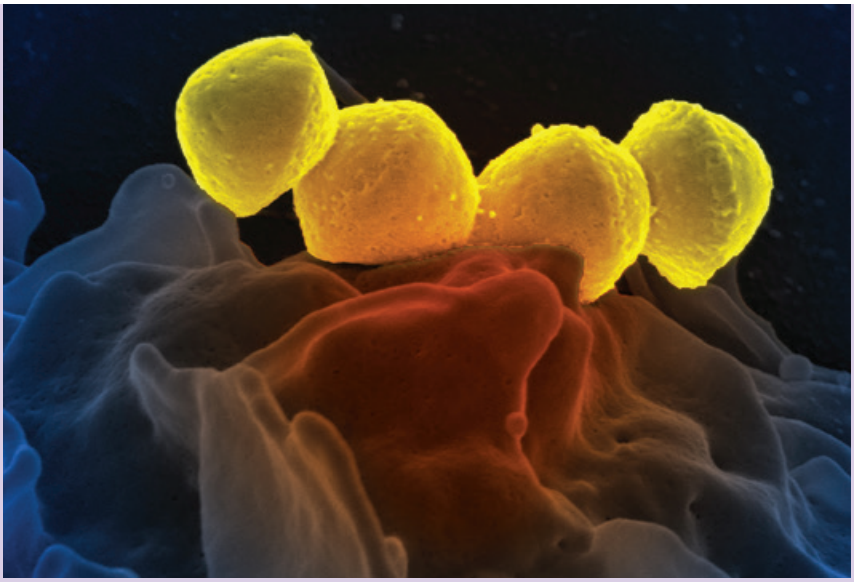
The lipid membranes inside the cell can similarly act as points of contact between cellular compartments, and they're involved in nearly every aspect of cellular function. Recent experiments have revealed hundreds of distinct types of lipids produced by cells.

The collection of lipids within cells has also been found to be remarkably flexible, capable of rapid, large- and small-scale rearrangements in response to different situations. For example, during early development, lipids within the membrane reorganize as a cell grows. Infectious viruses can slam into and rupture the membrane of human cells, causing localized lipid reshuffling.

Disruptions of the lipid components of cellular membranes are associated with diverse diseases, including cardiovascular disease, autoimmunity, osteoporosis,

▶ Microbiome

The complete set of genomes belonging to microbes—single-celled organisms that include bacteria and fungi—in a system such as the human gut. Current estimates suggest microbe genes in our bodies greatly outnumber our own genes.



—NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Streptococcus **bacteria (yellow) on a human neutrophil, or white blood cell (blue).**

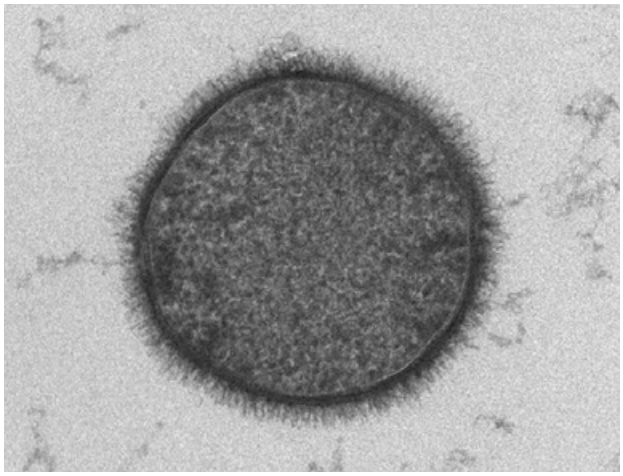
neurological disorders and cancer. Experiments investigating the lipidome of specific cells with known roles in particular diseases could help researchers identify novel treatments.

Glycome

The glycome is the complete set of glycans, also known as carbohydrates or sugars, that cells produce. Many of these glycans are linked to proteins and lipids on cell surfaces, where they can interact with molecules on other cells. Single sugars can also act as signaling molecules inside cells, altering gene editing, protein folding and other cellular functions.

A recent study of 650 different species suggests that about 5 percent of an organism's DNA codes for the proteins that synthesize, degrade and/or recognize and bind to carbohydrates. Mutations in these genes can result in the dysfunction of many organs, underscoring the importance of carbohydrates to human health. In addition, changes in the patterns of glycans in a person's cells can be an indication of a range of diseases, including cancer, inflammatory bowel disease and cardiovascular disease. One day, scientists may use imaging techniques to rapidly identify a cell's glycome to diagnose specific kinds of cancer, for example.

Cells also use the glycans on their outer surface, commonly referred to as carbohydrate coats, to recognize one another (see "Spotlight on Videos," page 9, to learn more about carbohydrate coats). Likewise, viruses can recognize and bind to carbohydrate coats. By analyzing the carbohydrate binding properties of the flu virus, for instance, researchers have been able to design antiviral drugs that interfere with the virus' ability to infect our cells. ■



—WIKIMEDIA COMMONS, ALLONWEINER

Thousands of glycans protrude from the bacterium *Bactillus subtilis,* forming a unique carbohydrate coat.

Proteome

All of the proteins made by an organism.

Regulome

The entire set of transcription factors—chemical compounds that regulate gene expression—in an organism.

Transcriptome

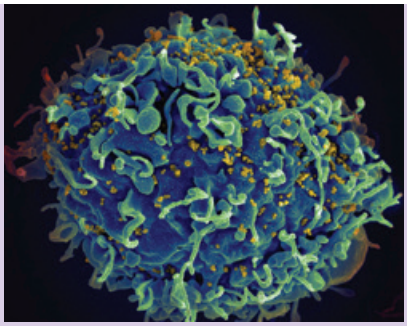
The complete set of RNA molecules—including messenger RNA, ribosomal RNA and transfer RNA—in an organism.

