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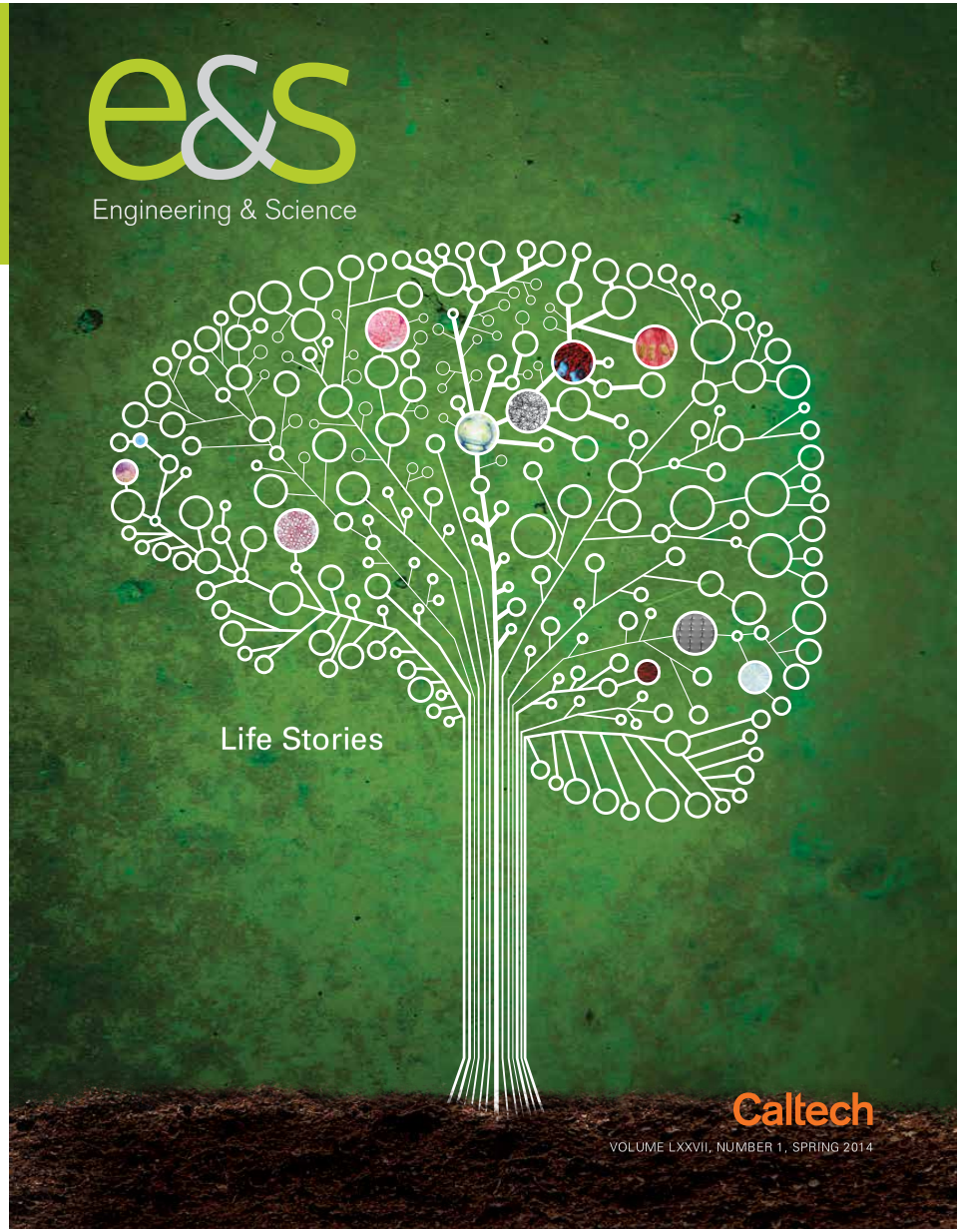

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Engineering & Science

VOLUME LXXVII, NUMBER 1, SPRING 2014

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@Wallpaper: Tonight we played our last show of 2013 for about 100 kids in 40° weather at @Caltech. Might've been the best this year. Amazing send off.

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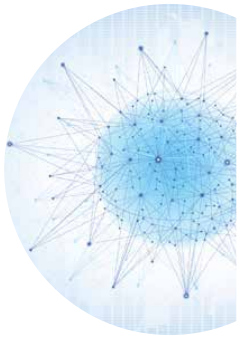
What's In a Name



When it comes to research, we don't do everything at Caltech. We are focused. We move into fields that we think are important. We do the science and engineering that we think has the potential to make a real impact on our world, on our understanding of it, on our society.

