Fall '14 Vol. 27 No. 3

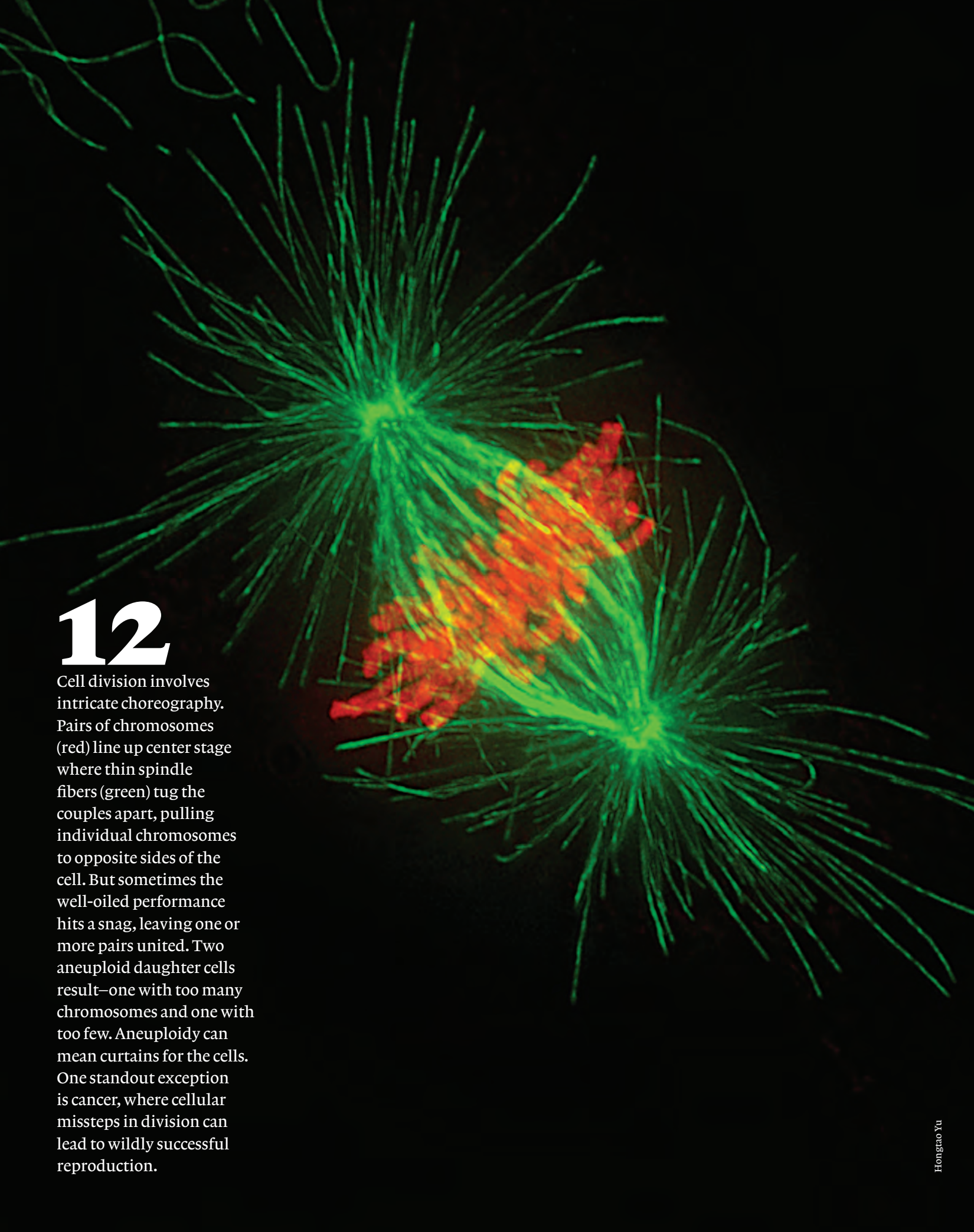
hhmi bulletin

in this issue

Bacterial Comrades
Meet the New Professors
Eco-friendly Fertilizer

When Cells Divide

Errors in the process can disable cells–unless they're cancerous



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Cell division involves intricate choreography. Pairs of chromosomes (red) line up center stage where thin spindle fibers (green) tug the couples apart, pulling individual chromosomes to opposite sides of the cell. But sometimes the well-oiled performance hits a snag, leaving one or more pairs united. Two aneuploid daughter cells result—one with too many chromosomes and one with too few. Aneuploidy can mean curtains for the cells. One standout exception is cancer, where cellular missteps in division can lead to wildly successful reproduction.

Hongtao Yu

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- **Listen as HHMI professors talk about overcoming challenges in science education.**
- **Go with Adam Cohen on a quest to jump-start science education in Liberia after years of civil war.**
- **Watch cells move, shuffle, and divide in a growing fruit fly embryo.**
- **Learn why an abnormal chromosome number might give cancer cells an edge.**

www.hhmi.org/bulletin

Cover image: atelier olschinsky

Contributors

A small, creative studio based in Vienna, Austria, **atelier olschinsky** (cover and "Errors in Division," page 12) represents the work of Peter Olschinsky and Verena Weiss, artists who operate in various fields, including graphic design, illustration, photography, and art direction.

Megan Scudellari ("Errors in Division," page 12) is a Boston-based freelance journalist specializing in the life sciences. Her work has appeared in *Newsweek*, *Nature*, and *Scientific American*, among other publications. When she's not writing about science, Megan is busy chasing her own biology experiments–her two children, ages two and a half and seven months–around the house.

Illustrator **Ruth Marten** ("A Twist of Fate," page 6) has a history of depicting hair. Having worked for more than three decades, including tattooing in the bad (good) old days, she now exhibits her work at Van der Grinten Galerie in Köln, Germany, and teaches watercolor at the School of Visual Arts in New York City.

Emily Shur ("The Silencer: MicroRNA," page 8) is a photographer living in an extremely old house in Los Angeles with her husband and their grumpy bulldog, The Baroness. She is a graduate of Tisch School of the Arts at New York University, and her client list includes *The New Yorker*, *The New York Times Magazine*, *Entertainment Weekly*, and *ESPN the Magazine*.

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President's Letter

James Kegley

Science Forward

IF YOU ARE A regular reader of the *HHMI Bulletin*, you may have noticed something different on the cover of this issue. It's our new logo. We've freshened up our identity at HHMI—a move that we feel better reflects the Institute's spirit of innovation and bold creativity. We acknowledge and celebrate our rich history of achievement, yet we have not been standing still. Indeed, we have been evolving and are a different Institute today than we were just 10 years ago. We strive to continue building our reputation and to better articulate our mission—our new visual identity reflects a greater openness along with our forward momentum.

Over the last decade, we've made notable strides to advance science and science education. We've launched and developed a new framework of collaborative, interdisciplinary research at the Janelia Research Campus. We've broadened our horizons by supporting researchers in new fields, such as plant science, and new countries—from South Africa to South Korea. We've launched a scientific journal and new online channels, and created a documentary film production studio to foster science literacy in the classroom and beyond. And we're partnering with other funders in the scientific, education, and philanthropic communities, collaborating to amplify our collective impact.

"Our new visual identity reflects a greater openness along with our forward momentum."
—ROBERT TJIAN

As we expand and broaden our activities, I continue to be inspired by the new knowledge that comes out of HHMI researchers' labs. In the cover story of this issue of the *Bulletin*, you'll read about how some of the researchers we support are getting at the root of aneuploidy—the uneven distribution of chromosomes that can occur during errors in cell division. HHMI Investigators Angelika Amon, Hongtao Yu, and others are discovering the molecular details behind how these errors can lead to unexpected consequences, including tumor formation. Understanding the basic mechanisms of cell division—how it works and what happens when the process goes awry—is a necessary step toward effective treatments for cancer and other diseases.

Also in this issue, you'll learn about our latest class of HHMI professors—top-tier scientists who receive support from HHMI to apply the same creativity in their classrooms as they do in their labs. We are excited to welcome this new group, which is notable for its diversity of ideas for innovating science education. Anne McNeil, a chemist at the University of Michigan, is one of our new HHMI professors. She plans to energize her school's introductory organic chemistry lab by creating real-world lab projects, such as having students transform used vegetable oil from restaurants into biodiesel fuel for local farmers. At Boston University, bioengineer Muhammad Zaman makes abstract problems concrete for students by asking them to solve global health challenges. Instead of measuring stresses on a beam, for example, students might calculate the stress on a pair of crutches for a disabled child—a real problem in Zambia, where disabilities are common.

These dynamic approaches—in the laboratory and in the classroom—are the hallmark of HHMI, and the essence of what we wanted to capture in our new logo. We hope its fresh, modern look will signal our desire to evolve and build momentum in our continuing commitment to move science forward.

Go to www.hhmi.org/bulletin/fall-2014 for a slideshow of Kohn's artwork and studio.

Artists in the Building

STEPPING OFF THE elevator on any floor of the Broad Institute in Cambridge, Massachusetts, visitors and scientists are greeted with art: vibrant, colorful curves; thick black lines; and green and orange spirals. The installation, called *Instance of a Dataset*, consists of square watercolor prints assembled in patterns on a wire grid. From top to bottom, it spans seven floors.

Created by the first Broad artist-in-residence, Daniel Kohn, it is the artistic fruit of the eight years he spent discussing, disagreeing, and collaborating with scientists at the Broad Institute.

Kohn sees his collection of paintings as a metaphor for what he observed scientists doing in the lab: trying to make meaning by manipulating and assembling banks of data.

HHMI Investigator Todd Golub launched the Broad Artist-in-Residence Program after viewing a Kohn painting at the Ute Stebich Gallery, in Lenox, Massachusetts. It seemed to speak of the current state of science: some areas are known in great detail, and others remain very much a mystery. Golub and Kohn started a conversation about the similarities between art and science.

From their talks, an idea was born: Kohn would "hang out" at the Broad—initially in an unfunded, informal way—and see what art he created after interacting with scientists. After three years, Golub formalized the artist-in-residence program and converted one of the lab bays into a work space for Kohn. The artist painted alongside the scientists as they worked with test tubes and gene sequencers.

"I cleared out some lab tables, brought in some plywood, and worked in watercolors, pencil, and charcoal," Kohn says. His usual oil paints and turpentine were too flammable for the lab.

The result of the residency was Kohn's seven-story installation. He also designed a digital app called "Assembly Space" so users could arrange the squares into whatever patterns they desired, save and share them, and even build off others' assemblies. When he moved the squares on his computer, he found they created a secondary order that reminded him of the way scientists work with data.

Art and science are much closer than they might at first appear, says Golub, chief scientific officer at the Broad Institute of the Massachusetts Institute of Technology and Harvard University. Rather than sitting at either end of a subjective-objective spectrum, both are, ultimately, human attempts to describe, understand, and represent the world.

"I think some of the most exciting advances in science amount to looking at an ancient problem in a new way," Golub says. "It seems to me that's what artists do: they reflect on what's happening in the world through a lens that allows both artist and viewer to see an old problem from a fresh perspective."

Kohn agrees, "They are both knowledge-generating fields, and once you look at it that way, you see they are on parallel tracks, not opposite tracks."

Since Kohn's residency, two other artists have spent months-long residencies at the Broad, creating works inspired by their conversations with scientists. Sculptor Maskull Lasserre is there now.

From the artists, Golub has learned to keep reinventing his approach as science evolves. He's also reminded that what scientists think are foundational truths are often just assumptions worth revisiting. "The point is for artists and scientists to provoke each other in new directions," Golub says.

–Lauren Arcuri Ware

Shout

To see a movie of Cohen's flashing cells, go to www.hhmi.org/bulletin/fall-2014.

Lessons from Liberia

WHEN ADAM COHEN was a high school student in 1994, he noticed his science club advisor collecting pens and pencils dropped in the hallways. Curious, he asked why. Asumana Jabateh Randolph replied that he sent them to nieces and nephews back in Liberia, where civil war made everything scarce. As a sophomore at New York's Hunter College High School, Cohen knew nothing about Liberia other than "that such a country existed." When he asked Randolph if he could visit Liberia, Randolph said no—too dangerous.

In 2009, Cohen asked again. By then, he'd earned physics doctorates at the University of Cambridge and Stanford University, been chosen by *MIT Technology Review* as a top innovator under age 35, and was teaching at Harvard University. This time, Randolph said yes.

That summer Cohen, accompanied by his friend Benjamin Rapoport who was an MD/PhD student and fellow Hunter grad, went to the West African country to mentor science teachers. Fourteen years of intermittent war had destroyed most Liberian schools. "The question was, how do you re-prime the education pump?" recalls Cohen.

He and Rapoport began by teaching the germ theory of disease. They fashioned Petri dishes by cutting the bottoms from water bottles and filling them with gelatin scavenged from stew pots. They showed local teachers that students could culture microorganisms from their fingers in the gelatin and then compare cultures from washed and unwashed hands.

To teach math, the two worked out low-tech experiments, "things you could do with no electricity, no running water—just your body, and counting." For instance, children measured their heart rates before and after jumping jacks. Cohen remembers two children so weak from malnutrition they couldn't jump. "That was quite an eye opener," he says. The men added nutrition to their curriculum.

Lessons on electricity came after they heard that someone had fried the nation's only x-ray machine by connecting it to the wrong generator. They taught teachers and students to build batteries from limes, iron nails, and copper wire. "You'd feel a little jolt if you touched the electrodes to your tongue," Cohen recalls. "It was fun." In 2010, the two men returned to lead a workshop for science teachers at the University of Liberia in Monrovia.

Since then, Cohen's research has ramped up, and he hasn't been able to visit Liberia again. An HHMI investigator at Harvard since 2013, Cohen develops tools to study molecules and cells; for example, his group devised a technique to convert electrical impulses in cells into flashes of light. The flashes allow scientists to visualize how drugs affect the cells, creating "a clinical trial in a dish."

The scarcity he saw in Liberia reminds Cohen to appreciate his own circumstances. He remembers that, when he visited in 2009, the average Liberian survived on $300 a year, while "we'll drop 300 bucks for a little mirror without thinking about it," he says. "I'm more conscious, of course, of how fortunate we are here."

Cohen asks his students to consider how science and engineering might remedy such inequities. "Sometimes there's a misperception that to make a difference, you have to go into activism, or law, or politics. I try to show them that good engineering and good technical approaches will not always suffice to fix problems like the ones people face in Liberia, but they can make a big difference." –*Cathy Shufro*

Liberian science students learned the importance of collecting data.

Adam Cohen

A Twist of Fate

A change in one regulatory gene determines hair color but leaves other important functions intact.

BLOND HAIR HAS gone in and out of style in Western societies for thousands of years. The heroes and gods of Greek mythology were often graced with golden tresses as a symbol of youth and beauty. In ancient Rome, light-haired women dyed their hair dark to stay in vogue. Through changing fashions and shifting cultural perceptions, the biological basis of hair color has remained poorly understood. Now, research that began with a little fish called the three-spined stickleback has helped answer a long-standing question about human appearance: what gives some people blond hair and others brown?

Sticklebacks have a lot of stories to tell about evolutionary biology. The fish have been adapting to freshwater habitats ever since their ocean-dwelling ancestors found themselves stranded in newly formed lakes and streams at the end of the last ice age. Their physical and genetic variations provide HHMI Investigator David Kingsley with clues about how organisms adapt to changing environments. Because evolution makes repeated use of the same genetic tools, following clues from the fish has sometimes led Kingsley's research out of stickleback-inhabited waters and into the genomes of other species.

In 2007, Kingsley's team at Stanford University discovered that changes affecting a single stickleback gene had given rise to pigmentation changes that helped the fish blend into their surroundings, improving their odds of evading predators.

The gene, called *Kit ligand,* encodes a signaling molecule that helps create pigment-producing cells. Having seen that the gene was used over and over again whenever sticklebacks evolved new skin colors, Kingsley wondered if similar changes might have altered pigmentation in other species.