—MATT BERTONE, NORTH CAROLINA STATE UNIVERSITY

The brown recluse makes one of the deadliest toxins found in any spider's venom.

▲ Venome

All of the toxins produced by each species of venomous creature, including scorpions, snakes, spiders and even mammals such as shrews and moles.



—SETH PINCUS, ELIZABETH FISCHER AND AUSTIN ATHMAN, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

This human T cell (blue) is under attack by HIV (yellow), the virus that causes AIDS.

▲ Virome

The comprehensive list of viruses in an environment.

The Extracellular Matrix, a Multitasking Marvel

BY ALISA ZAPP MACHALEK, RUCHI SHAH AND KATHRYN CALKINS

When we think about how our bodies are made and what they do, we usually focus on organs, tissues and cells. These structures have well-known roles. But around, within and between them is a less understood material that also plays an essential part in making us what we are.

This gelatinous filler material is known as the extracellular matrix (ECM). Once thought to be the biological equivalent of bubble wrap—serving only to provide protection—we now know that the ECM is a dynamic, physiologically active component of all our tissues. It guides cell shape, orientation and function.

The ECM is found in all of our body parts. In some tissues, it's a thin layer separating cells, like mortar between bricks. In other tissues, it's the major constituent.

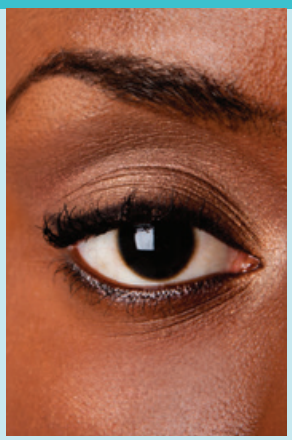
The ECM is most prevalent in connective tissue, the material that forms our skeletons, cushions our internal organs and winds between blood vessels and around nerves. In connective tissue, the ECM is more abundant than the cells suspended within it.

What makes the ECM unique is its variability: Its texture, composition and functions vary by body part. That's because the ECM's deceptively simple recipe of water, fibrous proteins and carbohydrates has virtually endless variations.

In general, the fibrous proteins give the ECM its texture and help cells adhere properly. Carbohydrates in the ECM absorb water and swell to form a gel that acts as an excellent shock absorber.

The extracellular matrix meets the needs of each body part.

In teeth and bones, it's rock-hard.



In corneas, it's a transparent gel that acts like a camera lens.

In tendons, it forms strong fibers that bind muscle to bone.

The extracellular matrix is essential for closing wounds.

Sealing and Healing Wounds

When we get injured, the first thing our body does is to form a blood clot to stop the bleeding. Skin cells then start migrating into the wound to close the cut. The ECM is essential for this step, creating a physical support structure—like a road or train track—over which skin cells travel to seal the injured spot.

The ECM is made up of a host of proteins produced before and after injury. Some other proteins called matrix metalloproteinases (MMPs) also crowd into wounds. Because humans have so many different MMPs—24 of them—it's been difficult for scientists to figure out what roles, if any, the proteins play in healing scrapes and cuts.

To find out whether MMPs help close wounds, Andrea Page-McCaw and colleagues at the Vanderbilt University Medical Center turned to the fruit fly. This model organism has just two MMPs, only one of which (MMP1) can move about to do things such as helping repair damaged tissues. The scientists used immature flies (larvae), whose soft outer layer is easier to work with and, surprisingly, more similar to the epithelia—the outer covering—of our own skin than

it is to the hard shell of adult fruit flies.

The researchers examined wounds in the larvae of two special fruit fly strains: one that can't make MMP1 and one that produces more than the normal amount of MMP1. In the strain that lacked MMP1, wounds failed to close. In the strain that had extra MMP1, wounds closed much more quickly than in normal flies. The researchers had their answer: Yes, MMP1 does help heal injuries because it's necessary for wounds to close—at least in fruit flies.

As for how MMP1 works, Page-McGraw's team has learned that within hours of an injury, large amounts of MMP1 amass at the edges of the damaged tissue. The researchers know that collagen—a strong, fibrous protein—also accumulates at these edges. Now they're trying to tease out how MMPs, collagen and other ECM molecules work together to enable our bodies to heal themselves.

Four types of proteins are closely associated with the Extracellular Matrix.

Cadherin
These protein molecules are like molecular pegs in the cells' membranes, providing tiny joints that attach the cells to each other.

Collagen
This protein—the most abundant in the human body—provides strength and integrity to the ECM.

Elastin
This fibrous protein in the ECM confers elasticity.

Integrin
This collection of protein molecules bind cells to the ECM.

Cells on the Move in Embryo Development with Help from the ECM

When we go for a run or stroll, we're usually unaware of how much coordination it takes. To safely move us forward, our feet must sense and quickly adjust to the friction of the surface beneath them—whether it's the nubby hardness of gravel or the slickness of ice.

Sensing and responding to mechanical friction is important for all sorts of movements, such as walking and even cell migration.

It turns out that such fine-tuned movement also takes place during a baby's first few days in the womb. Even when the embryo is still less than an inch long, a whole lot of to-and-fro cell movement is going on, with many cells migrating en masse to form tissues and organs. If cells journey to the wrong place or fail to travel at all, birth defects can result. So, scientists wondered, what role does the ECM play in these early mass cell migrations?

This question was on the minds of Douglas DeSimone and colleagues at the University of Virginia School of Medicine. Using embryos of a type of clawed frog called *Xenopus* as stand-ins for human ones, the researchers studied cadherins, protein molecules that are like molecular pegs in the cells' membranes, providing tiny joints that attach the cells to each other. When the researchers used sophisticated biophysical techniques to tug at the cadherins, they saw that this pull causes the cells to change their shape and to begin migrating away from the direction of the pull.