Last year, what was Caltech's Division of Biology became its Division of Biology and Biological Engineering (BBE), marking the first time in 43 years that the Institute has renamed a division; at the same time, the Division of Engineering and Applied Science created the Department of Medical Engineering (MedE).

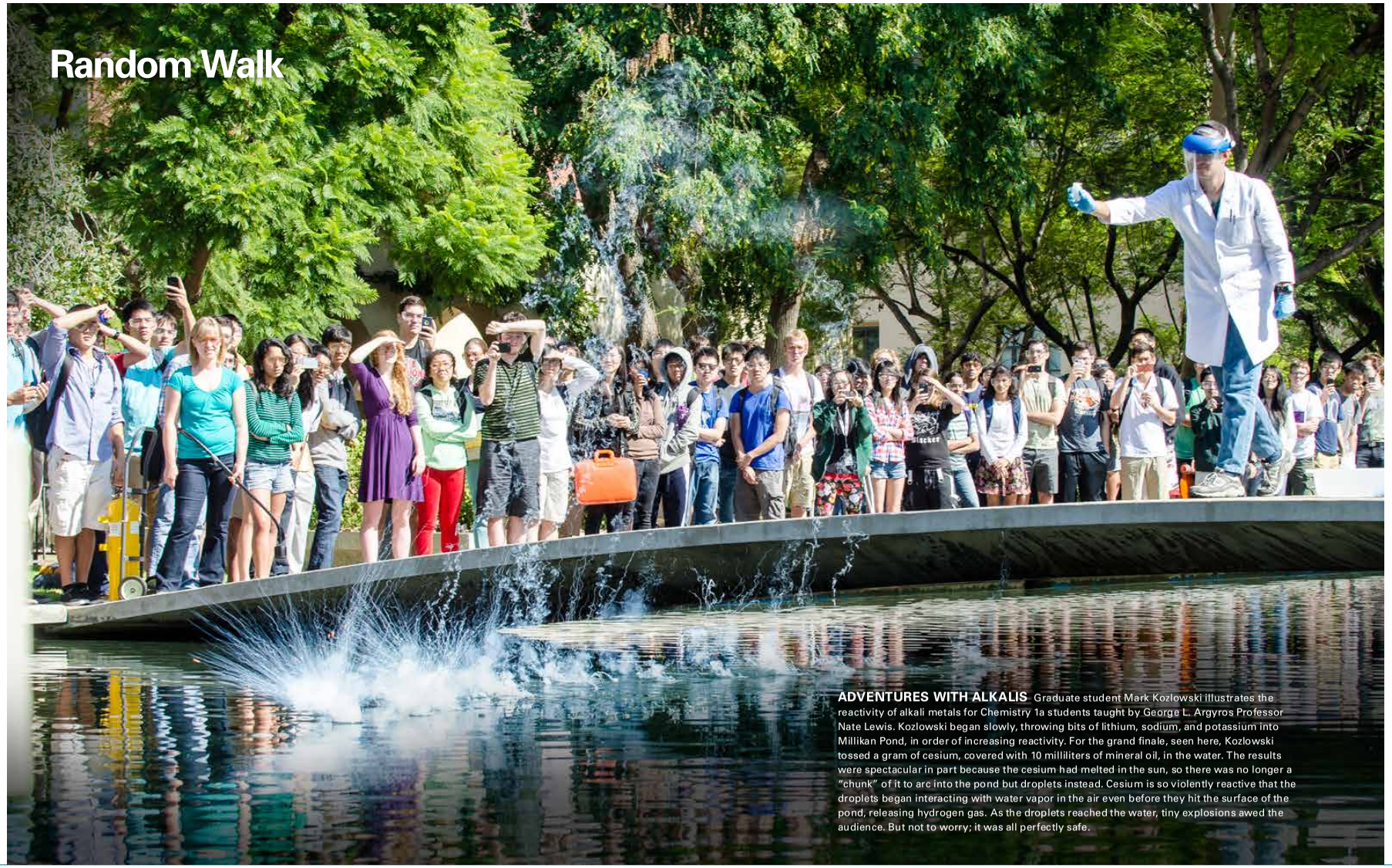
On the surface, those changes might seem cosmetic. After all, they are acknowledging what is already going on at Caltech; they are a reflection of not only our strengths in the basic biological and medical sciences, but in taking the findings from those areas and applying them to change lives.