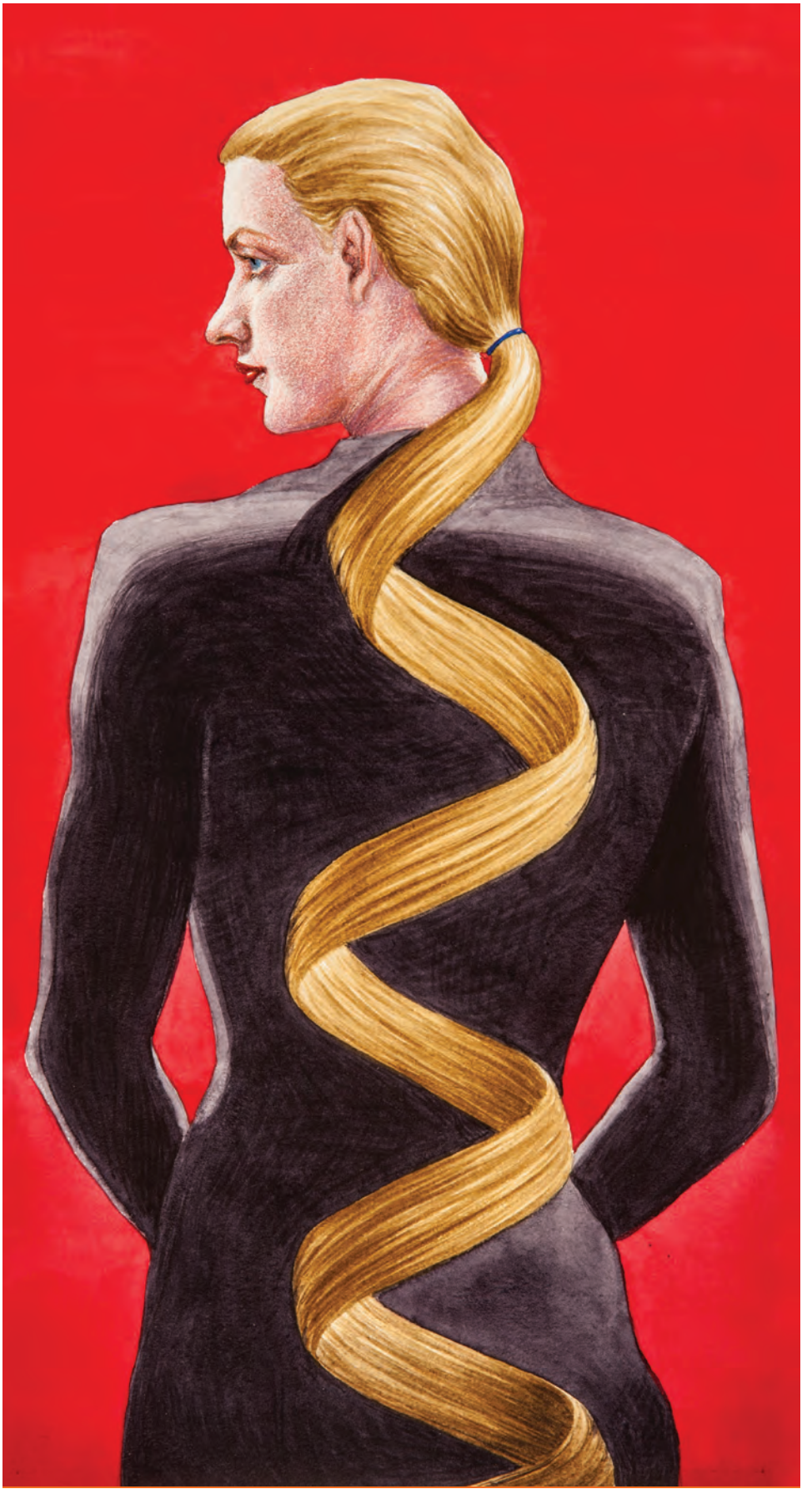
His team soon showed that different versions of *Kit ligand* were associated with variations in human skin color. Around that time, another group's genetic analysis of Northern Europeans linked a region of DNA near the human *Kit ligand* gene to blond hair color. These changes did not alter the *Kit ligand* gene directly, however. Instead, in both fish and humans, the alterations were in regions outside the protein-coding gene sequence, where regulatory elements that influence gene activity often lie. "The key marker that's associated with blond hair color in Northern Europeans is 350,000 bases away from the gene," Kingsley says. Thus, a regulatory mutation was likely responsible for changing pigment in fish and in humans—consistent with an emerging pattern of evolution-driving alterations that Kingsley has observed throughout his stickleback research.

But the *Kit ligand* gene does much more than promote pigment production. Kit ligand is one of the most important signaling molecules in vertebrate development. It helps guide formation of blood cells and sperm and egg progenitor cells, in addition to pigment cells. Kingsley wanted to know how a modification to the DNA surrounding *Kit ligand* could drive common changes in coloration without compromising the protein's other crucial functions.

Catherine Guenther, a research specialist in Kingsley's lab, pinpointed a snippet in human DNA near *Kit ligand* that affected hair follicle function. On closer examination, the team realized that, in Northern Europeans, a single letter of genetic code in this region differed between blonds and brunettes. Swapping out that letter converted the regulatory region from the brunette sequence to the blond sequence.

Placing the gene under the control of the "blond" switch reduced the gene's activity in cultured human cells by about 20 percent compared to the "brunette" switch. Although the change was small, Kingsley and Guenther suspected they had identified the critical point in the DNA sequence. They tested that idea by engineering mice with a *Kit ligand* gene under the control of the human brunette or the blond hair enhancer, so that a pair of mice differed only by the single letter in the hair follicle switch.

The otherwise identical mice were easy to tell apart: the animal carrying the blond version of the switch had markedly paler fur. "Sure enough, that one base pair is enough to lighten the hair color of the animals," Kingsley says. "The genetic mechanism that



Ruth Marten

controls blond hair doesn't alter the biology of any other part of the body. It's a trait that's skin deep, and only skin deep." He and his colleagues reported on the regulatory switch in the July 2014 issue of *Nature Genetics*.

The *Kit ligand* regulatory switch is not the only genetic element responsible for blond hair in humans, however. A few other genetic associations have been tracked down to particular mutations, but actual DNA sequence changes responsible for many human traits remain poorly understood, in part because subtle regulatory adjustments are difficult to identify. "A little up or a little down next to key genes—rather than on or off—is enough to produce different traits," Kingsley says. "The trick is, which switches have changed to produce which trait?"

Kingsley's team is searching for other potential regulators of *Kit ligand*, which they suspect might also regulate the gene's other functions with similar precision. But he hasn't forgotten about his favorite fish. "We're still using the stickleback to identify how general principles of evolution work," he says. "The lessons we learn from the fish turn out to apply to lots of other organisms, including ourselves." *–Jennifer Michalowski*

The Silencer: MicroRNA

Tiny RNAs help plants thrive by stifling other RNAs. Where they do their work and how they avoid destruction is becoming clearer.

AN UNUSUAL *ARABIDOPSIS* plant with dark, curly leaves and clusters of tinier-than-normal flowers seeded Xuemei Chen's interest in small strands of RNA that do big things. Only 20 to 24 nucleotides long, microRNAs make an outsized difference in how plants develop, says Chen, an HHMI–Gordon and Betty Moore Foundation investigator at the University of California, Riverside.

"MicroRNAs are really short, and they don't encode any protein," explains Chen as she prepares a cup of herbal tea for a visitor. "Instead, they regulate the fate of messenger RNAs." MicroRNAs find and turn off specific messenger RNAs (mRNAs) to fine-tune gene expression.

MicroRNAs were considered an "oddity" when first discovered in worms in the 1990s, says Chen. Hers was one of three laboratories to determine, in 2002, that plants have them too. Her strange-looking *Arabidopsis* had a mutation in a gene, *HEN1*, which, it turned out, the plant needed to produce all microRNAs. Chen's postdoc, Wonkeun Park, showed that the *HEN1* mutants had lower levels of microRNAs than normal plants.

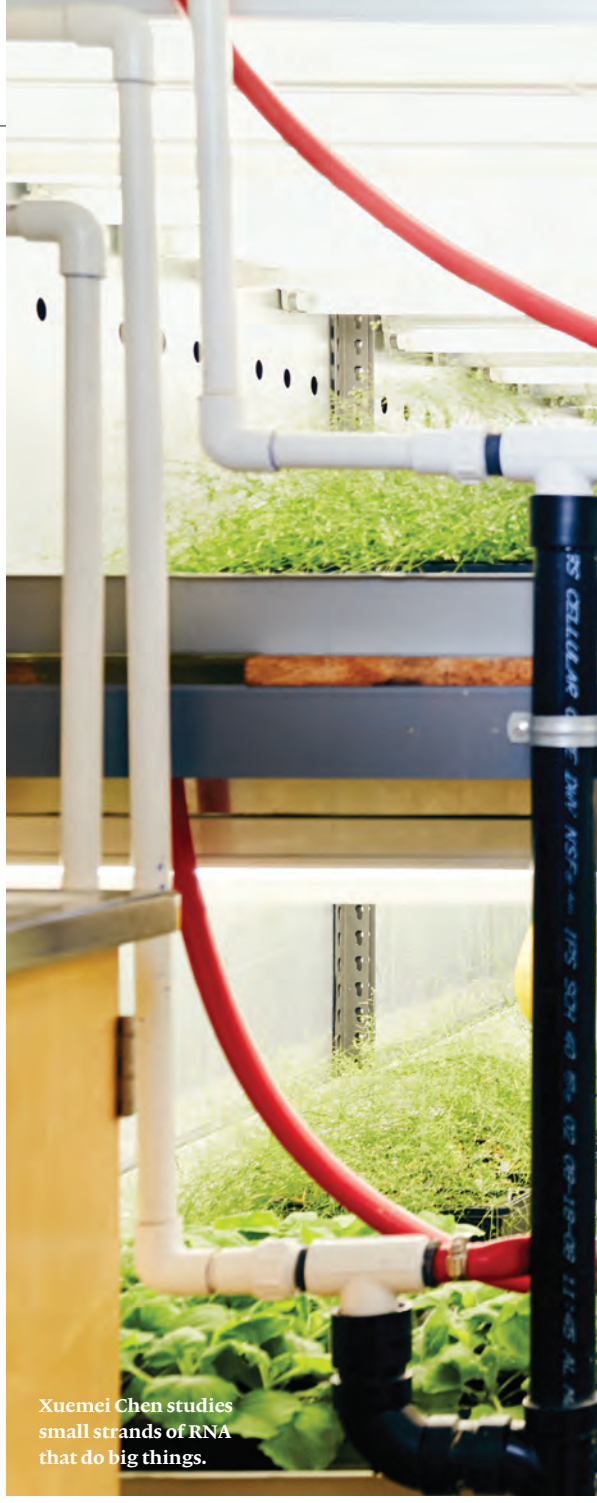
"When he showed me [the data] I thought, wow, hallelujah," recalls Chen. The *HEN1* mutants were malformed because many genes, missing their corresponding microRNAs, were out of whack. Researchers were surprised that such teeny bits of RNA, which they hadn't even known existed in plants, were so crucial to the organism's shape.

Chen spent the next decade studying how microRNAs are made, and she recently turned her attention to their degradation and where in the cell they do their work. After its synthesis in the nucleus, the precursor microRNA matures as enzymes cut out unneeded parts. The first trimming steps take place in the nucleus; then the microRNA exits to the cell's main compartment (the cytoplasm) and gets its finishing touches, including the addition of small chemical tags attached by enzymes like HEN1. Ready to go, the finished microRNA teams up with a group of proteins to find its target mRNA, which it identifies by a nucleotide sequence that matches its own. The microRNA and its protein partners quash production of the protein encoded by the mRNA, either by blocking translation or by destroying the mRNA.

Sometimes a plant wants to get rid of a microRNA so it can keep the corresponding mRNAs around. The fate of the microRNA comes down to two of those little chemical tags: the methyl group added by HEN1 and another tag called uridine. An enzyme called HESO1 decorates the microRNA with a chain of uridines, according to a paper Chen's team published in *Current Biology* in 2012. Each tag is a sign to the cell: the methyl says, "Keep me," and the uridines say, "Destroy me."

For a while, Chen was puzzled as to why microRNAs needed a "Keep me" methyl group; wasn't the absence of a "Destroy me" uridine tag sufficient? She reported the reason in the April 29, 2014, issue of the *Proceedings of the National Academy of Sciences*. HESO1 could, potentially, add the same "Destroy me" signal to the mRNAs, which sit right next to the microRNAs in the protein complex. The only way HESO1 can tell the difference between mRNAs and microRNAs is the methyl group. The methyl is the microRNA's protective gear: it prevents HESO1 from adding uridines, thereby warding off the microRNA's destruction.

Chen's also been looking at where in the cell microRNAs do their mRNA silencing. Scientists presumed that microRNAs blocked mRNAs floating free within the cell's watery cytoplasm, but few had actually checked. So Chen and her colleagues used fluorescent proteins to label some of the



Xuemei Chen studies small strands of RNA that do big things.

Emily Shur

"I hope the entire RNA silencing field will pay attention to the membrane connection."
—XUEMEI CHEN

proteins that participate in mRNA silencing. Under their microscopes, they saw the fluorescent green and yellow signals in the cell's endoplasmic reticulum—a series of membrane tubules involved in protein synthesis. That does not necessarily rule out RNA silencing in the cell interior, Chen reported in *Cell* in 2013; it just shows that the endoplasmic reticulum is one site where it definitely happens.

This finding has important ramifications, Chen says. Because researchers assumed that RNA silencing took place outside organelles, they have often done their experiments in test tubes with no membranes present. That could be a mistake, Chen says, since it doesn't match the natural environment of RNA silencing. "I hope the entire RNA silencing field will pay attention to the membrane connection," she says.

Chen plans to learn as much as she can about these controlling bits of RNA. Because microRNAs are important in animals as well as plants, Chen's work could have far-reaching implications. Scientists already know that microRNAs participate in some human diseases, such as cancer.

"At the molecular level, people are not that different from *Arabidopsis*," Chen says.
–Amber Dance

Bench Report

A Phosphate Fix

An ancient bacterium provides the key to a novel plant fertilization and weed control system.

IF YOU HOP INTO a car in the border town of Eagle Pass, Texas, and drive south for four hours, past stunted mesquite and blinding white gypsum dunes, you'll reach an isolated corner of the Chihuahua Desert called Cuatro Ciénegas, or Four Marshes. It's not your typical desert. Nestled among the white dunes is an oasis of wildlife centered around a series of pools whose hues of blue and green appear in stark contrast to the monochromatic desert sand.

Fed by underground springs percolating up through the desert floor, the pools, or pozas, are home to creatures found nowhere else in the world. Groups of grass shrimp populate zones rich with algae and schools of inch-long pupfish thrive in the hot, salty water. HHMI Senior International Research Scholar Luis Herrera-Estrella is most interested in *Pseudomonas stutzeri* WM88, a bacterium that may hold a key to plant survival, as the world's easily accessible phosphorus supply runs dry.

Herrera-Estrella and his lab team have managed to tap into the bacterium's ability to thrive in the pools, where phosphate—a salt form of phosphorus that occurs in natural environments—is rare.

The desert pools of Cuatro Ciénegas are home to many unique organisms, including bacteria that thrive in low phosphate conditions.

MiguelMalo

Plants need phosphorus. It's an essential component of their DNA. Most plants obtain phosphorus from phosphate in the soil, but nearly 70 percent of the world's soil is phosphate deficient, so farmers must use a lot of fertilizer to help their crops grow. And the phosphorus supply is shrinking.

"Phosphorus is a non-renewable resource," explains Herrera-Estrella, a plant biologist at the Center for Research and Advanced Studies of the National Polytechnic Institute in Irapuato, Mexico. "The planet has a certain amount of phosphorus, and we are using it very rapidly. We are consuming about 40 to 50 million tons per year." At this same rate, phosphorus stores will be depleted and unavailable for agriculture and industrial use in the next 70 to 200 years, according to estimates.

Phosphorus is the seventh most abundant element in Earth's crust, but its chemical properties are its downfall. It is highly reactive with soil, quickly forming insoluble compounds that plants can't use. As a result, as little as 20 to 30 percent of the phosphate applied as fertilizer is actually taken up by cultivated plants. The rest ends up as agricultural runoff, eventually making its way to rivers and oceans where it is absorbed by algae, resulting in toxic algal blooms.

Phosphate is also in short supply in the soil because every organism living there needs it to grow.

"Microbes, weeds, fungi, and crops all compete for phosphorus," says Herrera-Estrella. He spent 15 years trying to engineer crops that use less of the resource by looking at how plants adapt to low-phosphate conditions. "We've had some advances but nothing that could really improve efficiency of phosphorus use," he says. "So we went to a very radical approach. We decided to search for organisms that use other chemical forms of phosphorus."

This search ended at the pools of Cuatro Ciénegas. Scientists believe the pools are relics of an ancient sea that contained lots of dissolved oxygen but not a lot of phosphate. To survive in the pools, organisms evolved to use alternative ways of acquiring phosphate. *P. stutzeri* WM88 did this with an enzyme called phosphite oxidoreductase (ptxD), which converts phosphite—abundant in the pools—to phosphate by adding an oxygen molecule.

To see if they could encourage plants to use phosphite to meet their phosphate needs, Damar López-Arredondo, then a graduate student in Herrera-Estrella's lab, inserted the *ptxD* gene into the genome of *Arabidopsis*, a model plant commonly used in research labs. Herrera-Estrella is no stranger to adding genes to plants. He was one of the first people to make a transgenic plant in the early 1980s, and he's been using that knowledge to improve agricultural crops, especially the ones in his native Mexico.

"Our first results were amazing," says López-Arredondo. Normal phosphate-using plants died under the same conditions in which the transgenic *Arabidopsis* thrived. Moreover, the transgenic plants needed half the normal amount of phosphorus fertilizer, when applied as phosphite, to achieve maximum yield. And phosphite's chemical properties are ideal for fertilizer—it is highly soluble and not very reactive with soil components—two attributes that ensure most of it is taken up by the transgenic plants rather than ending up as agricultural runoff. As a bonus, weeds and microbes can't use phosphite, so they don't compete for the molecule and, therefore, the system reduces the need for herbicide.

Tests showed that phosphite levels in the transgenic plants were minimal, suggesting that most, if not all, the phosphite taken up by the plants was indeed converted to phosphate. The scientists published their findings in the September 2012 issue of *Nature Biotechnology*.

Herrera-Estrella is excited about the potential of the team's discovery, pointing out that a reduction in fertilizer and herbicide use for food production could have a positive ecological impact and would help produce food less contaminated by agrochemicals.

"The outcome of what Luis and his colleagues have done is nothing short of fantastic," says HHMI–Gordon and Betty Moore Foundation Investigator Jeff Dangl, a plant biologist at the University of North Carolina at Chapel Hill. "One of the things that limit corn growth in Mexico and Central America is phosphate-depleted soils. Now you have the ability to add phosphite to those soils and to make transgenic corn that can use that phosphite. This increases the overall fertility of the system and allows you to grow more corn."

Herrera-Estrella and López-Arredondo have formed a company called StelaGenomics to develop their system and have started field testing the *ptxD* gene in corn and soybeans. They also have a small grant from the Bill & Melinda Gates Foundation to develop the technology for corn strains that grow in Africa. Their plan is to make the transgenic system available to everyone.

"I am convinced that the phosphite technology has great potential and could promote many changes in agriculture worldwide," says López-Arredondo. "I want to be part of those changes."