Because similar forces yank and pull on cadherins when neighboring cells physically interact with each another in a tissue, the researchers think that cadherins help relay these mechanical forces to coordinate the cells' movements. This coordination is essential so that the cells move not in a slapdash fashion but in a well-orchestrated march.

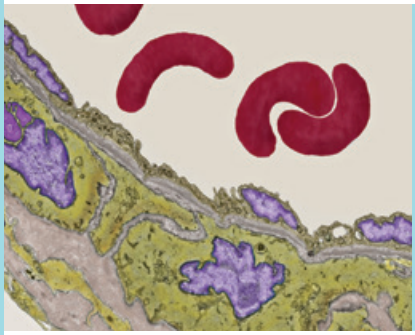
It turns out that the ECM helps cells coordinate these movements. Protein molecules called integrins fasten cells to the ECM. When they do so, they activate cellular machinery that primes cells to move in response to tension—again sensed via cadherins—and helps roving groups of cells orient in one direction. Assembling cells into tissues, organs and, eventually, a whole new person—just another service the ECM provides. ■

spotlight on the cell

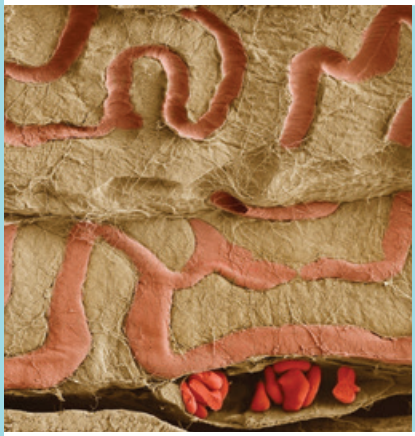
Here s a collection of images featuring the Extracellular Matrix.

Photos are from the National Center for Microscopy and Imaging Research at the University of California, San Diego.

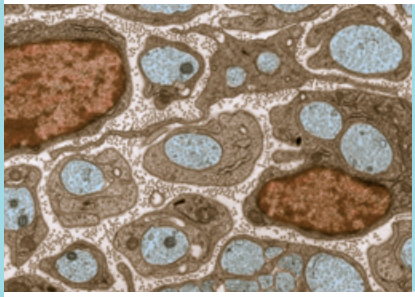
The main component of the ECM—and the most abundant protein in our bodies—is collagen. It accounts for about a quarter of our total protein mass. By assembling into a rope-like shape, it plays a variety of important roles, such as forming stretch-resistant fibers that give strength to our tendons, ligaments and bones and providing scaffolding for skin wounds to heal. There are about 20 different types of collagen in our bodies, each adapted to the needs of specific tissues.



Elastin, another fibrous protein in the ECM, is abundant in artery walls like the broad, pastel-colored structure near the bottom of the photo (the smaller, curved, dark red structures near the top are red blood cells). As its name indicates, elastin confers elasticity. Fibers made of elastin are at least five times more stretchy than rubber bands of the same size. Tissues that expand, such as blood vessels and lungs, need to be both strong and elastic, so they contain both collagen and elastin.



Scientists know less about the ECM in muscle than in other tissues, but studies are making it increasingly clear that ECM is critical to muscle function. Disruption of ECM is linked with many muscle disorders. Scientists have also found that the ECM in muscles can store and release substances called growth factors that stimulate cell growth, suggesting that the ECM might play a key role in cellular communication. This image shows the ECM on the surface of a soleus (lower calf) muscle. The winding, pink structures are blood vessels. At the bottom, a vessel has opened, revealing small clumps of red blood cells.



Although there is less ECM in nervous tissue than in connective tissue, it is found between the stems (axons) of nerve cells. In this image, nerve axons are blue. Surrounding the axons are Schwann cells (brown), which produce a fatty covering called myelin that acts as insulation. The open, somewhat colorless areas are ECM. Within the ECM, collagen fibers appear as tiny brown spots.

Lighting Up the Promise of Gene Therapy for Glaucoma

BY ALISA ZAPP MACHALEK

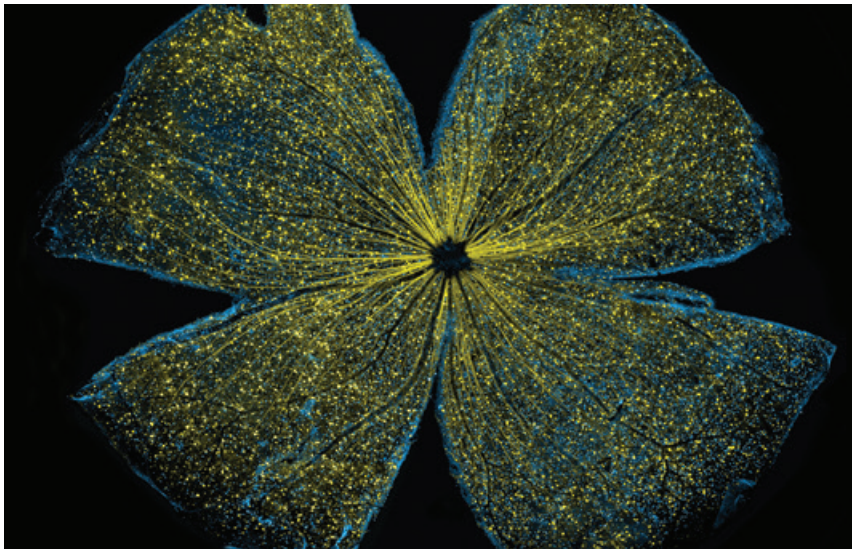
What looks like the gossamer wings of a butterfly is actually the retina of a mouse, delicately snipped to lay flat and sparkling with fluorescent molecules. Researchers captured this image while investigating the promise of gene therapy for glaucoma, a progressive eye disease. It all happened at the National Center for Microscopy and Imaging Research (NCMIR) at the University of California, San Diego.