In truth, however, these changes go deeper. They came about because we—as an Institute—have changed. We have evolved. We have learned. We learned from experience and are ready to take the next leap forward. By including aspects of bioengineering in the names of a division and a department, Caltech is declaring this field's importance to the Institute. By naming it, we are harnessing the energy of all the disparate scientists and engineers who work at the intersections between disciplines on aspects of the same important problems.

We are harnessing the energy of all the disparate scientists and engineers who work at the intersections between disciplines on aspects of the same important problems.

In a way, the story of how BBE and MedE came to be is an echo of Caltech's own life story. After all, these kinds of changes don't happen quickly at Caltech; they do, however, happen purposefully. And that's why we've devoted this issue of E&S to telling a few of the stories about how life and science and engineering intersect at Caltech—in labs devoted to understanding aging at the cellular level, to getting to know how the microbes in our guts impact our health, to creating robotic jellyfish from silicone and muscle tissues, to taking basic findings in the life sciences and turning them into technologies and applications that really make a difference.

Random Walk



ADVENTURES WITH ALKALIS Graduate student Mark Kozlowski illustrates the reactivity of alkali metals for Chemistry 1a students taught by George L. Argyros Professor Nate Lewis. Kozlowski began slowly, throwing bits of lithium, sodium, and potassium into Millikan Pond, in order of increasing reactivity. For the grand finale, seen here, Kozlowski tossed a gram of cesium, covered with 10 milliliters of mineral oil, in the water. The results were spectacular in part because the cesium had melted in the sun, so there was no longer a "chunk" of it to arc into the pond but droplets instead. Cesium is so violently reactive that the droplets began interacting with water vapor in the air even before they hit the surface of the pond, releasing hydrogen gas. As the droplets reached the water, tiny explosions awed the audience. But not to worry; it was all perfectly safe.

On the Grounds

This letter tray, filled with metal type, is located somewhere on campus. Should you decide to run off a broadside or two, all you'd need to do is dip into the tray to get the letters you need, put them in the 6.5"x10" chase (a metal frame that holds type), and ink away. This printing device, a replica of the popular Chandler and Price "Pilot" first produced in 1886, was a hit in the late 19th century among teenage boys who wrote and printed their own newspapers, calling themselves "amateur journalists." Today it is used to teach Caltech students the technology they will need to succeed in desktop publishing should the power grid fail.

Answer: The printing press's letter tray—along with the press itself—can be found in Dabney Hall, in the office of Chris Hunter, assistant professor of English.

FACULTY FOOTNOTES

In September 2013, Assistant Professor of Theoretical Astrophysics Philip Hopkins joined the faculty in the Division of Physics, Mathematics and Astronomy. Hopkins investigates what he calls the formation of "big things"—like stars, galaxies, black holes, and planets. But despite all of the romance associated with looking up into the skies, Hopkins says most of his days are spent sitting at a desk designing computer code. Combining observational data with new models and simulations, Hopkins is working to discover the effects of feedback, or how the activities of one individual star can affect where mass is located within galaxies—and within the universe as a whole.

However, here are a few facts about Hopkins you won't find on his CV:

▸He doesn't come from a long line of scientists.

"My parents were an art history major and a sociology major who never took a math or science class after their freshman year of college. They don't know quite what happened with me."

▸ He once dabbled in writing movie scripts.

"Growing up, a friend and I were really into movies. We haven't done anything like this more recently, but when we were kids we wrote a lot of scripts—we had active imaginations. Now I live near Hollywood, where another friend and his brother actually have an editing studio, which is pretty cool!"

▸ He's looking forward to life in Southern California.

"I have a lot of friends and family in Southern California in general, some in astronomy and some not. It also helps that my wife—a fellow astronomer—got a job next door at Caltech's Infrared Processing and Analysis Center. She is originally from Queensland, so she's extremely excited to live somewhere warm."

Beyond the Bubble

In December 2013, Edward C. Stone, Caltech's David Morrisroe Professor of Physics, paid a visit to *The Colbert Report*, a late-night television show on Comedy Central. He was there to talk about a historic milestone for the Voyager mission: the NASA spacecraft had traveled beyond the solar magnetic "bubble" and entered interstellar space. Stone has served as project scientist for the mission, now in its 37th year, since its inception. As an expert on travel beyond the solar system, he was able to answer host Stephen Colbert's questions with ease. Nonetheless, Colbert was able to catch him off guard in the final segment when, dressed like an astronaut, he presented Stone with the NASA Distinguished Public Service Medal (pictured above). "I was on the Colbert Report to talk about what I think of as humankind's greatest—and certainly most extensive—journey of exploration, and I certainly didn't expect the host to hand me an award," says Stone, who is also a former director of NASA's Jet Propulsion Laboratory. "That surprise on my face was real." The medal is the highest honor for a nongovernment individual. Video segments of the show can be viewed by searching the words Ed Stone at colbertnation.com.