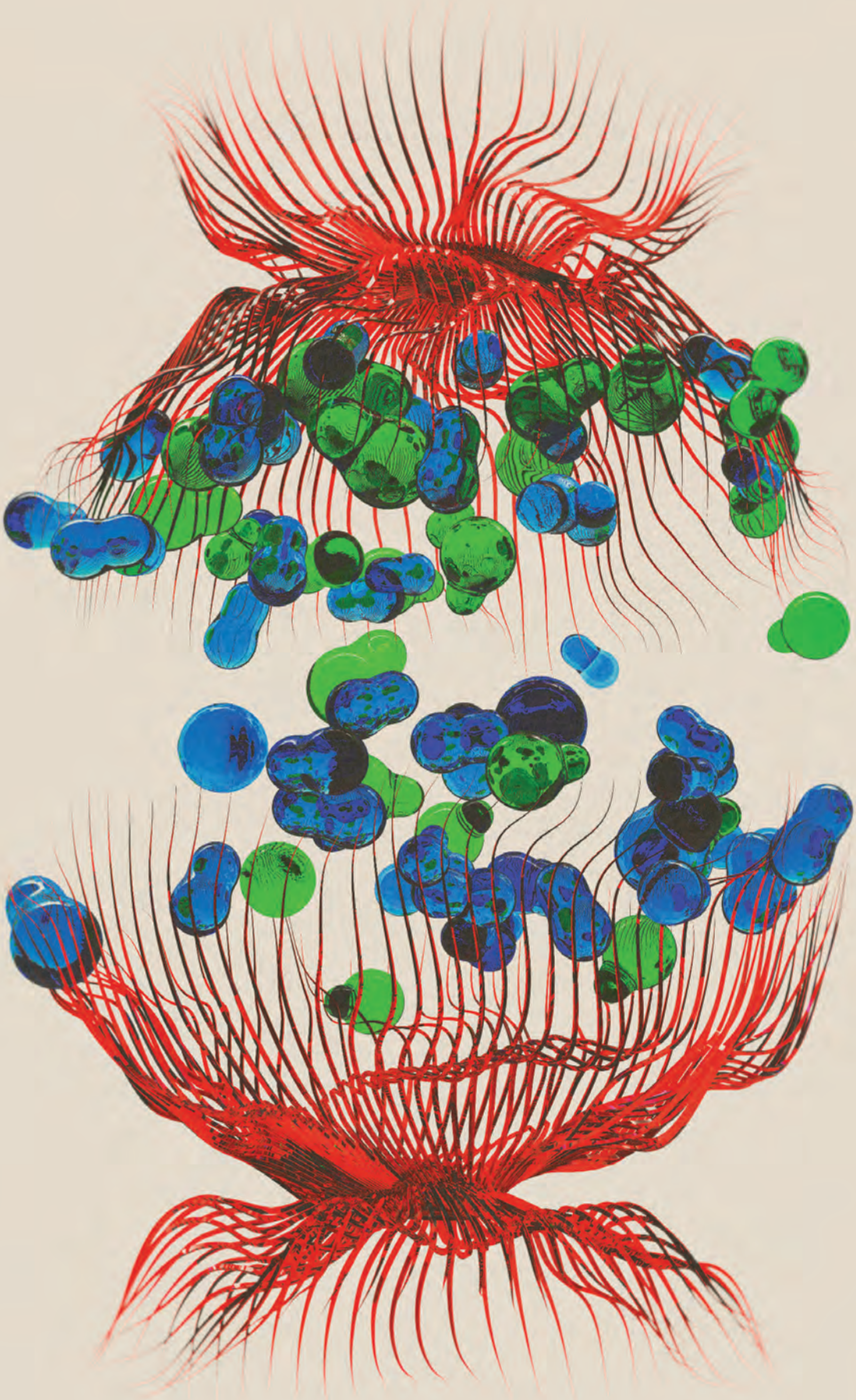
–Nicole Kresge

Errors in Division

When cells divide, chromosomes aren't always doled out equally. The consequences can be dire.

BY MEGAN SCUDELLARI

ILLUSTRATION BY ATELIER OLSCHINSKY



Angelika Amon has witnessed plenty of cell division errors in her career as a yeast geneticist. In yeast, the process of meiosis—where germ cells divide to form reproductive gametes—is error prone. As cells divide, thread-like spindle fibers are supposed to pull stubby chromosome pairs apart and send the two chromosomes to opposite ends of the cell. Sometimes, however, a pair of chromosomes is mistakenly delivered to a single side. After the cytoplasm divides, the resulting two daughter cells are aneuploid: one carries an extra chromosome; the other is missing a chromosome.

Sitting at a microscope to examine a set of aneuploid cells in her lab at the Massachusetts Institute of Technology (MIT), Amon knew the cells would be sickly. Aneuploid yeast rarely replicate; they often die. That's because organisms—whether they have one set of chromosomes (haploid, like some yeast), two (diploid, like mammals), or 12 (dodecaploid, like the Uganda clawed frog)—rely on balanced genomes. An equal number of chromosomes assures a balanced ratio of gene products. When that balance is out of whack—when a nucleus has one or more extra or missing chromosomes—the cell almost always fails to develop or function properly.

Almost always. Cancer cells, which are overwhelmingly aneuploid, are an exception. They thrive and divide with a fury. The contradiction nagged Amon, an HHMI investigator, for years. How could aneuploidy—the kiss of death for most cells—be a hallmark in those cells with an unparalleled ability to proliferate? It didn't make sense.

What was worse was that, outside of Down syndrome (a well-studied genetic disorder caused by an extra chromosome 21), aneuploidy was a mystery. Despite the prevalence of aneuploidy in cancer cells—more than 90 percent of solid tumors and about 75 percent of blood cancers display it—scientists had little understanding of how aneuploidy affects the physiology of a cell.

"It always bugged me," says Amon. "So I decided to look into it." Starting in 2002, Amon set out to determine the cellular impact of having an abnormal number of chromosomes and to resolve the aneuploidy paradox. Before long, she had a lot of company.

Today, a roster of experienced cancer researchers and molecular biologists is tackling aneuploidy's effect on cells and its role in cancer. Their efforts are not purely academic: aneuploidy could be a useful target for new cancer drugs.

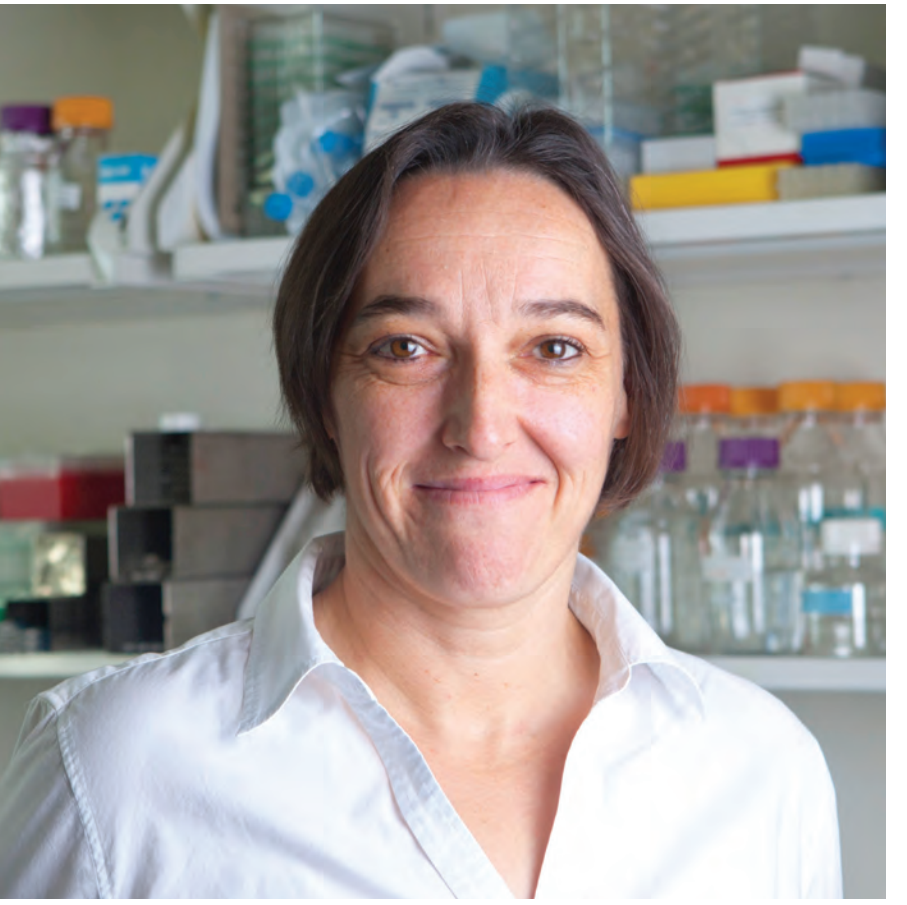
Leaning forward in a chair in her fifth-story office, Amon props her elbows atop a table, firmly clasps her hands, and declares, "I want to identify genetic or even chemical compounds that kill aneuploid cells preferentially." Then, her voice growing soft, Amon describes watching her younger sister with breast cancer persevere through numerous rounds of treatment with Taxol, a common anti-cancer drug. "It's brutal. If we could combine potential aneuploidy-selective compounds with Taxol, we could be more effective and lower the dose of Taxol. We could make the lives of people with cancer so much better."

Extra Gain, Extra Pain

Amon's first foray into aneuploidy was a shot in the dark. "I had a talented technician named Monica Boselli. She and I used to do crazy experiments all the time," says Amon. In 2002, she asked Boselli to make a few aneuploid cell lines so they could get a good look at them—easier said than done. First, Boselli learned an arcane chromosome transfer strategy using molecular markers to select and move individual chromosomes from one yeast cell to another. She created 13 strains of haploid yeast, each with one or two extra chromosomes. Then, Boselli closely monitored the transplanted chromosomes, as yeast have a talent for ridding themselves of extraneous genetic material.

Boselli's efforts worked, and she and Amon, along with Amon's then postdoc Eduardo Torres, immediately observed that the extra chromosome was not dormant. In every case, the chromosome was active: hundreds of genes were being expressed from its DNA, and, Amon later confirmed, those gene transcripts were translated into proteins.

Next, Amon examined the appearance and activity of the aneuploid yeast. All 13 aneuploid cell lines, regardless of which of the yeast's 16 chromosomes was added as the extra, shared common traits. They all had defective cell cycles: they multiplied more slowly—some couldn't even form colonies—and many were 10-20 minutes slower to initiate cell cycle division than their normal, wild-type counterparts. This confirmed a common assumption that aneuploidy reduces a cell's ability to reproduce normally. The yeast also exhibited increased glucose uptake and



Angelika Amon is searching for the link between aneuploidy and cancer.

sensitivity to growth conditions that hindered protein folding and the breakdown of proteins.

All in all, the findings suggested that aneuploid cells require extra energy for survival, and that they struggle to fold and degrade proteins. The protein degradation pathways appeared to be working at full tilt trying to rid the cell of unfolded and misfolded proteins and parts of proteins. The subunits of many protein complexes are encoded across multiple chromosomes, so an extra or missing chromosome will result in isolated subunits with no partners. In fact, work published this April in *Cell* by HHMI Investigator Jonathan Weissman, at the University of California, San Francisco, showed that healthy cells produce equal amounts of the proteins that function together in a complex. Thus, any change in those carefully maintained ratios is likely to cause problems in a cell.

"It was pretty obvious [aneuploid cells] had major issues in the protein quality control department," says Amon. She, Torres, and Boselli published the results in 2007. A few years later, Amon followed up with images of aneuploid yeast choked with clumps of fluorescently labeled protein aggregates shining like green warts in the cells.

Amon loves yeast: the smell of yeast, the pink and ivory colonies, the teeny bubble-like yeast spores. But after one too many colleagues insinuated that her aneuploidy findings were applicable only to yeast, Amon turned to mouse cells to determine if what they found in yeast was also true in mammals.

As she expected, the mouse cells had cell cycle defects and stressed protein control pathways. "It was the same," says Amon of the mammalian work published in 2008 in *Science*. "Definitely the same." A paper published this year by Zuzana Storchova and colleagues at the Max Planck Institute of Biochemistry in Germany confirms Amon's findings, this time in human cells: aneuploid human cells, from a variety of sources, upregulate metabolic and protein degradation pathways.

"It was pretty obvious [aneuploidy cells] had major issues in the protein quality control department."

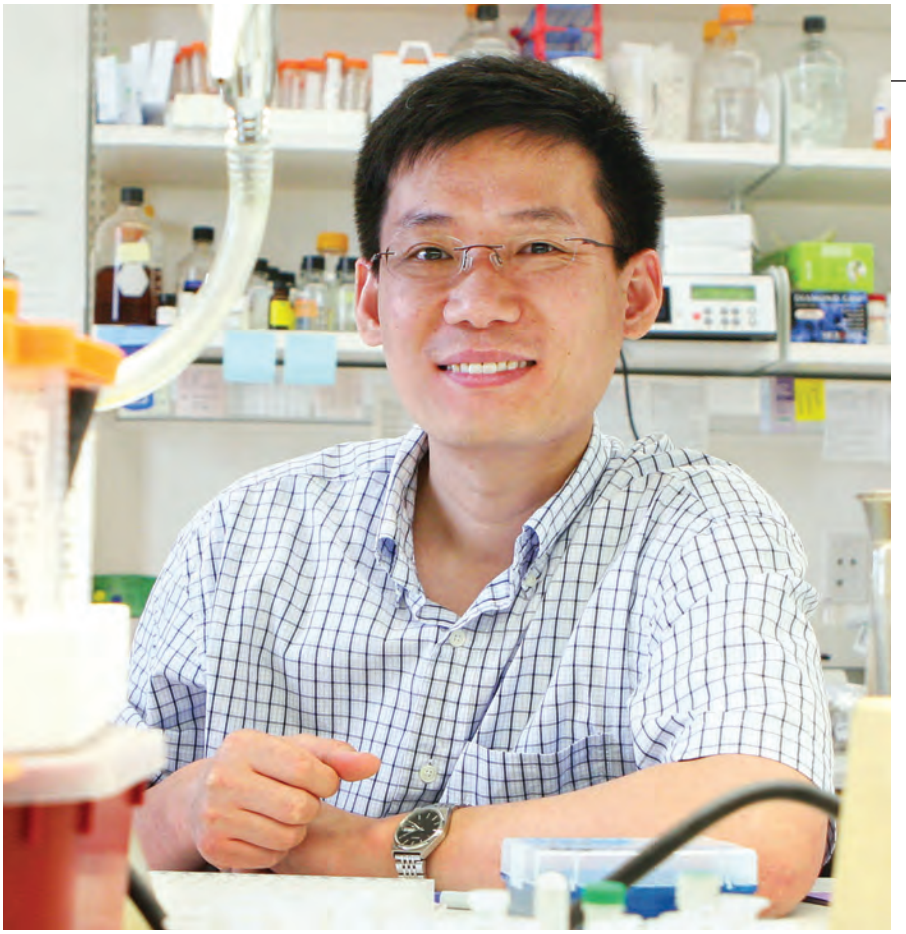
—ANGELIKA AMON

Tug of War

Three miles south and across the Charles River, David Pellman, also an HHMI investigator and yeast aficionado, was simultaneously trying to figure out how aneuploidy affects the function of cells and obtain more details about how it occurs in the first place.

In addition to an abnormal number of chromosomes, most aneuploid cells have an abnormal number of centrosomes–small organelles that control the position and action of chromosomes on spindle fibers during cell division. Healthy cells have just two centrosomes during mitosis–division of somatic, or non-germ, cells–but aneuploid cells often have three or four. In 2008, at the Dana-Farber Cancer Institute and Boston Children's Hospital, Pellman and colleagues began generating cell lines (a variety of mouse and human) differing only in centrosome number. At the time, it was well established that extra centrosomes generate aneuploidy, but the mechanism by which that occurred had not been directly observed.

Aynsley Floyd



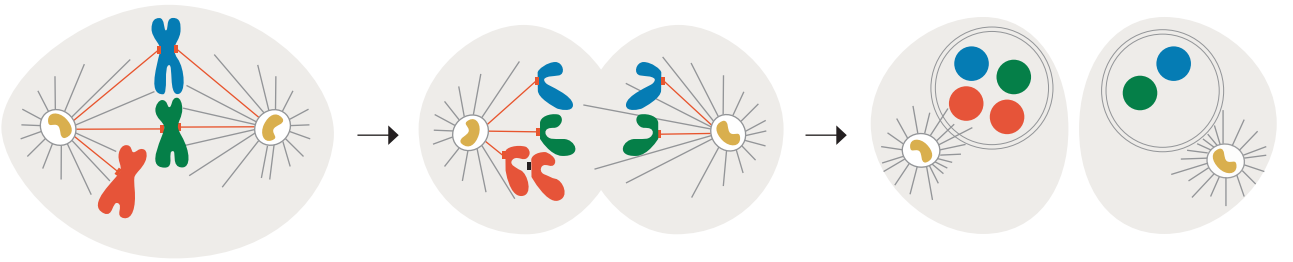
Hongtao Yu studies how subtle changes in spindle fiber proteins can cause chromosome mis-segregation.

Watching the cells by using a live imaging system, Pellman's team found that cells with extra centrosomes divide into two, just like normal cells, yet the extra centrosomes produce additional spindle fibers that pull chromosomes in the wrong directions. This tug of war can result in lagging chromosomes that don't make it to the correct side of the cell prior to division. The daughter cells, therefore, are aneuploid. "It was an unexpected mechanism," says Pellman, but one that confirmed that centrosomes are active participants in chromosome segregation errors that lead to aneuploidy.

Aneuploidy can also be caused by a weakened or damaged spindle checkpoint, the security system in the cell that ensures chromosomes are accurately separated, says Hongtao Yu, an HHMI investigator at the University of Texas Southwestern Medical Center in Dallas. A host of spindle checkpoint proteins, such as Mad2 and BubR1, monitor the attachment of spindle fibers to kinetochores, sticky protein hubs at the center of chromosomes. In the case of incorrect fiber-kinetochore attachments, checkpoint proteins bind and inhibit a protein complex that would activate the next stage of cell division.