Glaucoma is the leading cause of irreversible blindness. It is characterized by the slow, steady death of certain nerve cells in the retina. If scientists can prevent the death of these cells, called retinal ganglion cells, it might be possible to slow the progression of glaucoma. Some researchers are examining the possibility of using gene therapy to do just that.

A major challenge of gene therapy is finding a way to get therapeutic genes into the right cells without damaging the cells in any way. Scientists have had success using a nondisease-causing virus (*adeno-associated serotype 2*) for this task.

Here's how it works: Researchers insert the desired gene into the virus, then let the virus do what it does best—enter cells. Once inside, the virus splits apart to release its genetic material, which gets incorporated into the genome of the host (mice, in this case). Then the inserted genes function just like other genes normally found in the host genome.

This image shows that the process worked—at least for some of the cells.



—KEUN-YOUNG KIM, WONKYU JU AND MARK ELLISMAN, NATIONAL CENTER FOR MICROSCOPY AND IMAGING RESEARCH, UNIVERSITY OF CALIFORNIA, SAN DIEGO

Retinal ganglion cells in the mouse retina that do (yellow) and do not (blue) contain a specific gene that scientists introduced with a virus.

> "It is amazing to see intricate and artistically organized microscopic structures. … I encountered an entirely new world invisible to the naked eye—a galaxy of infinite secrets and endless potential for discovery."
>
> —Keun-Young Kim, lead researcher

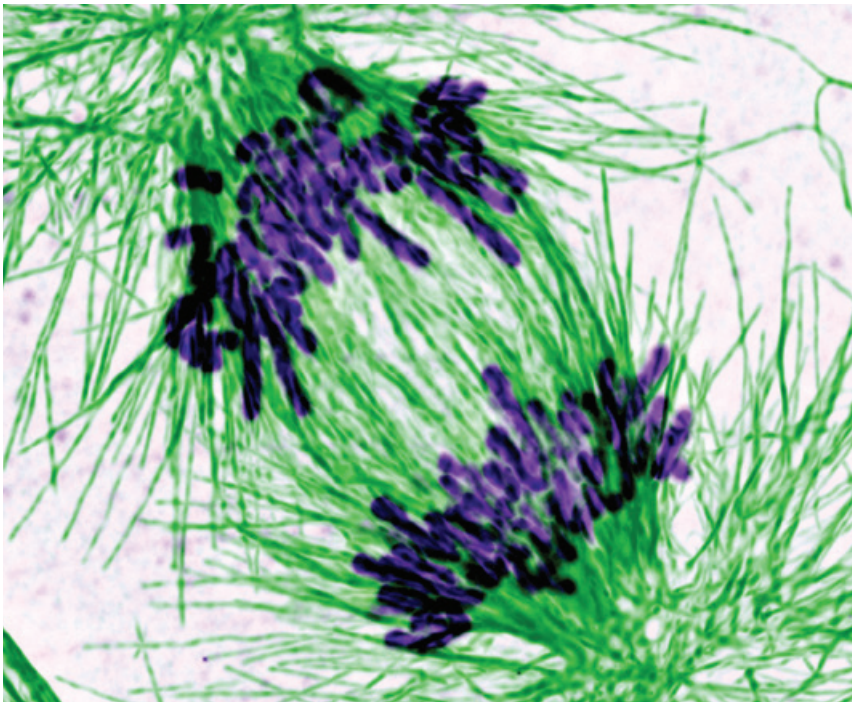
Retinal ganglion cells that contain a functional copy of the test gene are yellow. Retinal ganglion cells that don't are blue. These results bring the concept of gene therapy for glaucoma one step closer.

The research was about more than delivering genes or treating eye diseases. It also showcases a powerful technique pioneered by NCMIR for obtaining high-resolution microscopy images of large samples, such as an entire mouse retina. The technique is similar to "Google Earth," in that it computationally stitches together many small, high-resolution images obtained with a powerful light microscope. In essence, scientists now have a vastly larger canvas on which to reveal, in high definition and fluorescent colors, all the cellular and molecular details of life. ■

The Science of Size:

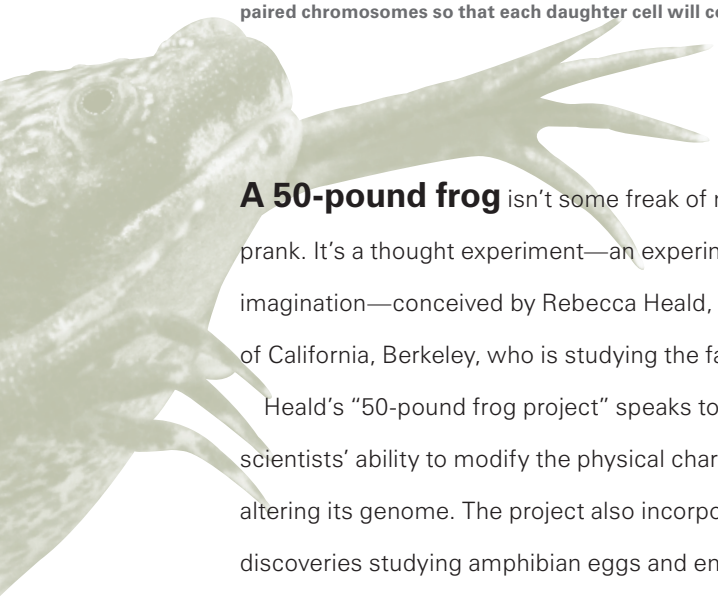
Rebecca Heald Explores Size Control in Amphibians

BY CHRIS PALMER



—NASSER RUSAN, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NATIONAL INSTITUTES OF HEALTH

The spindle, composed of thousands of microtubules (green), grabs hold of chromosomes (purple), which replicate during cell division. As the cell divides, the spindles will separate the paired chromosomes so that each daughter cell will contain a complete set of chromosomes.