Complete loss of the spindle checkpoint wholly kills cells, says Yu. But lesser defects, such as low levels or decreased activity of Mad2 or BubR1, result in irregular attachments, continued cell division, and chromosome mis-segregation. "Subtle changes of the

A Mitotic checkpoint defects



B Cohesion defect

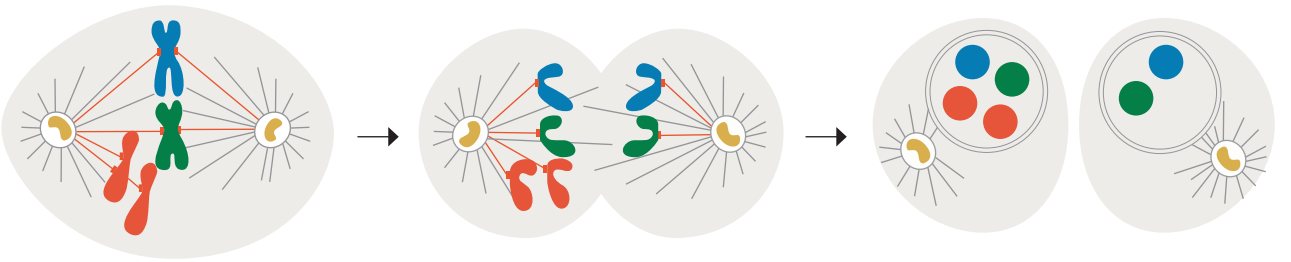


Photo: Amy Gutierrez

If extra chromosomes reduce cell viability, how and why do aneuploid cancer cells thrive?

spindle checkpoint system allow cells to live, but cause aneuploidy," says Yu.

Paradoxically, it turns out that too *much* of a spindle checkpoint protein can also cause aneuploidy. Overexpression of Mad2 in mouse cells causes aneuploidy, a finding published by Rocio Sotillo, an HHMI international early career scientist at the European Molecular Biology Laboratory in Monterotondo, Italy, in 2007. The excess protein initially arrests cells in the phase of the cell cycle when the chromosomes are lined up along the cell's equator. A few cells manage to "escape" that block, says Sotillo, and proceed with mitosis. But they overwhelmingly escape with baggage—extra or fewer chromosomes.

Other cell division defects and spindle checkpoint errors cause aneuploidy as well, and evidence from organisms such as *Drosophila* and plants reaffirms that the results of aneuploidy are slowed cell proliferation, sickness, and death. Unfortunately, these observations still failed to answer the question that nagged at Amon, Pellman, and others: if extra chromosomes reduce cell viability, how and why do aneuploid cancer cells thrive?

Elephant in the Room

In 1902, while observing the abnormal development of aneuploid cells in sea urchin embryos, German zoologist Theodor Boveri theorized that a tumor might develop from such a cell. Later scientists indeed found that most tumors are aneuploid, but many cast the finding aside as an oddity. For decades, the role of aneuploidy in cancer was largely ignored.

"If you look at old cancer reviews, they never put aneuploidy in there," says Stephen Elledge, a geneticist and HHMI investigator at Harvard Medical School. "It has always been the elephant in the room." That may be because, during the 1970s and 1980s, it was significantly harder to identify the cellular effects of a whole additional chromosome, as opposed to a single oncogene, Elledge suggests. "It just hurt people's heads."

With the advent of new imaging and sequencing tools beginning in the early 1990s, aneuploidy received renewed attention—but soon became stymied by controversy. Leading cancer researchers suggested aneuploidy was simply a by-product of cancer, an unimportant consequence. Others vehemently argued that it could be the sole cause of cancer. "There was a

As chromosomes are partitioned during cell division, errors can occur along several pathways, resulting in aneuploidy.

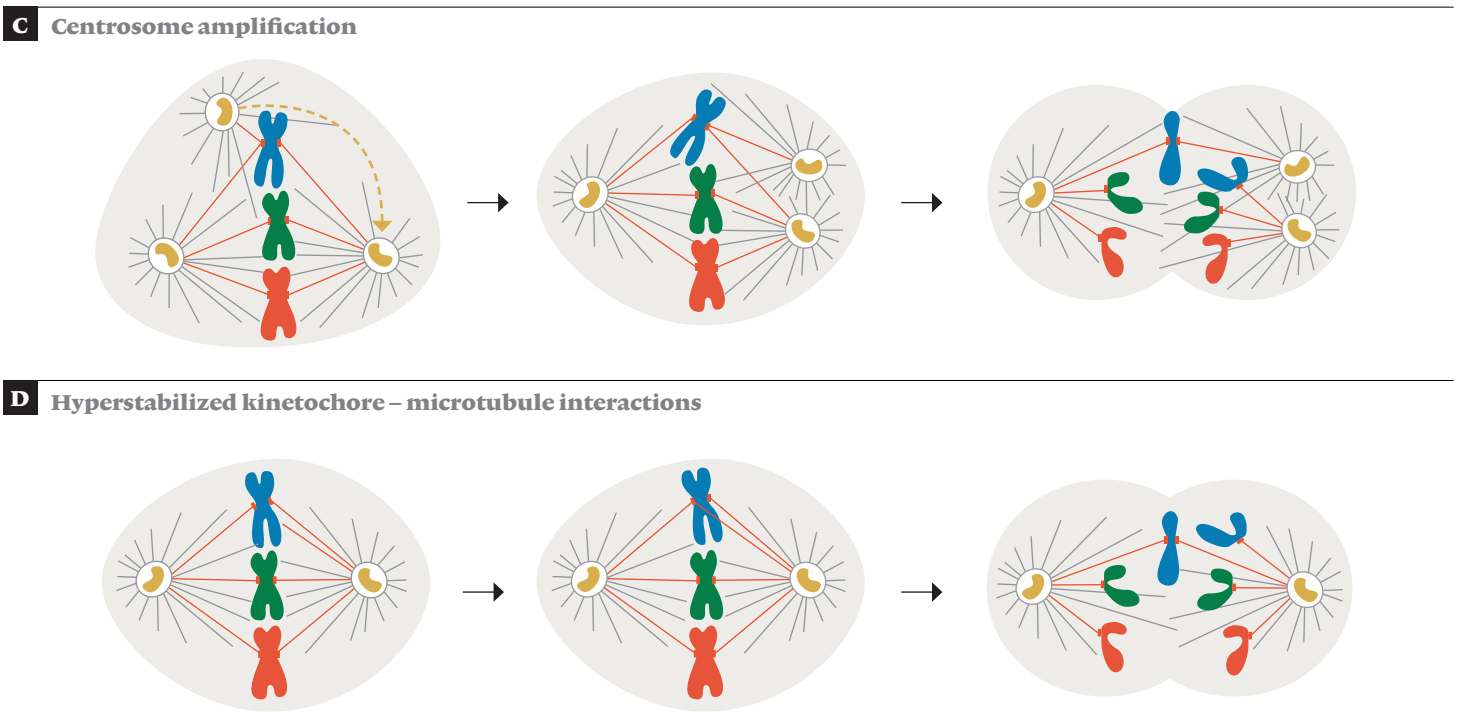


Diagram: Adapted from AJ Holland and DW Cleveland, *EMBO Reports* 13(6) pp 471-576, 2012

"We're at the point where there's pretty strong trust that aneuploidy is driving cancer."

—STEPHEN ELLEDGE

huge debate," says Pellman. But it didn't scare him away from the field.

Prior to working full time in the lab, Pellman was a pediatric oncologist. Like Amon, a view through a microscope drew him to the study of aneuploidy: over and over, he observed abnormal structures in the nucleus that indicated aneuploidy in the cells of his young cancer patients. "I spent a lot of time looking at these abnormal nuclear structures," says Pellman. "There was an obvious connection."

So he decided to put one aspect of Boveri's hypothesis—that whole genome duplication, which causes high rates of aneuploidy, might cause cancer—to the test. Pellman instructed one of his postdocs, Takeshi Fujiwara, to produce tetraploid (twice the normal chromosome number) mouse cells, which have a high rate of chromosome mis-segregation and thus rapidly become aneuploid. Then, Fujiwara was to inject those cells into mice. Although Pellman thought it was important to test the idea, he felt it was almost too simple, "too good to be true," for the tetraploid cells to cause cancer. Fujiwara's initial results showed that the cells indeed caused aggressive tumors in the mice. "It was what we were after, but it was nevertheless very surprising that it worked so well," Pellman recalls. The discovery provided strong evidence that tetraploidy, and the resulting aneuploidy, promotes tumor development.

Since then, Pellman's lab has been working to determine how aneuploidy might cause tumors. In 2012, his team showed that inside micronuclei—small membrane-bound bodies that partition extra chromosomes away from the cytoplasm—chromosomes are subject to extensive DNA damage. This suggests that one way aneuploidy causes cancer is the old-fashioned way: through mutations that activate cancer-causing genes or inactivate tumor suppressors. Additionally, Pellman's lab recently discovered evidence showing that extra centrosomes, independent of generating aneuploidy, can lead to the activation of Rac1, a protein involved in cancer cell signaling and tumor invasion (published June 5, 2014, in *Nature*).

More evidence is mounting that aneuploidy promotes cancer by altering oncogenes and tumor suppressors. Last year in *Cell*, Elledge and colleagues at Harvard reported that cancer genomes select for extra chromosomes that contain potent oncogenes, and select against extra chromosomes rich in tumor suppressors (see "The Method in Cancer's Madness," Spring 2014 *HHMI Bulletin*). At the Mayo Clinic in Minnesota, molecular biologist Jan van Deursen and colleagues have

Stressed-Out Cancer Cells: The Benefits of Aneuploidy

Aneuploidy—an abnormal number of chromosomes—appears to help a normal cell transform into a cancer cell. But not by giving it an edge to grow. Evidence suggests that aneuploidy actually slows cell division. So how exactly does aneuploidy benefit tumors?

Scientists have two main hypotheses. The first is that aneuploidy helps cancer cells adapt quickly under extreme pressure. In 2012, geneticist Yitzhak Pilpel and colleagues at the Weizmann Institute of Science in Israel tested this theory in yeast cells by exposing them to high heat. The yeast that acquired chromosome duplications—especially of chromosome III, which contains special proteins that aid in heat tolerance—survived better than yeast that did not. When Pilpel reduced the temperature back to normal for these chromosome III aneuploids, the cells quickly lost the extra copy of the chromosome during subsequent replication.

Interestingly, however, when Pilpel kept the aneuploids at a high temperature, they *also* lost the extra copy, but only after evolving a different, more efficient way to express the heat-tolerance proteins over time. Pilpel and his team concluded that having an extra chromosome is a "quick fix," but not a permanent solution, to deal with stress. That ability to quickly adapt would be a great benefit to cancer cells during metastasis. When a breast tumor cell spreads to the bone, for example, it must survive in a completely different environmental niche. "As the disease progresses, adaptation potential provided by aneuploidy could be very beneficial," says Angelika Amon, an HHMI investigator and yeast geneticist at MIT. The hypothesis has yet to be tested in cancer cells, however.

Another hypothesis is that aneuploidy promotes structural abnormalities known to cause cancer. In studies of yeast, Amon's team has shown that aneuploidy causes genomic instability—a high frequency of mutations in the genome, from small mutations of two to three nucleotides to larger structural changes. Amon assayed 13 aneuploid yeast strains in a series of tests for different types of genomic instability, such as increased mutation rates and increased rates of recombination. "It was really remarkable. Every aneuploid strain we looked at scored in at least one assay," says Amon, and most tested positive for multiple types of genomic changes. The finding suggests that aneuploidy, no matter which chromosome is duplicated, causes genomic instability. And that instability predisposes the cell to mutations that cause cancer.

Aneuploidy may help cancer cells adapt quickly to stress in the body and nudge cells toward mutations that directly promote tumorigenesis, according to this recent work. "But so far, all this work is done in [cultured] cells, and that's not good enough," says Amon. Her team and others are planning to test these two hypotheses in mouse models of aneuploidy. – M.S.

found that aneuploidy predisposes mice with only one working copy of *p53*, instead of a normal pair, to lose that copy of the suppressor gene and develop tumors.

Based on current understanding, aneuploidy appears to promote tumor production through multiple mechanisms, but not by increasing a cell's ability to multiply. That, at least, helps resolve the aneuploidy paradox. "We think [aneuploidy] offers tumor cells something other than proliferation, something else that is good for tumorigenesis," says Amon. (See sidebar, "Stressed-Out Cancer Cells: The Benefits of Aneuploidy.")

But does aneuploidy cause cancer on its own? Van Deursen's work suggests that it does not. For more than a decade, van Deursen has been engineering mice to produce low levels of individual spindle checkpoint proteins, including Bub1 and BubR1 (complete loss of such proteins is lethal to embryos). Some of the mice develop cancer, from lung cancer to lymphoma to liver tumors, but not all. What's more, van Deursen can't predict which checkpoint protein that he knocks down—and he has tried a dozen—will result in a tumor.

"If it were merely aneuploidy that drives malignant transformation, then we'd expect that all the mice would have cancers, and many cancers. But that really isn't the case," says van Deursen. "It's likely the answer is aneuploidy *plus* something else. So you will have two, three, or four independent, tumor-promoting activities."

Today, most researchers, including Amon, agree that oncogenes are the main drivers of cancer, and aneuploidy contributes variation and instability to the tumor cells. If oncogenes are the spark, aneuploidy is the kindling. "We're at the point where there's a pretty strong trust that aneuploidy is driving cancer," says Elledge. "The question is, how potent is it?"

Targeting Stress

Until that question is answered, most aneuploidy research remains focused on basic mechanisms. But a few inquisitive scientists are dipping their toes into translational research, looking for ways to target or exploit aneuploidy to preferentially kill cancer cells.

"Aneuploidy is definitely stressing the cells, and the cells must depend on stress support pathways more than normal cells do," says Elledge. "So if you can tinker with that, you can potentially make the cell vulnerable or kill it. This could certainly augment other therapies."

Some of Pellman's work suggests that targeting cells with too many centrosomes might be a way to selectively target cancer cells. Several drug companies are pursuing small molecule drugs to inhibit a specific motor protein that Pellman identified as essential for the survival of extra centrosome-containing cancer cells.

At UT Southwestern, Yu and colleagues recently completed an experiment in which they silenced each of the 20,000+ genes in human cancer cells, one by one, and then treated the resulting cells with Taxol. Their goal was to see which genes help cells avoid death by Taxol, which is believed to cause massive aneuploidy, and which genes promote Taxol-triggered death. Many of the genes they identified encode components of the spindle checkpoint, suggesting potential drug targets to help Taxol work better, says Yu. Those targets could lead to the kind of drugs Amon has long dreamed of, to improve the effectiveness of current chemotherapy regimens and reduce side effects.

Back at MIT, Amon's translational work is in full swing. In collaboration with a Harvard screening facility, Amon has been searching through libraries of compounds for chemicals that preferentially prevent aneuploid cells from multiplying. She has identified several. One of them is a chemical involved in the formation of lipids that appears to target highly aneuploid cells.

Amon's team found that by combining Taxol with the new compound at concentrations where each could kill 10 percent of cancer cells if given separately, the mixture was able to destroy cancer cells with an efficacy of 90 percent. "Now we're working to treat mouse models of cancer and determine the mechanism," she says. "We're really excited about it." ■

Stephen Elledge has found evidence that aneuploidy alters the balance of tumor suppressors and promoters.

Bizuayehu Tesfaye / AP © HHMI

Bold Experiments

The 2014 HHMI professors are bringing innovation from the lab into the classroom.

BY ERIN PETERSON

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DAVID R. MARCHANT

CHRISTOPHER D. IMPEY

ANNE J. MCNEIL

JOSEPH M. JEZ

UNIVERSITY RESEARCH SCIENTISTS are expected to be pioneers in their labs. A new group of HHMI professors will be meeting those same high expectations in the classroom.

The traditional systems of rewards and recognition and allocation of resources at research universities often encourage an imbalance: most science faculty members are far more focused on their work as research scientists than their work as educators.

"It has been a great, missed opportunity," says Sean B. Carroll, vice president for science education at HHMI. "Research universities attract some of the brightest young minds in the nation, and they are home to some of the best scientists. They offer a potentially superb environment for engaging students in both the classroom and the laboratory."

Since 2002, HHMI has been promoting a better balance between research and teaching by supporting some of the country's leading research scientists who also engage students in the classroom as HHMI professors. A total of forty scientists given HHMI professor grants have applied the same kind of creative approaches and rigorous measurement in their classrooms as they have in their labs. They have demonstrated that top scientists can be top educators, by expanding and enhancing student research opportunities, finding innovative ways to offer mentoring, and encouraging other faculty to engage in effective teaching.

Fifteen additional researchers were named HHMI professors in June. Each will receive a grant for $1 million over five years to continue to push science education forward through projects as varied as creative writing about science and group research projects via online courses.

With every approach, the professors strive to help students grapple with—and deeply internalize—authentic research and scientific thinking. "The HHMI professors push hard at the boundaries of science education. They raise the profile of the conversation about education," says HHMI senior program officer Sarah Simmons. "The new professors leverage their credible voices in the scientific community to pull together the educational and research sides of science."

Here are the stories of six of the new HHMI professors—top-tier researchers whose work ranges from biology and chemistry to geology and astronomy. Their work promises to bring the excitement of science into the classroom and fuel a new generation of STEM majors.

ANNE MCNEIL

University of Michigan

Project: Building meaningful labs—and crowdsourced data—into first-year organic chemistry.

Anne McNeil knows the alarming statistic that more than 60 percent of students who enter college with an interest in a STEM degree fail to earn one.

She was suspicious that her school's dry introductory organic chemistry laboratory, taken by 2,000 undergraduates at the University of Michigan each year, contributed to that failure rate. "The lab is really basic—things like titrations and separations—with essentially no organic chemistry," she says. "It's de-motivating for students." Unfortunately, it's an all too common introductory lab experience.

McNeil is committed to transforming her school's lab from loathed to loved, and that process will start with biodiesel. Students will use the fairly simple techniques of refluxing and separation to transform used vegetable oil from local restaurants into biodiesel for use by local farmers. The techniques are simple and the results are meaningful. And the students, she hopes, will be hooked.

The experience won't be a single paint-by-numbers lab. After following a standard "recipe," students will spend the next lab changing a variable—temperature, solvent, concentration—and hypothesizing how the change will affect the outcome. By adding their data to a shared spreadsheet, students will have access to a large dataset to make comparisons and draw conclusions.

"I want students' initial lab experiences to inspire them to pursue other research opportunities."

As part of her organic chemistry lab overhaul, McNeil plans to include an array of other experiments, such as labs in which students extract natural rubber from milkweed.

Concrete projects can boost students' enthusiasm for—and desire to continue in—science, she says. As a first-year student in 1996, McNeil's passion for science was propelled by a professor who drew parallels between abstract concepts, such as substitution reactions, and their real-world applications, such as the chemical weapon mustard gas. Today, McNeil's research group develops sensors that help contractors and inspectors check for harmful lead in paint at construction sites. These chemical tools, known as gelators, may someday be used to find explosives at airport checkpoints or enzymes involved in certain diseases.

With the new lab projects, McNeil hopes that her students will see that labs are about discovery and problem solving rather than learning abstract concepts. "I'm trying to replicate the research experience—within the constraints of the system—for as many people as I can," she says.

MUHAMMAD ZAMAN

Boston University

Project: Use real-world problems to help students understand global health issues in the context of biomedical engineering.

Muhammad Zaman believes it is not enough to give his students the tools to solve important global health problems. It's his responsibility, he says, to impress upon them the value of the work.

In his own research, Zaman and his colleagues have developed PharmaCheck, a technology that can quickly and cheaply detect counterfeit and expired antimalarial and antibiotic drugs, in part by revealing the concentration of active ingredients. *Scientific American* hailed the innovation as one of 10 "World Changing Ideas" in 2013.

"We want students to grapple with global problems that speak to their social consciousness."

Zaman wants to motivate students to develop similar practical global health solutions. He's developed a comprehensive program at Boston University to do that in different, and reinforcing, ways.

The first is an idea repository—a database of real-world problems that professors can contribute to and draw from to help make abstract concepts come alive for their students. Zaman cites a simple example from his own class: instead of having students calculate stresses on a beam, they calculate stresses on a wooden crutch for a disabled girl, or a metal crutch for a middle-aged man. "This is a real problem in Zambia, where disabilities are [common]," he says.

The second is bringing to the campus guest speakers who can discuss global health policy. Finally, he plans to send students to a biomedical engineering summer school at one of several schools in Africa to get firsthand experience with difficult global health problems.

The most important aspect, he says, is the integration of all of these components into a cohesive whole throughout the students' college careers. Students don't just tackle global health issues in a single course or summer. "We want ideas to be reinforced multiple times," Zaman says.

His end goal is far more profound than creating the world's best engineers. "My job is to make them better citizens of society," he says. "I want them to be people who are able to contribute to the society at large."

SUSAN MCCONNELL

Stanford University

Project: Developing and expanding courses that help students merge art and science.

Growing up, Susan McConnell imagined herself as the next Jane Goodall. Goodall's grand adventures studying chimpanzees in Tanzania—and her captivating storytelling—cracked open the joy of scientific research for the young McConnell.

After receiving her PhD from Harvard University, McConnell found her own way to pursue scientific success. As a neurobiologist, she studies how neurons in the developing cerebral cortex are produced, assigned specific characteristics, and wired together into functional circuits.

But even from her lab, McConnell felt the tug of Goodall's larger vision. Great science was a starting point. Even greater power came from sharing the research in ways that inspire others to pursue and support it. "[Scientists] can't just write to other scientists," she says. "We need to be able to communicate to the general public."

That idea served as the catalyst for two new classes at Stanford: "Personal Essay in Biology" and "Senior Reflection in Biology." Both courses allow students to bring an artistic sensibility to the science they study.

In the first course, students spend a term working with award-winning writer Andrew Todhunter to complete a personal, deeply researched scientific essay in the style of magazines such as *The New Yorker* or *National Geographic*. In the second, students use a visual medium of their choice—photography (McConnell's specialty), painting, or multimedia, for example—and spend a year working closely with faculty mentors in both science and the arts to create and polish their science-linked work for viewing in a campus gallery.

In pilot programs, one student wrote a gripping personal essay that combined research about the neurochemistry of mental illness and the story of her roommate's suicide. Another used sand animation to explore the impact of parasites in local water sources in Ghana; she shared a version of the project at a TEDx event and earned a standing ovation.

"We must present stories about science that are accessible, engaging, and informative."

McConnell says this twist on scientific thinking, through projects that she describes as "kind of 'out there' alternative models," has the potential to transform the way students think about the science they do and the way they share that work with others.

As an HHMI professor, McConnell plans to further develop and expand the popular programs, and add humanities students who are interested in using science as the foundation for their art. Communicating science in beautiful, accurate, and unexpected ways, she says, can help students wrestle with important problems.

TRACY JOHNSON

University of California, Los Angeles

Project: Develop a program that emphasizes mentorship and collaborative learning with a scalable, research-intensive course on RNA splicing as its capstone.

It's not easy for first-year biology students to picture the complex dance of cellular processes. That's why Tracy Johnson never relies on lectures as her sole teaching tool.

To help describe a classic experiment that demonstrated DNA's compact form within a cell, for example, she pulls students from their seats to have them represent the proteins central to this formation, uses yarn to represent the DNA, and then asks other students to play the enzymes that cut the DNA. "Doing it this way," she says, "led a whole new group of students to say, 'ah, I get it.' "

Participatory learning works, and that's why she's developing a new course that allows first-year students—drawn in part from high schools with sizeable populations of underrepresented minorities—to help her with her research. Johnson studies RNA splicing and how it is regulated.

During the year-long program, Johnson and about 25 students will work with *Saccharomyces cerevisiae*, yeast cells that have fast doubling times and important similarities to human cells. Students will perform open-ended genetic screens to help identify molecules that play a role in RNA splicing. The work will include in-depth faculty and peer mentoring—elements that help science stick, says Johnson. When students work together on these projects, they learn more than just the mechanics of the project. "They learn how to articulate and defend their ideas, and how to work collaboratively," Johnson says.

"Real science is collaborative."

Using online data integration and analysis tools, students will connect the different data to develop testable models that describe the mechanisms of RNA splicing. The students will present their findings before an audience of experts. If the program goes well, Johnson hopes to share the module with other schools interested in having their students do research during their freshman year. For now, she wants to make sure that her students know that they're doing more than just absorbing knowledge: they're creating it. "Great lab courses offer authentic research experiences," she says. "Students generate data that can make an impact."

DAVID MARCHANT

Boston University

Project: To bring a few undergraduate students to Antarctica to study its landscapes—and to give thousands more a backstage pass to the work.

Geologist David Marchant has been studying climate change in Antarctica for decades, but until now, he's never been able to bring a team of undergraduate researchers along to help—that opportunity has typically been reserved for graduate students and postdocs.

But with the help of the HHMI professors grant, Marchant will take up to three undergraduates to Antarctica each year. "I'm taking undergraduates because I want to invest in them," he says.

"The success of the entire expedition might lie in their hands."

Students may initially be attracted to the sense of swashbuckling adventure that comes with studying Antarctica's frozen landscape, but they're even more energized by the potential impact of the research.

Among other things, Marchant studies the world's oldest glacial ice. He measures atmospheric gasses over million-year timeframes to understand Earth's natural variability in carbon dioxide and examines the geologic record for ice loss. The National Science Foundation's U.S. Antarctic Program supports his fieldwork in Antarctica.

His new 18-month program starts with a class of about 15 students, from which Marchant will choose his research companions for Antarctic trips of up to eight weeks. Among the travelers' many research responsibilities will be to take super-high-resolution photographs of glacial features and collect samples of volcanic ash for radiometric dating. While students are in Antarctica, they also give talks about their work to distinguished visitors, including senators and CEOs.

Students who remain stateside will use the super-high-resolution photographs to create virtual field expeditions and perform real-time landscape analysis. Marchant will also develop a seminar course and a laboratory course in which students conduct geochemical analyses on Antarctic samples. A new website will give anyone in the world a virtual tour of the areas where he and his students work.

For those who travel with him to Antarctica, he says, the trip will have a lasting impact. With their fast pace and steep learning curves, these trips transform students into confident researchers in a few short weeks, he says. "You can see it when they're back [on campus], too. There's nothing you can give them after this experience that they'll fail at. They'll just keep trying until they get it."

"They learn how to articulate and defend their ideas, and how to work collaboratively."

—TRACY JOHNSON

CHRISTOPHER IMPEY
University of Arizona

Project: Bringing interactive learning and research to massive open online courses.

Astronomer Christopher Impey has been trying to answer big questions about the universe: How did galaxies grow to their current sizes? How do some of the universe's most immense black holes grow?

But in the years to come, he'll pursue his biggest, most audacious vision yet: harnessing the power of tens of thousands of student scientists to move his research forward.

"Students are capable of classifying galaxies [just] as well as PhD astronomers."

In 2013, Impey launched his first massive open online course (MOOC) through the website Udemy. The course, "Astronomy: State of the Art," attracted a stunning 14,000 students from 175 countries.

While the enthusiasm for MOOCs has swung in recent years from red-hot ardor to cool suspicion, Impey believes that the potential of MOOCs is only beginning to be explored. In his 27 years as a teacher, Impey has implemented several interactive techniques, including real-time comprehension surveys and hands-on group work. He's ready to bring the most successful approaches to online learning.

Impey plans to build student participation into his online courses by adding real research and collaborative websites called wikis. He will replicate classroom lectures with short video lectures. Small online groups of students will agree to meet at a specific time; they'll work together in real time to fill out wikis about the video's topic, with the help of a facilitator.

As students progress, Impey will ask them to do modest–but real–research, for example, classifying galaxies, which come in diverse shapes and sizes. "Students get a set of archetypes to learn from," he says. "They learn what makes a spiral, what makes an elliptical, how to recognize imagery, what symmetries to look for, and so on."

Through these projects, Impey hopes to lead his students to the kind of "light bulb moments" that turn interactions into learning. "There's a time in the classroom when groups get engaged in discussions, even arguments, as they try to assimilate unfamiliar material. It's chaotic–a mixture of heat and light–where learning takes place," he says. "I want to try to take those light bulb moments online." ■

2014 HHMI Professors

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Ithaca, New York

Susan S. Golden
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Developing Relationships

Two studies hint at bacteria's deep-rooted influence on animal development.

BY NICOLE KRESGE
ILLUSTRATION BY MARI KANSTAD JOHNSEN

Bacteria are everywhere: floating through air, drifting in water, clinging to surfaces. So it's not surprising that many animals and plants have formed beneficial relationships with the microorganisms.

We are surrounded by examples of bacteria helping animals and plants. Bacteria can protect plants against extreme drought. The bacterial mix living in an animal's gut makes digestion possible. The good bacteria that coat skin fight off harmful microbes. But as scientists delve deeper into the ties that bind animals, plants, and bacteria, they're finding some unexpected, fundamental connections: in some cases, the chemical signals released by bacteria trigger development. They may even hold clues as to why organisms became multicellular.

Two recent studies reveal the molecular nature of some of these chemical cues. But what do the bacteria get out of the relationships? "Animals evolved in a bacterial world," says Dianne Newman, an HHMI investigator who studies bacteria at the California Institute of Technology. "I think we're just at the very beginning of really starting to appreciate that and what it means."

Bacterial Welcome Mat

The tubeworm *Hydroides elegans* begins its life as a tiny larva, floating freely through the ocean. Eventually, it needs to grow up, settle down on a hard surface such as a rock or the hull of a boat, and build its "house"—a calcified, tube-like outer shell. The trigger for this transition from free-swimming larva to stationary juvenile comes from a carpet of bacteria called a biofilm. The biofilm covers the surface where the *H. elegans* lands to settle down. The transformation is fascinating, but it's also a bane for the shipping industry. This accumulation of bacteria and marine animals, known as biofouling, creates extra drag on boats and increases fuel consumption.

Michael Hadfield, a biologist at the University of Hawaii, has spent 25 years studying the tubeworm as it settles into adulthood. He's focused on one of several biofilm-forming bacteria that trigger the metamorphosis—*Pseudoalteromonas luteoviolacea*, or *P. luteo*, which is by far the most efficient. In 2012, Hadfield's graduate student Ying Huang zeroed in on four genes in the bacteria that trigger tubeworm transformation. But the specific cue that sparked the worm's lifestyle change remained unknown.

Two years later, Nicholas Shikuma, a postdoctoral fellow in Newman's lab, collaborated with Hadfield to uncover the products of the four genes. "I thought the bacteria were putting out a peptide or something that the larvae would have specific receptors for," says Hadfield. It turns out the tubeworms were responding to something much bigger and more complex: a structure composed of hundreds of protein components. "This really changed our whole perspective," says Hadfield.

Big MACs

Shikuma discovered that the signals produced by *P. luteo* were actually needle-like macromolecules that he and his colleagues dubbed metamorphosis-associated contractile structures, or MACs. Each MAC consists of three parts: a narrow tube that can be used as a projectile, a hollow sheath that surrounds the tube and pulls back when triggered, and an anchoring baseplate. The structures bear a strong resemblance to the syringe-like tails found in some bacteriophages—a type of virus that infects bacteria (the viruses use the narrow tube contained in the needles to pierce bacterial envelopes and then inject a payload of viral DNA inside).

"The MACs are like spring-loaded molecular daggers," explains HHMI Investigator Grant Jensen, who collaborated with Shikuma to get an up-close look inside the bacteria by using a technique called electron cryotomography. "Their outer sheath contracts like an accordion, ejecting the inner rod and its chemical payload into the target."

Even more intriguing was the finding that the needles formed porcupine-like arrays that, when fully extended, were larger than the cells that produced them. At the base of the array, the MACs are tightly gathered like the stems in a bouquet of flowers. At the other end, the rods project out like a bundle of tiny spring-loaded syringes.

"This type of assemblage was structurally really different from what had previously been seen for phage tail-like particles," says Newman. "And what's more, unlike previous cases where such particles were linked to pathogenesis, the MACs mediate a beneficial interaction." The group published its findings in the January 31, 2014, issue of *Science*.

Only about 2 percent of *P. luteo* cells in a given biofilm produce MACs, and they give themselves fully to the process. They convert their entire contents to MACs, packing their insides wall to wall with the arrays. Eventually, they get so full they burst, releasing the arrays, which spring open like umbrellas.

Although the scientists aren't exactly sure how the MACs trigger metamorphosis, they think that the needles may act like molecular guns, firing a payload of who knows what into the *H. elegans* larva that starts the change from innocuous organism to invasive pest.

Alternatively, perhaps the tubes themselves act as arrows to puncture the larva's cells. "To me they look like a whole bunch of cocked crossbows," says Hadfield. "If they hit the right cell—a sensory cell on *Hydroides*—and poke holes in it, it could be sufficient to trigger metamorphosis."

How the bacteria benefit from this relationship and why they produce MACs are also unclear. Perhaps the worms are protecting *P. luteo* by ingesting their zooplankton predators. Whatever the mechanism and the relationship, it's clear that the bacteria are signaling to the tubeworms that it's time to grow up.

A Quest for Colonies

Much like *H. elegans*, the tiny water-borne organisms called choanoflagellates rely on bacterial cues to enter a new stage of life. Choanoflagellates spend their time gorging on bacteria in oceans, lakes, ponds, and even puddles. Generally, they are single celled. But some species, like *Salpingoeca rosetta*, can also form large colonies. As its name

"Animals evolved in a bacterial world. I think we're just at the very beginning of really starting to appreciate that and what it means."

—DIANNE NEWMAN

implies, as *S. rosetta* cells divide, they arrange themselves into a rosette, radiating around a central point. Little is known about the lifestyle of these organisms, but since they are among the closest living relatives of all animals, their biology may shed light on how and why our ancestors became multicellular.

HHMI Investigator Nicole King became fascinated by choanoflagellates when she was a postdoctoral fellow in 2000. Since then, she has been on a quest to figure out how and why they form colonies. In the wild, *S. rosetta* readily develops into rosette colonies. In the lab, it was a different story. For years, King managed to coax the organisms to develop into colonies only once in a while.

So she decided to sequence the genome of *S. rosetta*, hoping for clues to this developmental process. That's when undergraduate researcher Richard Zuzow made a serendipitous discovery. To prepare the cells for sequencing, Zuzow needed to remove contaminating bacteria. So he treated the cells with antibiotics. Certain cocktails of antibiotics, he noticed, caused the choanoflagellates to stick together, while others prevented rosette formation.

"Even when we washed out the antibiotics, the colonies never came back," explains Rosie Alegado, who at the time was a postdoc in King's University of California, Berkeley lab. "Either the antibiotics were directly affecting choanoflagellates or we killed off something in the culture that was triggering this effect."

A Simple Signal

It turned out to be the latter. Zuzow figured out that certain bacteria—*Algoriphagus machipongonensis*—were prompting rosette formation; the antibiotics used to prep the cells for sequencing were killing off the bugs. Alegado, now at the University of Hawaii, teamed up with Jon Clardy, a natural products chemist at Harvard Medical School, to purify the substance that was causing the rosettes to form.