A 50-pound frog isn't some freak of nature or a creepy Halloween prank. It's a thought experiment—an experiment carried out only in one's imagination—conceived by Rebecca Heald, a cell biologist at the University of California, Berkeley, who is studying the factors that control size in animals.

Heald's "50-pound frog project" speaks to the power of evolution and to scientists' ability to modify the physical characteristics of an organism by altering its genome. The project also incorporates many of Heald's fascinating discoveries studying amphibian eggs and embryos.

In amphibians, unlike in mammals, there are striking correlations among the size of the animals' genomes (an organism's complete set of genes; for more about genomes see "There's an 'Ome' for That" on page 10) and several aspects of the animals' size. For example, amphibians with large genomes tend to be bigger than those with smaller genomes. Larger genomes also correspond to larger cells and larger organelles (specialized cellular structures such as the nucleus). Heald has also demonstrated that these seemingly fixed parameters can be tweaked in the lab.

International Woman of Science

Way before dreaming up ways to design the frogs of people's nightmares in her lab, Heald was fond of science. She remembers starting out with more mundane experiments in middle and high school, such as distilling gases from burning wood, dissecting fly embryo salivary glands and examining microorganisms under a microscope.

"I definitely thought microscopy was just this whole new world, a whole new way of seeing things," she recalls.

Even earlier than these formative experiences, Heald found herself attracted to life as a scientist for other, more ethereal reasons. She would often accompany her

chemistry professor father to his lab at Thiel College, a small liberal arts school in northwestern Pennsylvania, where she recalls enjoying the ambiance. She was even more impressed by living with her parents in Australia and New Zealand during their sabbaticals.

"I think those experiences had a big influence on my interest in the academic lifestyle, that you could go live other places and work with interesting people," says Heald.

After completing a Ph.D. at Harvard Medical School, Heald arranged her own international excursion by working as a researcher for 3 years in Germany.

"It was exciting to see how a different culture does science," she recalls.

During her time in Germany, Heald studied the football-shaped cellular structure called the spindle, which is composed of thousands of thin fibers called microtubules. During cell division, chromosomes replicate, yielding two copies of each chromosome connected together. Spindle fibers attach to the chromosomes, pull them apart and move the previously paired chromosomes to opposite ends of the cell. The goal of the whole process is for each daughter cell to contain a single copy of each chromosome—a complete genome.

Heald discovered that spindles can form in the absence of chromosomes. Instead of attaching onto chromosomes, the spindles unite around DNA-coated beads through a process of "self-organization." This finding earned her a faculty position at Berkeley, where she set out to compile the minimum parts list necessary to make a functional spindle.

Because spindles are made of microtubules along with about a thousand other proteins and other various components, Heald estimates it could take more than a decade to tease out what are the critical factors that, when combined, would be sufficient to reconstitute the spindle.

> "Microscopy was a whole new world, a whole new way of seeing things."

When it came time for her first sabbatical a few years after landing her job at Berkeley, Heald again looked abroad, spending a year doing research in Toulouse, France. Her project focused on how

Heald's globetrotting adventures allowed her to experience how different cultures "do" science.

"Mammals are actually quite boring," says Heald.

RESEARCHER

Rebecca Heald

MARK HANSON

GREW UP IN
Greenville, Pennsylvania

STUDIED AT
Hamilton College, Rice University, Harvard Medical School

JOB SITE
University of California, Berkeley

FAVORITE HOBBY
Cycling

microtubules organize during muscle development. An avid cyclist, she took advantage of down times in the lab by racing through the Alps and Pyrenees mountain ranges.

At home in Berkeley, Heald enjoys cycling down by the San Francisco Bay and powering up the Berkeley Hills to the east. For the past 10 years or so, she has completed what she calls "Triathlon Thursdays." These early-morning blitzes begin at 7:00. Instead of the traditional bike, swim and run, Heald meets up with a friend or colleague for a long bike ride. She then comes home and sinks into a bath. She wraps up by taking her dog, Louis, for a walk before heading to her lab.

Spindle Science

Heald first fell in love with frog eggs as a research system during her early studies of cell division. She was fascinated that spindle formation requires neither proper chromosomes nor intact cells. All it needs is isolated cytoplasm—the gel-like substance in which a cell's organelles are embedded—and some DNA, either in the form of chromosomes or DNA-coated beads.

To figure out which molecules are necessary for spindle assembly, Heald uses a cytoplasm extract, which contains all the components necessary to build a cell but lacks chromosomes. To obtain this extract, she and her colleagues collect thousands of eggs from the African frog *Xenopus laevis*. They then remove the eggs' jelly-like outer coating and put them in a centrifuge tube. Spinning the eggs in a centrifuge crushes them and separates the egg contents so that the cytoplasm can be isolated.

The scientists then add chromosomes (usually from frog sperm) to the extract, together with fluorescent tags attached to various spindle proteins, and use microscopes to observe the spindle form.

By manipulating the proteins in the egg extract mixture and substituting different kinds of DNA-coated beads for the chromosomes, Heald learns which factors are needed for spindle assembly. She uses this information to support her long-term goal of building a spindle from a defined set of parts.

— STEVE HILL

Rebecca Heald rides through the Pyrenees mountain range in southern France.

—WIKIMEDIA COMMONS, H. KRISP

The African clawed frog (*Xenopus laevis*) is ideal for studying the connection between body size and spindle size.

Size Matters

While her research into spindles was progressing, a colleague at Berkeley introduced Heald to a related frog, *Xenopus tropicalis*, that is smaller than the one she had been working with and also has a smaller genome. *X. tropicalis* is the size of a kiwifruit, whereas *X. laevis* is the size of an orange. Heald was enthralled with the fact that *X. tropicalis* was smaller and its eggs, as well as the spindles formed in its egg extracts, were too.