It was a much simpler signal than the MAC arrays that spur tubeworm metamorphosis. *A. machipongonensis* releases a lipid molecule that belongs to the sulfonolipid family. Similar compounds had been seen before, but their functions were unknown. The team named the molecule rosette-inducing factor 1, or RIF-1, and published its findings in *eLife* on October 15, 2012.

"First we find that a bacterium is actually regulating whether choanoflagellates are single celled or colonial. That's exciting because choanoflagellates eat bacteria, and they're getting cues about their environment from the bacteria," King says. "Then we find out that it's the special class of molecules that hasn't been characterized before."

As with the tubeworms, many questions about the choanoflagellate-bacteria relationship remain. Alegado and King think that RIF-1 is released into the water via vesicles that "bleb off" the bacterial membrane. These lipid bubbles either fuse with hydrophobic molecules in *S. rosetta*'s membrane, or they are engulfed by the choanoflagellate. Then they trigger rosette formation—and this is where things get murky.

"At this point, I feel very comfortable talking about how things are happening," says King. "I'm just less certain about why." For example, she has no idea why *A. machipongonensis* produces RIF-1 or why *S. rosetta* responds to it. One hypothesis for the latter is that colonies are better at capturing bacteria, so the choanoflagellates form rosettes to better exploit a resource.

Both the tubeworm and choanoflagellate studies illustrate that, in some cases, intricate relationships have evolved between bacteria and the organisms they live with. They also raise many questions about how and why the relationships formed, and whether or not they are exceptions or the norm. "They are both anecdotes of how bacteria are intentionally or unintentionally driving the behavior of multicellular and transiently multicellular organisms," says Alegado. "The two papers indicate that there's a rich chemical dialogue going on that we know very little about. It just shows that we have to continue to look." ■

Perspectives & Opinions

Orchestral Approach in the Classroom

Nobel-Prize-winning physicist Carl Wieman believes research-based science instruction trumps traditional lecture-style classes. Getting other scientists and research institutions to embrace active-learning methods and collect data on the impact of their teaching, however, is an uphill battle, says the Stanford University professor of physics and the graduate school of education.

Carl Wieman

—

Carl Wieman was associate director of science in the White House Office of Science and Technology Policy from 2010 to 2012.

At a majority of universities, science teaching means lecturing in front of a crowd of students who are often surfing the web, texting, or struggling to stay awake. Teaching should instead reflect the way science is actually done—through dynamic, small-group work on engaging and challenging scientific problems. In this approach, the instructor acts as the conductor of the student orchestra, providing the "sheet music" along with feedback and guidance.

This sort of "active learning" yields better outcomes. A massive analysis of hundreds of research studies on undergraduate science instruction, published in the June 10, 2014, *Proceedings of the National Academy of Sciences*, showed significantly greater learning and lower failure rates with active, research-based teaching methods than with traditional lectures (22 percent versus 34 percent failure rates). When students actively apply and process information during class—answering questions using electronic clickers, completing worksheet exercises, and solving problems with fellow students, for example—coupled with frequent targeted feedback from the instructor, they develop the capability to think like a scientist. It's like learning to play music—being in the orchestra is more effective than just listening to it.

Though I am a physicist, I have spent the past two decades exploring the best strategies for science, technology, engineering, and mathematics (STEM) teaching. Scientists rely on research and data to advance fields of study, and we must rely on research and data to advance education as well. It's time to stop debating whether active learning surpasses the traditional lecture format. The data are conclusive. Let's now move on to the routine use of active learning strategies and collecting data on which of those strategies are most effective. We can determine which tasks and methods of feedback work best at motivating students and developing their expertise.

Few research institutions seem ready for this next step, however. On most campuses, including my own, the traditional lecture is the norm. But I have seen what can happen when academic departments and scientists embrace new teaching strategies. At the University of Colorado, Boulder, and at the University of British Columbia, where I launched Science Education Initiatives, STEM departments made great progress toward switching from passive lecture-style teaching to research-based, active learning approaches.

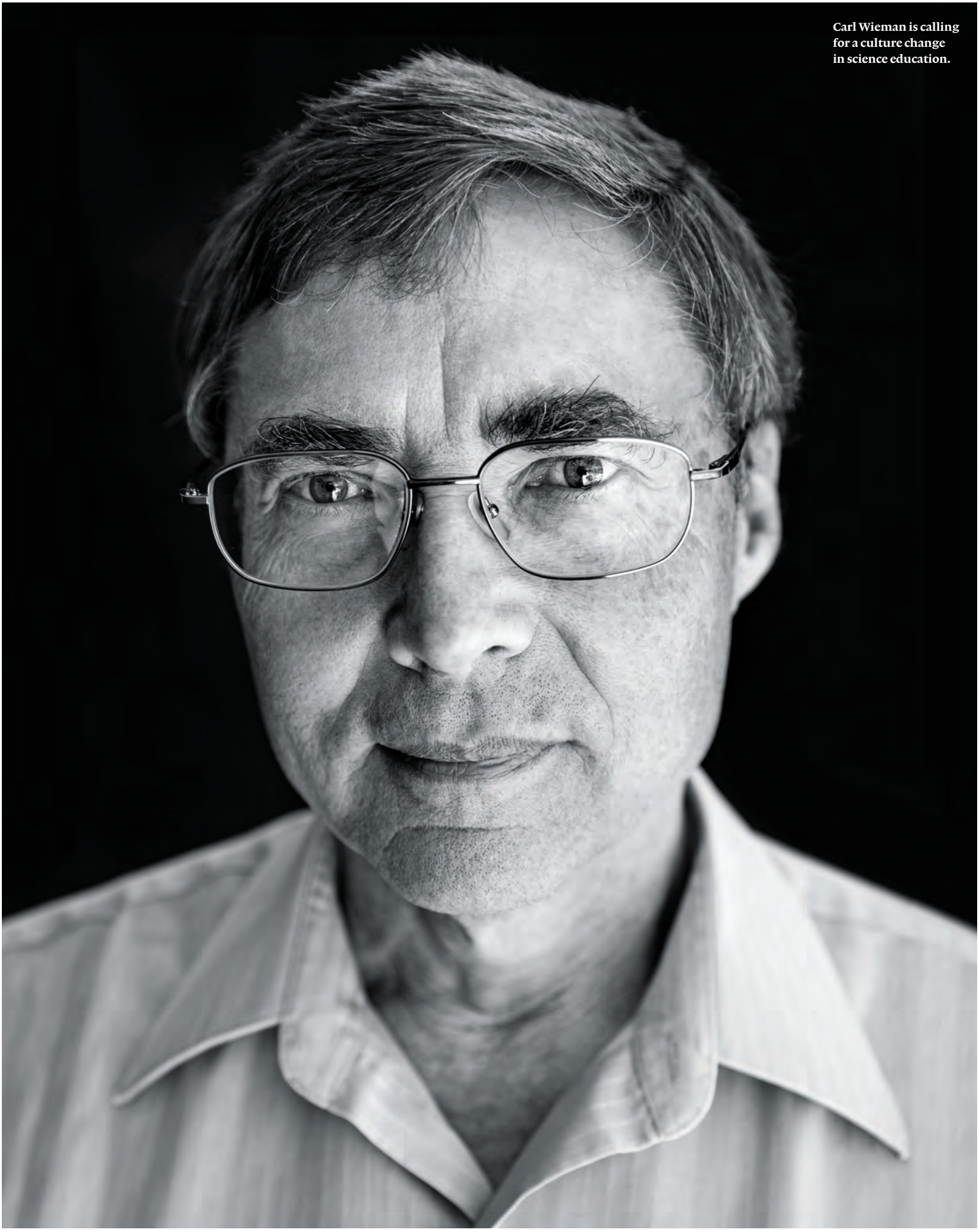
Changing those departments required changing the incentives. Research is what is traditionally measured and rewarded, so there's little motivation for science faculty to focus on teaching practices instead. To prompt those new practices, we provided financial incentives to departments, plus coaching and incentives to faculty, including summer stipends and extra teaching or research assistant support, as professors learned new teaching techniques and modified courses. These carrots provided some motivation, but what attracted faculty the most to these new teaching techniques, and kept them using them, were the results: Students were far more engaged. They came to class, paid attention, asked deeper questions, and increased their learning. It was just more fun to teach.

For other institutions to follow suit, a focus on data and incentives is critical. Usually, the only way a professor is evaluated on his or her teaching is from student feedback surveys, which provide little useful information. A more effective alternative involves collecting data on the teaching methods being used in each course, and how those methods translate into student learning. But few, if any, institutions are collecting such data, let alone incentivizing the use of the most effective methods.

I'm seeking a culture change in scientific education, and that does not come easily. Universities currently viewed as top-notch in STEM by the current research-focused measures are unlikely to look as strong if judged according to the effectiveness of their teaching methods. When I tried to establish federal policies that would encourage institutions to make available data on their STEM teaching methods, there was significant opposition. However, I've seen some progress. The Association of American Universities—which has not previously been involved in teaching issues—launched a STEM initiative to bring about greater use of active-learning methods. HHMI and the National Science Foundation have also started funding institutional improvement in STEM teaching. This headway is encouraging.

—Interview by Michelle R. Davis

Lisa Wiseman



Carl Wieman is calling for a culture change in science education.

Perspectives & Opinions

Q&A

What challenges do educators face when trying to implement hands-on undergraduate science classes at universities?

Hands-on projects can transform education by fostering critical thinking and allowing students to apply what they've learned. But implementing these projects can be difficult. Here, four HHMI professors share some of the challenges.

–Edited by Nicole Kresge

Brian R. Crane
HHMI Professor, 2014-present
Cornell University

Large classes make it difficult to engage students in a personal way and create environments in which they receive interaction and feedback. Technology may help bridge this gap, but for the most part we haven't developed really good tools to supplement and augment (not replace) the undergraduate science class. Involving students in real research early on can be very successful, but in large classes it's challenging to find projects that can be massively parallel but still unique to the student.

The varied backgrounds of students also present a challenge. Some (maybe even many) students coming to a university lack the quantitative reasoning skills needed for discovery-based learning. Without such basic abilities, even the best designed hands-on experience can be lost on a student.

Darcy B. Kelley
HHMI Professor, 2002-2010
Columbia University

The major challenge in creating a more active learning environment at a private research university is stimulating faculty interest. Senior faculty members who came into science through traditional lectures may not see any need for change. Letting junior faculty members create courses from scratch will motivate them to use or create other approaches.

University culture also plays an important role. If laboratory research programs are the chief criteria for funding and advancement [decisions], pedagogical research will be a lower priority for faculty. The HHMI Professors program has raised the profile of the creative educational approaches of top researchers. The challenge now is to bring these approaches to the science faculties.

Susan S. Golden
HHMI Professor, 2014-present
University of California, San Diego

The biggest challenge is inertia. Academic scientists are trying to juggle many different jobs, all of which are important, and only one of which is teaching science to undergraduate students. Once we establish a rhythm that keeps all of the balls in the air, it's hard to commit the energy required to change the direction or speed of one of those balls. A major change in teaching methodology will affect the other balls, too. The beauty of the HHMI Professors grant is that it facilitates that change, by providing resources for teaching activities that are creative and fun–and thus worth the disruption–and by integrating some of those other activities with the teaching component.

Richard M. Amasino
HHMI Professor, 2006-2010
University of Wisconsin-Madison

It's possible to have hands-on undergraduate science classes that don't manage to "turn brains on," and it's possible to have brains-on undergraduate science classes that are not hands on, as long as active learning is involved. But ideally, most hands-on undergraduate science classes should be brains on as well.

I define active learning as using one's brain in an active way. Listening to a lecture is passive. Students solving problems posed to a class is active, as is defending one's answer to a problem. Hands-on learning can be passive, however, if it is an exercise during which students' brains can "zone out" while they are doing it. Active learning is important because students must work, and even struggle a bit, with the subject material to learn it in a meaningful way.

Crane, Golden, Kelley: Paul Morigi; Amasino: Brian Ebne

Chronicle

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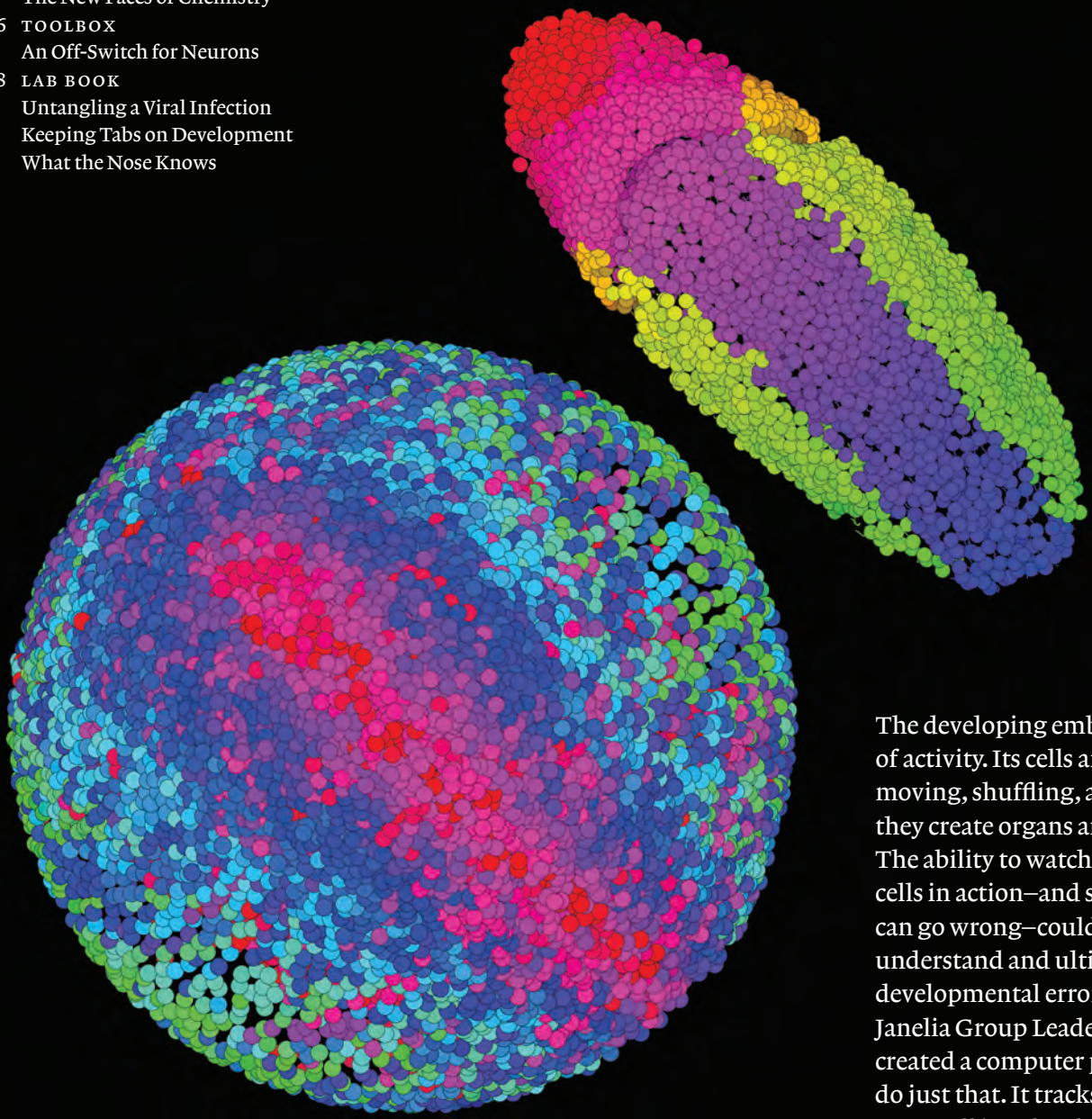


Kristin Branson, Fernando Amat, William Lemon, and Philipp Keller (HHMI/Janelia)

The developing embryo is a whirlwind of activity. Its cells are constantly moving, shuffling, and dividing as they create organs and limbs. The ability to watch these embryonic cells in action—and see where things can go wrong—could help scientists understand and ultimately prevent developmental errors. A team led by Janelia Group Leader Philipp Keller has created a computer program that can do just that. It tracks the movements of every cell in a developing embryo by mining data captured by using high-resolution microscopy. The results are both striking and informative. Each dot in these embryos of a fruit fly (top right) and a zebrafish (bottom left) is an individual cell, color coded to reveal its developmental origins.

Read more about Keller's technique in "Keeping Tabs on Development" on page 39.

Chronicle / *Science Education*

To watch some of the team's videos, visit www.hhmi.org/bulletin/fall-2014.

The New Faces of Chemistry

Brief videos by student chemists hit their mark.

IT BEGAN WITH the white guys in beards. Teaching freshman chemistry at the Massachusetts Institute of Technology (MIT), Cathy Drennan noticed that the textbooks taught the basics—but from a dusty, historical perspective.

"A lot of students would look at the pictures and think, 'Chemistry is something that is done by dead white men,'" she says. "Students didn't see why it is useful now."

So Drennan, an HHMI investigator and HHMI professor, launched a project. Rather than resurrect Dmitri Mendeleev or Amedeo Avogadro from the pages of chemistry's history, Drennan enlisted young chemists to talk about what they do today. And she kept the conversations short—less than three minutes.

Backed by HHMI, Drennan created a series of short videos to help educators make chemistry accessible, desirable, and relatable. The result was success—the students fell in love with the chemists along with their chemistry.

The project began with a search for the right chemists. They had to be engaging on camera, diverse, and doing research that illustrates a fundamental chemical principle. With the help of chemistry instructor Beth Vogel Taylor, Drennan queried, cornered, and cajoled the best candidates at MIT. In that search, the two happened upon George Zaidan, a former undergraduate chemistry major at MIT with a knack for video production. They also found PhD chemist Mary O'Reilly, who has a gift for illustration, particularly molecular abstractions for video. The two became crucial to the production team.

During the interviews, Drennan added a throwaway question: how the budding chem-actors first got interested in science. The answers opened doors to much more than pure science.

"When I was younger I read a lot of comic books," said postdoc Nozomi Ando in her video. "I read a classic series on ninjas. I really wanted to become one." Ando explained how she modeled her scientific education after ninja training—a long apprenticeship, a mentor, and discipline as an art form. She also described the principle of chemical equilibrium as it plays out in understanding chemotherapeutic drug targets.

Samuel Thompson, now a graduate student, talked about growing up as an artistic, intellectual, and gay teen in a small town in Texas. He also explained how understanding acids and bases is critical for probing living cells. Postdoc (now assistant professor) Hector Hernandez, born in Honduras, shared how he first studied chemistry as a community college student at the almost ancient age of 29. Then, he got into solubility as it relates to manipulating microbes to counteract climate change. Former graduate student Lourdes Alemán connected chemical bonding and structure to treating disease, and revealed that her inspiration was her father, a scientist in Cuba who was banned from practicing science because he was Catholic.

The videos made their mark, first on budding MIT students and then on a broader audience of university and high school students, some of whom were surveyed after watching.

"It wasn't like this is some godly researcher that we will never be close to," said one viewer in a follow-up interview. "It was like, 'Okay. This is a person. I could probably talk to this person if we met in real life.' "

Measuring Motivation

Drennan's team measured impact through experiment. The team showed a series of six videos to MIT undergraduate chemistry students over the course of half a semester. During the other half, the students saw no videos. Drennan's team then compared student responses to questionnaires during both halves. They did this three times, for two different semester classes.

The students ranked their motivation on a scale of 1 (lowest) to 7 (highest). The videos appeared to significantly boost drive and interest in chemistry. The results also turned up a surprise. While Drennan had made a conscious effort to showcase diversity, minority and non-minority students showed equal enthusiasm for the videos.

Owen Gatley

"Together, the 12 videos present a picture of who contemporary chemists are: inspiring people students can relate to."
—BETH VOGEL TAYLOR

The main difference occurred between genders. After viewing the videos, female students' motivation jumped 1.3 points (from an average 3.8 to 5.1), while motivation among males rose 0.7 points (from 4.2 to 4.9).

Why the gender difference? Although her team didn't explore this question experimentally, Drennan has observed that more female students than males need to feel the subject is of real world value to want to continue. Basically, Drennan explains, chemistry, like other scientific subjects, is a demanding, lengthy investment. Women are willing to pursue it—and possibly delay starting a family, for instance—if they believe a specific pursuit will make the world a better place— for example, by improving medicine or the environment.

"Some of the culturalization is that women, if they want to have a career, have to justify why that is a useful thing to do," Drennan, herself a mother, sums up. "Whereas, a lot of the men are just like, chemistry was hard, and I did it. Yes!"

The passion can—and should—start much earlier than college, Drennan asserts. She and her team are showing the videos to high school and middle school teachers to encourage use in science classes and spark that passion earlier. It's an easy sell, because the videos are unique: short, easily inserted into a class, and full of diverse and youthful characters, says Anique Olivier-Mason, a technical instructor at MIT who is heading Drennan's outreach effort. Some teachers, she says, are handpicking certain videos for specific students—for example, showing the Hector Hernandez video to a young Hispanic man who is thinking of community college.

"Even in high school, not every student is ready for all the science," says Olivier-Mason. "But the personal videos are approachable to students of all levels."

"Together, the 12 videos present a picture of who contemporary chemists are," says Beth Vogel Taylor. "Inspiring people students can relate to." –*Trisha Gura*

Chronicle / *Toolbox*

An Off-Switch for Neurons

Neuroscientists have built a light-sensitive switch for shutting down neural activity.

WHEN FACED WITH a thorny problem, researchers often turn to nature for a solution. One shining example is channelrhodopsin, a protein derived from green algae. The light-sensitive protein can, with the flick of a light switch, instantaneously activate neurons in which it is genetically expressed. Given life's spectacular diversity, finding a complementary switch—one that reliably extinguishes neural activity in the same way—seemed only a matter of time. But nearly a decade after channelrhodopsin began turning on neurons, a similar molecule for turning off neurons with light has eluded discovery.

"So," says Stanford University neuroscientist Karl Deisseroth, "we decided to try to make one."

Deisseroth, an HHMI investigator and practicing psychiatrist, developed the first channelrhodopsin on-switches in 2005. Channelrhodopsins are essentially ion channels—tubular proteins embedded in neuronal membrane through which ions can flow. In unicellular green algae, the proteins act as photoreceptors to guide the microorganisms' movements in response to light. Deisseroth and his colleagues demonstrated a technique for genetically inserting the light-sensitive channelrhodopsin into rodent neurons. Shining a pulse of blue light on those neurons triggered the opening of the pore so that positively charged ions flowed into the cell, causing the cell to fire. Thousands of labs around the world now routinely use channelrhodopsins to study the neural basis of a wide range of disorders ranging from Parkinson's disease to depression and anxiety.

As helpful as they are, channelrhodopsins provide neuroscientists only half the control they need to fully manipulate brain activity. Researchers needed a reliable method to switch neurons off as well. In 2006, Deisseroth's team found a workable solution in halorhodopsins, light-sensitive ion pump proteins extracted from nature—this time from the microorganism halobacteria, which make opsins, or light-sensitive proteins, selective for the negatively charged ion chloride. By 2010, his lab team had successfully engineered these chloride pumps into tools for inactivating neurons. However, unlike channelrhodopsins, which allow hundreds of ions to pass through per photon of light, all opsin pumps move only a single ion through per photon. Put simply, if a channel is a fire hose, a pump is a dripping faucet. "You still get inhibition, but it's inefficient inhibition," says Deisseroth.

After several more fruitless years of searching genomic databases for an inhibitory light-sensitive channel, Deisseroth decided to reengineer channelrhodopsin to make it selective for negative ions. He knew he'd have to change the polarity of the pore's lining from negative to positive, so that negative ions, such as chloride, could be shuttled through. One way to do that was to introduce DNA mutations that would swap out negatively charged amino acids in the pore lining for ones that were positively charged. Fortunately, his team had been tinkering with the genetics of channelrhodopsin to make it more light-sensitive and to keep the channel open for longer periods of time. So, they knew such genetic manipulations were possible. They just had to figure out which of the hundreds of amino acids to tweak.

Starting in 2010, Deisseroth's team, along with biophysicists at the University of Tokyo, committed to solving the structure of a chimera of two channelrhodopsins, called C1C2, using x-ray crystallography. After two years, they published a crystal structure that offered a road map of amino acids to target with mutations. Still, there were hundreds of possibilities, which took another two years to test. Several mutations conferred selectivity for chloride, but the channels failed to conduct current. So, Deisseroth's team, led by postdoc Andre Berndt, screened more than 400 combinations of mutations, and through a systematic process, ultimately constructed

Deisseroth says he is particularly pleased with how his lab was able to weave together years of projects to derive the channelrhodopsins.

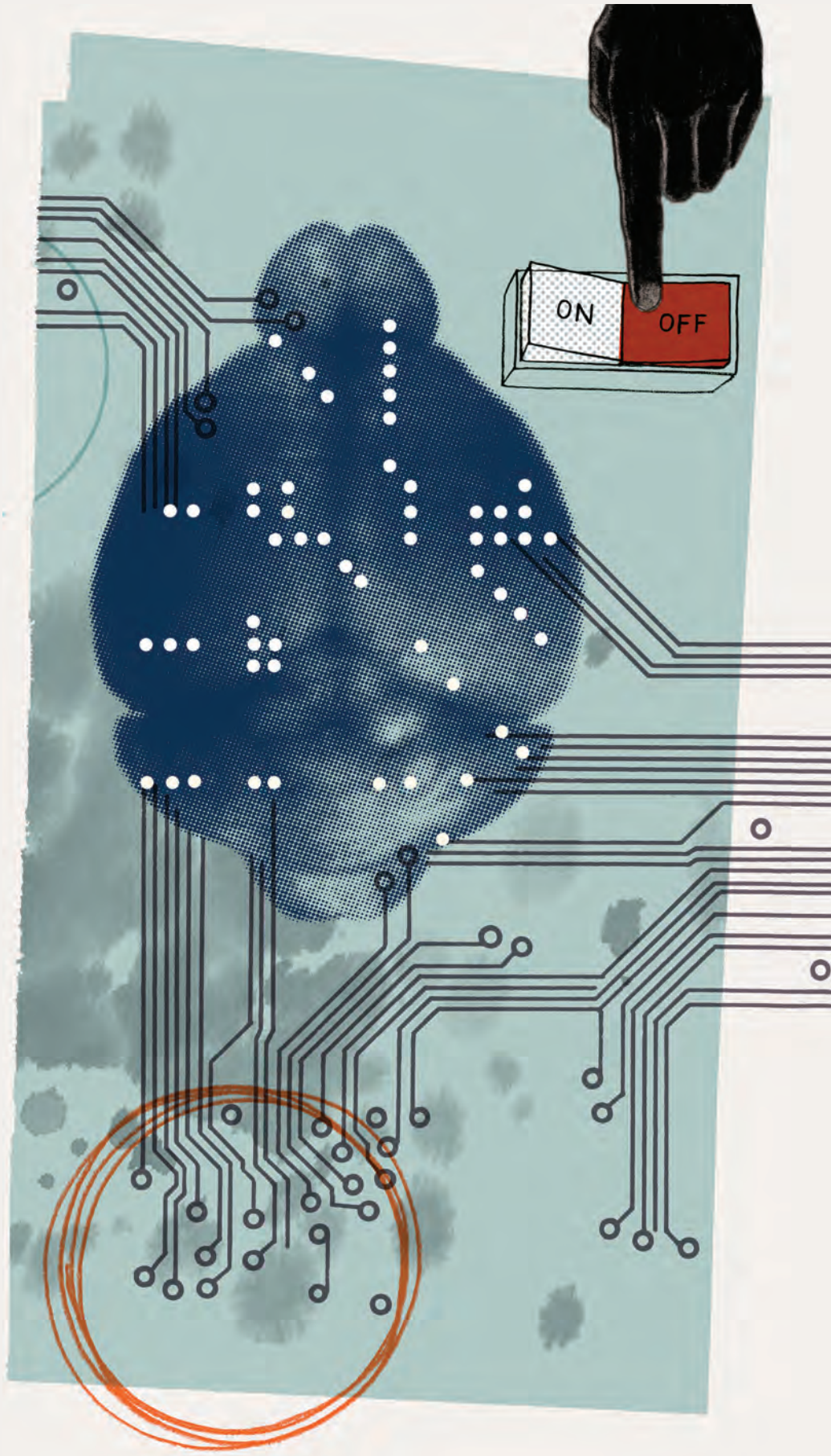
a channel with nine amino acid mutations that conducted chloride currents.

The new channel–dubbed inhibitory C1C2, or "iC1C2," and described in the April 25, 2014, issue of *Science*–inhibits neuron firing in two ways: chloride rushing in makes the cell more negatively charged, keeping it from reaching its firing threshold, and, more importantly, all those open channels make the neuron's membrane leaky. "By making the membrane leaky, you make the neuron harder to fire," says Deisseroth. "You can't do that with ion pumps."

With one final mutation, Deisseroth's team made the new channel much more sensitive to light overall. The mutation also gave the researchers greater control over the channel. Blue light can open this additional switching tool, called SwiChR, for minutes at a time; red light makes it close quickly. Such control has proven useful in long-term studies where events such as neural development and plasticity play out over minutes to hours. The extended channel-open times also mean less light is needed to inhibit the neurons. Using a weaker light source reduces tissue damage, increases the ability to reach deep brain structures, and opens the possibility of controlling brain functions involving large regions of the brain. According to Deisseroth, these capabilities should facilitate the use of inhibitory channels in animals with large brains, such as primates.

Deisseroth says he is particularly pleased with how his lab was able to weave together years of projects involving crystallography, genetic engineering, and behavioral testing to derive the chloride-conducting channelrhodopsins. "It was certainly a high-risk project," he says, "and in the end, it was surprising how well it worked and how much we learned about these amazing proteins."

– Chris Palmer



Aude Van Ryn

Chronicle / *Lab Book*

Untangling a Viral Infection

A host cell enzyme is commandeered by a knot-like structure in flavivirus RNA.

FLAVIVIRUSES ARE RESOURCEFUL. The agents behind West Nile and dengue fever trick their host's invader-fighting enzymes into helping the virus infect more cells. HHMI Early Career Scientist Jeffrey Kieft is resourceful too. He's figured out how these pathogens perform their trickery and devised a potential way to put an end to it.

"Scientists discovered a long time ago that when flaviviruses infect a cell, they produce a subgenomic RNA molecule that is essential for viral infection," explains Kieft. The molecule, called small flaviviral RNA (sfRNA), is actually created by a host enzyme named Xrn1. Ironically, Xrn1 can help defend the host by destroying foreign RNA. But in this case, it helps the invader attack.

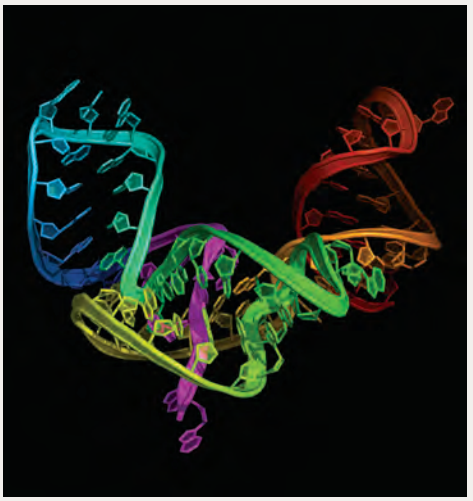
To its credit, Xrn1 manages to chew up most flavivirus RNA, but then it stops, and the fragment that remains is the damage-inflicting sfRNA. Kieft and his team at the University of Colorado Denver characterized the spot on the viral RNA that blocks the enzyme from moving along the foreign RNA. It turned out to be a knot-like fold in the RNA that acts as a blockade.

"Xrn1 is chewing down the RNA, progressing really easily, and it runs into this tangled-up RNA structure and just can't get by," explains Kieft. "It can't figure out how to untie the 'knot.'"

The scientists also learned that if they disrupt the knot-like structure by changing certain nucleotides in the RNA, Xrn1 can successfully chew through the RNA and prevent production of the pathogenic sfRNA. They published their findings in two papers—one in the April 1, 2014, issue of *eLife* and the other in the April 18, 2014, issue of *Science*.

If researchers can find a way to prevent viral RNA from forming the knotty snarl, they will have a treatment for flavivirus diseases. "Now that we've got a full picture of the structure and have a model for how it stops Xrn1, we can get serious about trying to target the blockade with small molecules to disrupt its structure," says Kieft.

– Nicole Kresge

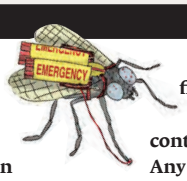


A knot-like fold in flavivirus RNA helps the pathogen trick host cell enzymes.

Photo: Jeffrey Kieft Illustration: Leif Parsons

IN BRIEF

TURBO SPEED



When a fruit fly detects a looming predator, it can launch itself into the air and soar to safety in just a fraction of a second. But what happens if even a fraction of a second is too long? According to scientists at HHMI's Janelia Research Campus, flies can employ an even quicker escape response that helps them evade their swiftest predators.

Janelia Group Leaders Gwyneth Card and Anthony Leonardo and their lab teams recorded the reactions of more than 4,000 flies exposed to a looming dark circle that simulated the approach of a predator. They discovered the flies have two distinct responses: a slow and steady takeoff in which they take time to raise their wings fully, and a quicker, clumsier escape that eliminates this step. "The fly's rapid takeoff is, on average, eight milliseconds faster than its more controlled takeoff," says Card. "Eight milliseconds could be the difference between life and death."

By monitoring neurons in the flies' brains, the scientists learned that different neural circuits control the two types of takeoff. Any sort of threat will activate the slow, controlled escape neural circuit. But if the threat is closing in quickly—for example, a swooping damselfly—the speedy escape circuit will kick in and override the slow one.

The findings, published in the July 2014 issue of *Nature Neuroscience*, help shed light on the neural circuits animals use to select one behavior over another.

SHARPER IMAGE

A big problem in microscopy is that biological samples bend and distort light in unpredictable ways. The larger and more complex the specimen, the more erratic the light—and the fuzzier the resulting image. To circumvent this obstacle, Janelia Group Leader Eric Betzig created a new microscopy technique that borrows from astronomy and ophthalmology.

Astronomers correct for atmospheric distortion by shining a laser skyward in the direction they plan to observe, and then measuring the distortion of the returning light. Betzig and his colleagues duplicated this process on a smaller scale by figuring out how a tissue sample distorts infrared light. They corrected for aberrations in the returning light with a method ophthalmologists use to adjust for the movement of a patient's eyes when capturing retinal images.

The techniques allowed Betzig and his colleagues to bring into focus the subcellular organelles and fine, branching processes of nerve cells deep in the brain of a living zebrafish. "The results are pretty eye-popping," says Betzig, who published the method in the June 2014 issue of *Nature Methods*.

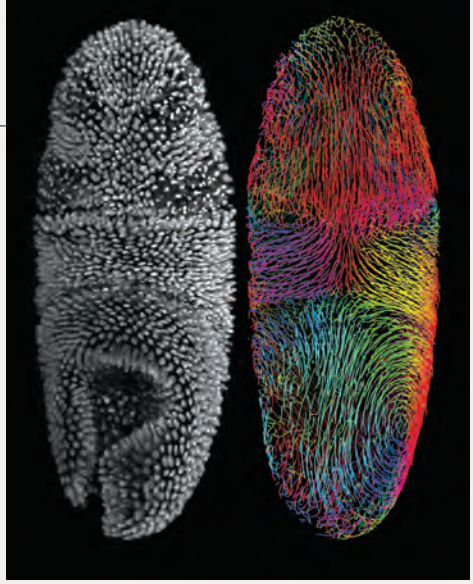
"We kept on pushing this technology, and it turns out it works," explains Kai Wang, a postdoctoral fellow in Betzig's lab. "When we compare the image quality before and after correction, it's very different. The corrected image tells a lot of information that biologists want to know."