Realizing that body size seemed to correspond to spindle size was exciting because it provided an experimental system to investigate how spindle size is determined. Heald and her colleagues learned that they could mix together the cytoplasm from the eggs of the two frogs and add in chromosomes. The result was hybrid spindles of intermediate size, suggesting that there is something in the cytoplasm that is determining spindle size.

Heald's group is now seeking to identify the factors—they call them scaling factors—that work to regulate the size of the spindle. Subsequent experiments in her lab revealed that spindle size is controlled in two ways: one that depends on the amount of certain proteins, and the other that depends on the specific sequences of those proteins. For example, an enzyme that cuts microtubules, called Katanin, has a slightly different amino acid sequence in the two different frog species. The version of Katanin in *X. tropicalis* is much more active at chopping microtubules, which makes the spindles in that animal smaller.

Even though, as Heald puts it, "mammals are actually quite boring; all of our genomes and cell-size relationships are pretty much the same," her work with amphibians has important implications for humans. Under certain circumstances, human cells, and the organelles within them, vary in size. For example, cancer cells are characterized by enlarged and misshapen nuclei. Researchers do not know whether these abnormal cells are a cause, or a result, of disease.

Cancer messes up cells in several other ways. For example, many of the thousands of factors that affect spindle assembly are altered in cancer cells, and it is not clear how these changes impact the spindle.

Cancer cells also tend to be unreliable when it comes to accurately divvying up chromosomes during cell division, resulting in daughter cells that have too many or too few chromosomes. Heald plans to study this phenomenon using the frog *Xenopus longipes*, whose genome of 108 chromosomes is significantly larger than that of the other frog species (*X. laevis* has 18 chromosomes, and *X. tropicalis* has 10). An important question for Heald is how these animals properly segregate such a massive number of chromosomes to two daughter cells.

Heald hopes her research can answer these questions and provide leads on potential cancer therapies and diagnostics.

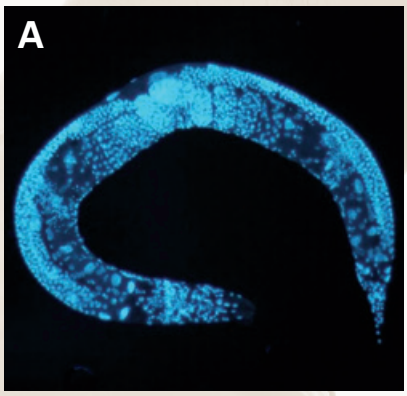
"One of the wonderful things about cell biology is that you have all these different animals . . . and you can figure out what is a good question and then find a great system in which to answer that question," says Heald. "I think amphibians are actually pretty much the ideal system for my research questions." ■

Superstars of Science Quiz

BY ALISA ZAPP MACHALEK

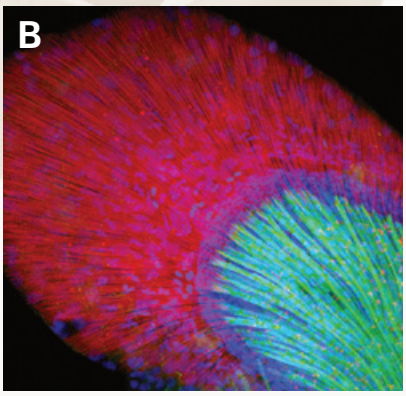
Many different animals (and even plants, fungi and bacteria) play a starring role in biological and medical research. Research organisms typically reproduce quickly, are easy to raise in a laboratory, and have characteristics that make them a window into certain aspects of biology. Studying such organisms teaches researchers how life works normally, what happens when things go awry, and how we might find better ways to diagnose, treat or prevent diseases.

See if you can match photos of each research organism (or parts of the organism) with the traits that make it useful to researchers. The photos were taken using microscopes. The colors, which help scientists study selected structures, come from chemical dyes or are created with graphic design programs.



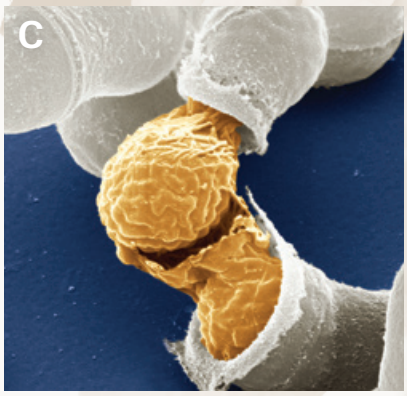
—NIH

Roundworm (*Caenorhabditis elegans*, or *C. elegans*)



—JESSICA PLAVICKI, UNIVERSITY OF WISCONSIN, MADISON

Zebrafish (*Danio rerio*)



—JÜRGEN BERGER, MAX PLANCK INSTITUTE FOR DEVELOPMENTAL BIOLOGY, AND MARIA LANGEGGER, FRIEDRICH MIESCHER LABORATORY OF THE MAX PLANCK SOCIETY, GERMANY

Yeast (*Saccharomyces cerevisiae*)

Carefully observe the images above, then read the captions below and match each image to the appropriate caption.

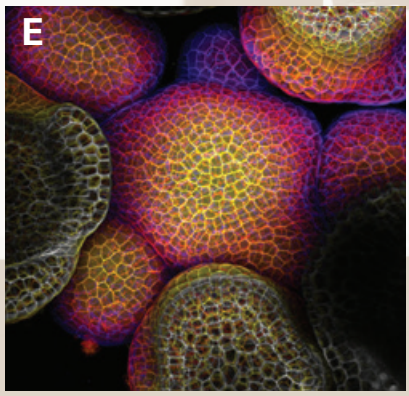
1 Like other research organisms, this one grows and reproduces quickly. It also has a genome that is easy to manipulate. Even though it's a flowering plant, its cells work in much the same way that human cells do. So researchers use it to investigate basic biological process such as how cells communicate, how genes turn on and off, and how stem cells develop into new tissues.