Y IS HERE TO STAY

The human Y chromosome has been shrinking. Over hundreds of millions of years, it has shed about 97 percent of its original genes. Could the loss of a few more genes tip it into extinction? Not according to HHMI Investigator David Page of the Whitehead Institute for Biomedical Research. He believes that the jettisoning of genes has stopped.

In an April 24, 2014, *Nature* paper, Page and his colleagues compared the sequences of Y chromosomes from eight mammals, including humans, to reconstruct that chromosome's evolution. Their results showed that, although there was a period of rapid degeneration and gene loss during the early days of its evolution, the Y chromosome retained a subset of ancestral genes that have remained

To see Keller's cell tracking in action, visit www.hhmi.org/bulletin/fall-2014.



A new computer program helps track cell movement in images like this one, of a developing fruit fly embryo (left).

Keeping Tabs on Development

New software simplifies cell tracking as an embryo grows.

THERE ARE TENS of thousands of cells in a fruit fly larva. Recent advances in imaging technology can provide snapshots of each of these cells as they divide and migrate during development.

Capturing an image of a growing embryo every 30 seconds or so during the course of a day, however, produces terabytes of data. A team led by Janelia Group Leader Philipp Keller has figured out a way to analyze the data by allowing computers to identify and track dividing cells as quickly as high-speed microscopes can collect the images.

The computer program is based on the idea of clustering three-dimensional pixels, called voxels, into larger units called supervoxels. Using the supervoxel as the smallest unit allowed the researchers to reduce complexity by a thousand-fold. The computer scans groups of connected supervoxels for shapes resembling cell nuclei. That information is then used to locate those nuclei in subsequent images.

Keller and his colleagues—including postdoc Fernando Amat; Group Leader Kristin Branson; and former Janelia lab head Eugene Myers, now at the Max Planck Institute of Molecular Cell Biology and Genetics—also incorporated a final step that allows scientists to check the accuracy of the calculations and fix any mistakes.

To test their program, the team collected images of entire fruit fly, zebrafish, and mouse embryos during development and computationally followed the dynamic behavior of the many thousands of cells in these data sets. They also used these data sets to analyze the development of the early nervous system in a fruit fly embryo at the single-cell level. As they reported online on July 20, 2014, in *Nature Methods*, they were able to track a large fraction of early neuroblasts—cells that will develop into neurons—and could even predict the future fate and function of many cells based on their behavior.

Keller hopes that others will use the program, which works with data from several types of fluorescence microscopes, to learn more about early development. His team has made the software, which can run on a desktop computer, freely available on his website (*www.janelia.org/lab/keller-lab*). *–Nicole Kresge*

Photo: Kristin Branson, Fernando Amat, William Lemon, and Philipp Keller (HHMI/Janelia) Illustration: Leif Parsons

remarkably stable for the past 25 million years.

Moreover, the nature of the surviving genes hints that a Y chromosome may do more than just dictate the gender of its owner. Most of the genes have little to do with sex determination or sperm production. Instead, they play roles in protein synthesis, RNA splicing, and gene regulation. What's more, they are expressed in the heart, lungs, and other tissues throughout the body. Page thinks these genes could be contributing to the ways in which disease affects men and women differently.

"This paper tells us not only that the Y chromosome is here to stay, but that we need to take it seriously—and not just in the reproductive tract," says Page.

CLUE TO LANGUAGE DEVELOPMENT

The human brain has different regions with different functions: vision in the occipital lobe, hearing in the temporal lobe. But how are these specialty regions formed? A study by HHMI Investigator Christopher Walsh at Boston Children's Hospital shows that selective regulation of a particular gene may control brain development on a section-by-section basis. Their findings may be relevant to understanding human brain evolution.

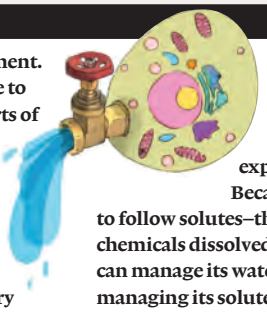
In a study published February 14, 2014, in *Science*, Walsh and his colleagues looked at five people with abnormal folds near a deep furrow in the brain known as the Sylvian fissure, a region that includes the brain's primary language center. As expected, the five subjects had impairments in cognition and language, yet none had mutations in the protein-coding regions of genes associated with brain function or formation.

All of them, however, were missing 15 nucleotide base pairs in a noncoding segment of their DNA. The mutations had inactivated a stretch of DNA that was promoting the expression of *GPR56*, a gene critical for normal brain fold development. "The mutation caused the gene to be deficient, but only in the parts of the brain that did not develop properly," Walsh explains.

Interestingly, evolutionary studies have shown that, around 100 million years ago, placental mammals acquired some additional DNA in the very area where Walsh's team discovered the inactivated element. Because those nucleotides determine whether or not *GPR56* will create brain folds around the Sylvian fissure, and may even account for the language center's existence, Walsh believes that it may have helped set the stage for humans to develop language.

A SWELL DISCOVERY

By its nature, a cell's membrane is permeable to water. So if water levels in the cell's environment increase, the cell will swell. If it can't pump out the excess water, the cell will burst. But most cells don't burst, and HHMI Investigator Ardem Patapoutian of the Scripps Research Institute has identified a gene that helps explain why.



Because water tends to follow solutes—the ions and other chemicals dissolved in water—a cell can manage its water content by managing its solutes. In the 1980s, scientists discovered that a cellular ion channel—called volume-regulated anion channel (VRAC)—opens in response to swelling to allow the outflow of negatively charged ions, which take excess water with them.

"Although scientists have known about the activity of VRAC for almost 30 years, its molecular identity has remained a mystery," says Patapoutian. To find the VRAC genes, his team created fluorescent cells whose glow was muted when VRAC channels opened. The researchers inactivated more than 20,000 genes, one by one, and watched the effect on the glowing cells. Silencing of only one allowed the glow to continue,

Chronicle / *Lab Book*

What the Nose Knows

Humans can tell the difference between at least a trillion smells.

EVERY DAY, WE'RE confronted by a multitude of smells, good and bad: perfume, body odor, baking cookies, ripe garbage. But how many smells can the human nose actually distinguish? According to a recent study by HHMI Investigator Leslie Vosshall, it's more than 1 trillion.

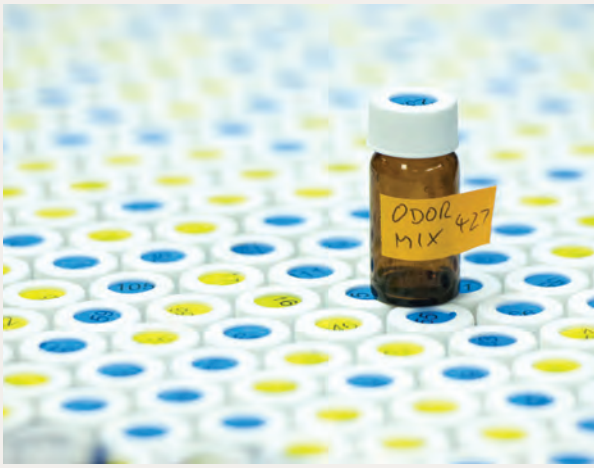
For decades, people believed that the human nose could discriminate between 10,000 different smells. That estimate, never empirically tested, didn't sit right with Vosshall. "The number was from theoretical work in the 1920s that came to be uncritically accepted by scientists and nonscientists alike," she says.

It also didn't make sense that humans could detect fewer smells than colors. The human eye can perceive at least 2.3 million different colors using three types of light receptors. By comparison, the human nose has 400 olfactory receptors. Surely we should be able to smell more than 10,000 odors.

Andreas Keller, a senior scientist in Vosshall's Rockefeller University lab, decided to determine a more accurate number. He selected 128 different odorant molecules that, when sniffed individually, could evoke smells such as mint or citrus. But when mixed in combinations of 10, 20, or 30, the odorants' smells were unfamiliar.

Twenty-six volunteers were presented with three vials of these scent cocktails; two were identical, the third was different. It was the sniffer's job to pinpoint the outlier. Each volunteer did this more than 250 times. On average, they could easily distinguish between mixtures with fewer than half their components in common; above that, discrimination became harder.

From the data, the team extrapolated how many different odors the average human can detect. Vosshall likens the process to a survey—rather than asking the entire country what presidential candidate they will vote for, you telephone a few thousand voters and use your findings to make an estimate of the entire population's preferences based on this sampling. The number, published March 21, 2014, in *Science*, was 1.7 trillion—a conservative projection, as there are many more than 128 odorants in the world.



Volunteers sniffed 250 different scent cocktails to help determine the limits of human odor detection.

No one encounters a trillion smells in a day, so the ability to distinguish between so many odorant molecules isn't really necessary. But being able to discriminate between similar smells, such as spoiled milk versus fresh milk, is certainly useful. *–Nicole Kresge*

IN BRIEF

implying that VRAC had been inactivated. They named that gene *SWELL1* and published their findings on April 10, 2014, in the journal *Cell*.

"When cells swell, the SWELL1 protein is activated and pumps chloride and other solutes out of the cell, which initiates the process to shrink a cell back to original volume," says Patapoutian.

Now that the team has a molecular understanding of VRAC, they plan to investigate how the channel senses volume change and the role SWELL1 plays in physiology and disease.

LEGO FOR THE LAB

Synthesizing a molecule is a lot like doing a jigsaw puzzle. You start with many pieces, figure out how they fit together, and eventually, after a lot of trial and error, you're done. HHMI Early Career Scientist Martin Burke has come up with a way to simplify the process using Lego-like building blocks that take the puzzling out of synthesis.

Burke and his team at the University of Illinois at Urbana-Champaign analyzed almost 3,000 polyenes found in nature. These molecules—commonly used as drugs, pigments, and fluorescent probes—contain chains of carbon atoms connected by alternating single and double bonds. The scientists realized that more than three-quarters of the natural products could be created with only 12 different chemical building blocks joined by a single type of coupling reaction. Like 12 pieces of Lego that can be combined to make just about anything, from a house to a dinosaur, the researchers mixed and matched the basic polyene building blocks to produce several different molecules.

The discovery, reported in the June 2014 issue of *Nature Chemistry*, provides chemists with a simple way to build polyenes that are challenging or too expensive to extract from their natural sources. Burke eventually hopes to expand his chemical Lego set to include more than just polyenes. "This paper covers about 1 percent of all natural products isolated to date," he says. "We want to determine how many building blocks it takes to reach most of the remaining 99 percent, and to create a highly optimized machine that can automatically stitch those building blocks together."

CLIPPING CONTROL

When a strand of DNA in a yeast cell breaks, one of the first responders is the endonuclease Sae2. The enzyme's job is to trim a little from the damaged ends of the DNA in preparation for repair. But if Sae2 lingers around too long, it might end up clipping some perfectly good DNA as well. HHMI Investigator Tanya Paull of the University of Texas at Austin has figured out how cells keep the enzyme in check.

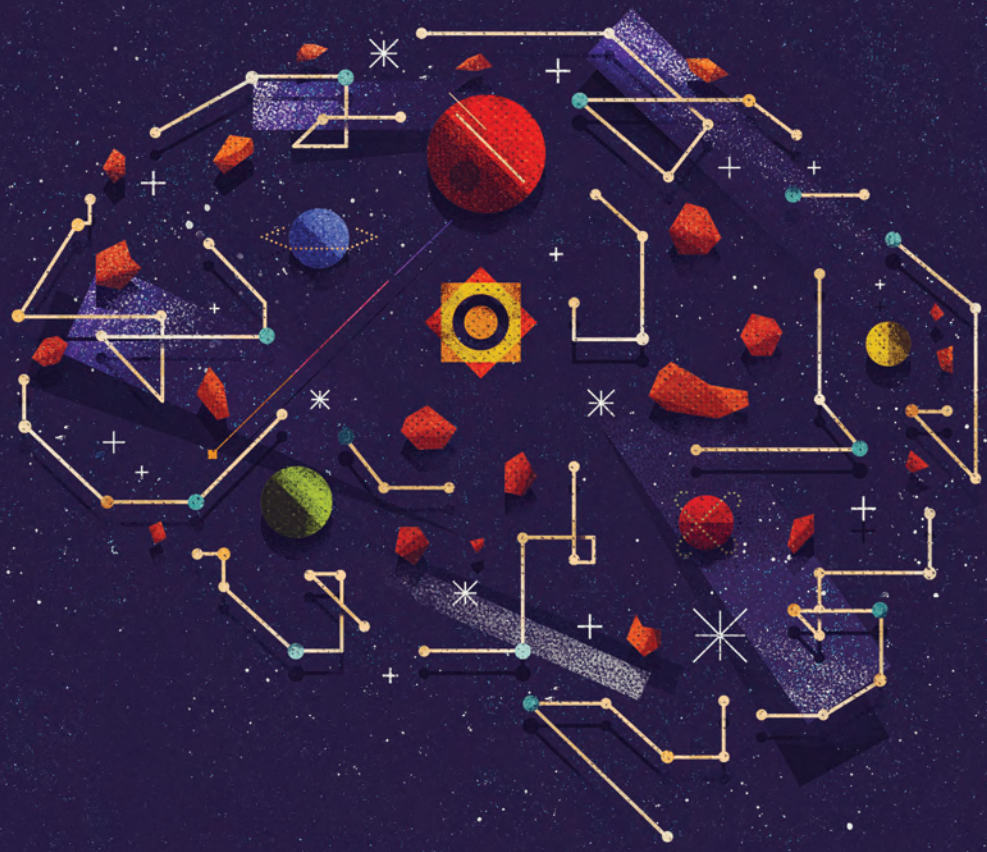
Paull's team discovered that Sae2 normally forms nonfunctional, insoluble protein aggregates in the cell. But after DNA damage occurs, an enzyme called cyclin-dependent kinase adds several phosphate molecules to Sae2. This causes the protein clusters to break apart, and the now-soluble single molecules of Sae2 become active. The DNA damage also triggers the degradation of Sae2, ensuring the cellular "clipper" is only transiently available. The findings were published March 2014 in *Molecular and Cellular Biology*.

"Sae2 is an endonuclease that is potentially very toxic to cells when unregulated," explains Paull. "So this strategy is ideal for sequestering the protein into a form that is not toxic, yet is available for immediate activation through phosphorylation."

Paull recently discovered that CtIP—the human version of Sae2—is an endonuclease with even more phosphorylation than Sae2. The results, published in the June 19, 2014, issue of *Molecular Cell*, have prompted her to investigate if CtIP is also regulated by changes in solubility.

Photo: Zach Veilleux, The Rockefeller University Illustration: Leif Parsons

Observations



Dan Matutina

Mysteries of the Mind

The seat of all our thoughts and emotions, actions and memories, the brain's capacity and complexity seem impossible to fully grasp. Yet, thanks to advances in recent years, neuroscientists can now envision a comprehensive picture of the brain in action, from molecules to cells and circuits to behavior. In April 2013, President Obama launched the BRAIN Initiative to underscore and accelerate this vision. Details of the initiative's plan are now available in a report released in June by a working group co-chaired by HHMI Investigators Cori Bargmann and William Newsome, whose poetic preamble sets a powerful framework for the effort.

We stand on the verge of a great journey into the unknown—the interior terrain of thinking, feeling, perceiving, learning, deciding, and acting to achieve our goals—that is the special province of the human brain. These capacities are the essence of our minds and the aspects of being human that matter most to us. Remarkably, these powerful yet exquisitely nuanced capacities emerge from electrical and chemical interactions among roughly 100 billion nerve cells and glial cells that compose our brains. All human brains share basic anatomical circuits and synaptic interactions, but the precise pattern of connections and interactions are highly variable from person to person—and therein lies the source of the remarkable variation we see in human behavior, from the breathtaking dance of a ballerina, to the elegant craftsmanship of a master carpenter, to the shrewd judgment of an expert trader. Our brains make us who we are, enabling us to perceive beauty, teach our children, remember loved ones, react against injustice, learn from history, and imagine a different future.

The human brain is simply astonishing—no less astonishing to those of us who have

spent our careers studying its mysteries than to those new to thinking about the brain. President Obama, by creating the BRAIN Initiative, has provided an unprecedented opportunity to solve those mysteries. The challenge is to map the circuits of the brain, measure the fluctuating patterns of electrical and chemical activity flowing within those circuits, and understand how their interplay creates our unique cognitive and behavioral capabilities. We should pursue this goal simultaneously in humans and in simpler nervous systems in which we can learn important lessons far more quickly. But our ultimate goal is to understand our own brains.

Excerpted from BRAIN 2025: ***A Scientific Vision*****, a Brain Research through Advancing Innovative Technologies (BRAIN) Working Group Report to the Advisory Committee to the Director, National Institutes of Health. Published June 5, 2014.**

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Deadly Beauty

This slow-moving marine snail, *Conus geographus*, packs venom so powerful that less than half a teaspoon can kill a person. Small fish within the striking zone of its venomous harpoon don't stand a chance. Paradoxically, components of the venom are extremely strong pain killers—up to 10,000 times more effective than morphine. HHMI Professor Baldomero Olivera has spent his career teasing apart the hundreds of toxins in the beautiful cone snail's venom, in hopes of turning the meat-eating mollusk's poison into medicine. One drug is already available for patients. Learn more about Olivera's research and his efforts to advance science education around the world in the *HHMI Bulletin* (www.hhmi.org/bulletin/summer-2014).

Alex Kerstitch