2 Almost all human genes have a counterpart in this common lab organism. The creature, a mammal like us, even develops diseases that are similar or identical to ours. It is frequently used to test experimental therapies and has helped us understand a range of conditions, including autoimmune diseases, obesity, diabetes, cancers and organ rejection. Researchers can order by mail specially bred or genetically engineered versions of this organism that have particular genetic profiles, symptoms or diseases.

3 You've probably seen this insect buzzing around overripe bananas. Research on it over the past century has taught scientists how genes affect development, appearance, behavior and lifespan in living organisms. Research using this organism has also shed light on many aspects of human biology, including biological rhythms, learning, memory and neurodegenerative diseases. The image shows this creature's ovary.

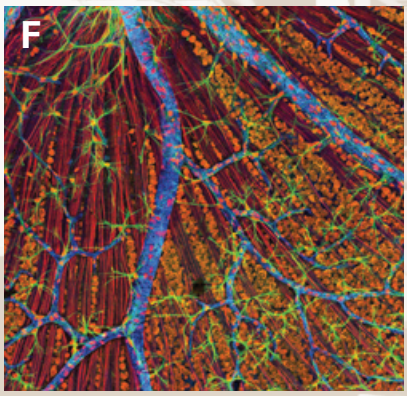
—HOGAN TANG AND DENISE MONTELL, JOHNS HOPKINS UNIVERSITY AND UNIVERSITY OF CALIFORNIA, SANTA BARBARA

Fruit fly (*Drosophila melanogaster*)



—ARUN SAMPATHKUMAR AND ELLIOT MEYEROWITZ, CALIFORNIA INSTITUTE OF TECHNOLOGY

Mustard plant (*Arabidopsis thaliana*)



—NATIONAL CENTER FOR MICROSCOPY AND IMAGING RESEARCH AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO

Mouse (*Mus musculus*)

4 This fungal organism plays an important role in making bread, beer and wine. Research on it has yielded vast knowledge about basic cellular and molecular biology as well as about myriad human diseases, including colon cancer and metabolic disorders. In this image, an offspring is being released.

5 Native to shallow ponds on the Indian subcontinent, this creature is now a popular species for home aquariums. Many researchers are drawn to it because its eggs and embryos are transparent, making it possible to watch organs develop in real time. By studying this creature, scientists have learned about birth defects, the impact of early exposure to environmental contaminants, and the proper development of organs that include the heart, bones, blood and the inner ear.

6 Normally, this tiny, transparent creature lives in dirt. But for the past 40 years, it has also lived in research labs around the world. Scientists studying the organism teased out the role of all 959 of its cells, learned that a large portion of its genes are similar to those in humans, and revealed many of the molecular underpinnings of organ development, aging and behavior.

Answers on inside back cover.

NIGMS Is on Instagram!

BY ALISA ZAPP MACHALEK

See gorgeous scientific images and videos of brightly colored cells, molecular animations, pathogen innards and more. It's all on Instagram @nigms_nih. If you've never used Instagram, just go to https://www.instagram.com, download and install the app and search for #NIGMS. You can also see our official Instagram feed using a web browser at https://www.instagram.com/nigms_nih. Let us know what you think!

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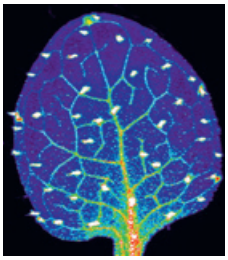
To ensure our material shows up on relevant searches, we use a collection of standard tags, such as: #science #scientific #biology #bioscience #biomedical #research #scienceisbeautiful #scienceiscool #sciart #nihfunded #nigms and #nih.

We also use specialized tags to connect each image with its relevant topic area, as shown with the images here.

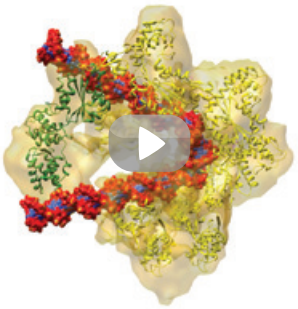
#zinc #microscopy #researchorganism #leaf #heatmap #microscopy #cellbiology #botany #plant #arabidopsis



—SUZANA CAR AND MARY LOU GUERINOT, DARTMOUTH COLLEGE

We need zinc. It's an essential nutrient for growth and development, fending off invading microbes, healing injuries and all sorts of cellular processes. We get the mineral through our diet, but people in certain parts of the world don't get enough. Researchers study how plants acquire and process zinc, hoping to find ways to increase the nutrient in food crops. Using synchrotron X-ray fluorescence technology, scientists created this heat map of zinc in a leaf from a plant called *Arabidopsis thaliana* (zinc levels from lowest to highest: blue, green, red, white).

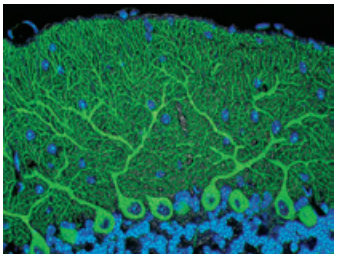
#DNA #celldivision #DNAreplication #cryoem #molecularbiology #imaging



VIDEO Check out the kink in this chromosome. Proteins (yellow and green) recognize a specific spot on DNA (red and blue) known as the origin of replication. Then, like a c-clamp on a copper pipe, they bend the DNA into a tight angle. Why? To ready the double helix to be unwound and copied as the cell prepares to divide. This research was done in yeast, but in many cases human cells behave similarly.

—HUILIN LI OF BROOKHAVEN NATIONAL LABORATORY, AND BRUCE STILLMAN OF COLD SPRING HARBOR LABORATORY

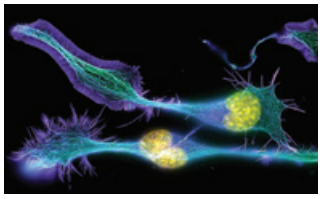
#cells #brainimages #neuroanatomy #cerebellum #neuroscience #neurobiology #brain



—TOM DEERINCK AND MARK ELLISMAN, NCMIR

Beautiful brain! This image shows the cerebellum, which is the brain's locomotion control center. Every time you shoot a basketball, tie your shoe or chop an onion, your cerebellum fires into action. Found at the base of your brain, the cerebellum is a single layer of tissue with deep folds like an accordion. People with damage to this region of the brain often have difficulty with balance, coordination and fine motor skills.

#mouse #researchorganism #animation #videos #electronmicroscopy #microscopy #nerves #nervecells #lifemagnified



—TORSTEN WITTMANN, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

This picture shows developing mouse nerve cells. The nucleus (yellow) is surrounded by a cell body, with long extensions called axons and thin branching structures called dendrites. Electrical signals travel from the axon of one cell to the dendrites of another.

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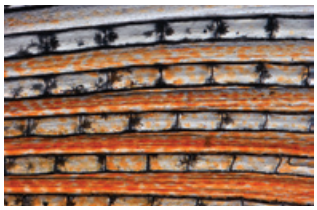
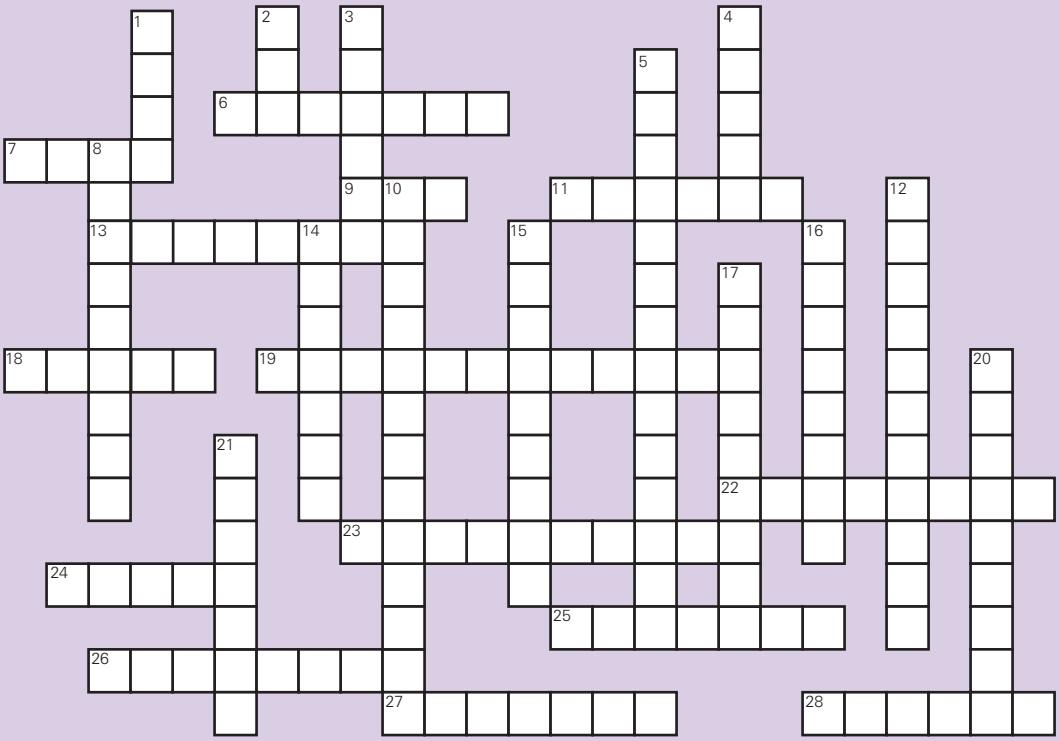
#marinebiology #marinescience #cells #pigmentcell #cellbiology #microscopy #researchorganism #cellbiology #cells #zebrafish



—DAVID PARICHY, UNIVERSITY OF WASHINGTON

Scientists can learn a lot by studying pigment cells, which give animals their colorful skins, eyes, hair and scales. We can even gain insight into skin cancers, such as melanoma, that originate from pigment cells. Pigment cells can form all sorts of patterns, such as these stripes on the fin of a pearl danio, a type of tropical minnow.

The Last Word



Across

6. Reduce, reuse…
7. A nerve's long stem.
9. Makes our tissues gooey or stiff.
11. Preventing cell death in the _____ might help treat eye diseases.
13. Leading cause of blindness.
18. Enrique De La Cruz studies how actin filaments _____ .
19. Cellular power plants.
22. Most powerful type of microscope.
23. Study of proteins.
24. Rebecca Heald's favorite research organism.
25. Sugary molecules.
26. Complete collection of lipids.
27. Separates paired chromosomes during cell division.
28. In amphibians, body size correlates with _____ size.

Down

1. Ouch!
2. Scientists use fluorescent ones to color-code molecules.
3. Really cool microscopy technique.
4. Forms filaments that allow cells to move, contract and keep their shape.
5. A whole new world.
8. Component of the cell.
10. Long chains of sugar molecules.
12. Induce unconsciousness.
14. Microscope that uses light.
15. Very small unit.
16. Most abundant protein in our bodies.
17. Inability to feel pain.
20. Stuff inside a cell, minus the organelles.
21. Really stretchy protein.

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Solve it online: An interactive version of the crossword puzzle and answers can be found at https://www.nigms.nih.gov/findings

Superstars of Science Quiz (page 22)
Answers: 1.E; 2.F; 3.D; 4.C; 5.B; 6.A

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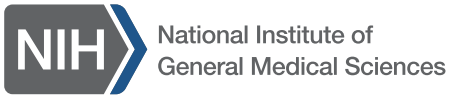

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