QUANTUM KIDS

A collaboration between Google Creative Labs and researchers at Caltech's Institute for Quantum Information and Matter has enabled a rare educational interaction between quantum mechanics researchers and gaming kids via the video game Minecraft. The popular game, downloaded more than 30 million times worldwide, allows players to freely build and create their own world by mining and stacking different types of bricks in a sandbox-like environment (left). In October, the team—along with educational partner MinecraftEdu—unveiled an add-on, or "mod," called qCraft. It allows Minecraft players to add special blocks to their environment that display several high-level quantum principles—the physics that governs the behavior of matter and light at the atomic (and subatomic) scale—including observational dependency, superposition, and entanglement. Utilizing the game's capabilities for superposition—the principle that allows particles to occupy more than one state at the same time—a number of enthusiastic users have even replicated Schrödinger's notorious simultaneously-dead-and-alive cat. —*JSC*

A Material World

As a group, the disciplines that make up the humanities are often considered rather heady and immaterial, and for a time in the late 20th century, this was especially true. As Caltech history and literature professor John Brewer, the Eli and Edye Broad Professor of Humanities and Social Sciences, says, "Everybody was interested in what everything symbolized, which was rather abstract and metaphysical and linguistic." But now humanists are coming to see a more down-to-earth aspect of their work. A painting by Leonardo da Vinci, for all its intangible meaning, is, as Brewer points out, "made up of linseed oil, wood, and paint, and an enormous amount of effort goes into conserving it, making sure that it's okay as a tangible object."

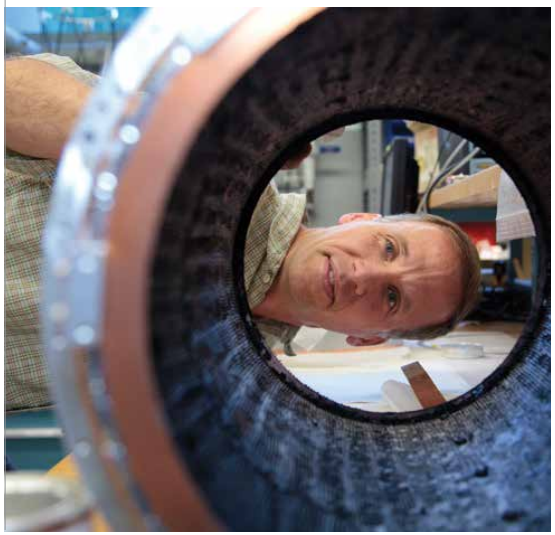
In recognition of this new focus on materiality, or the physical mediums of objects studied in the humanities, Caltech and the Huntington Library, home to the largest and most competitive fellowship program in the humanities in the United States, have joined forces to create Materialities, Texts, and Images (MTI). A two-year interdisciplinary pilot program, MTI will examine the role the material plays in the subject matter of the humanities disciplines by bringing two visiting associates to town, one with an office at Caltech, the other with an office at the Huntington, just a few blocks from campus. Midway through the year, they will swap locations. This spring and summer, each postdoc will design a workshop featuring speakers from a variety of different disciplines to discuss what happens to humanities research when one concentrates on materiality.

This year's associates, selected with an eye to their differences rather than similarities, are Alexander Wragge-Morley, a historian of science looking at the interplay of science, art, medicine, and literature in late 17th- and 18th-century Britain, and Stefanie Sobelle, an English professor examining the overlap of literature and architecture in 20th-century America.—*CE*

Spider Sense: Detecting the Inflation of our Universe

Professor of Physics Jamie Bock hopes the baffle tube he's peering through in the photo below will help him also peer into the early universe. The baffle tube is a component of one of the six telescopes on one of his recent projects, called Spider, which Bock will use to study the inflationary expansion of the universe, an event that is thought to have occurred just a fraction of a second after the Big Bang. Spider's instruments will search the thermal radiation, a fossil relic of the Big Bang, for polarization signals—a telltale signature of background gravitational waves produced by the inflationary expansion. "Inflation is thought to have happened just 10^{-32} seconds after the Big Bang. To think that we might be able to measure something from that period is rather mind blowing," Bock says.

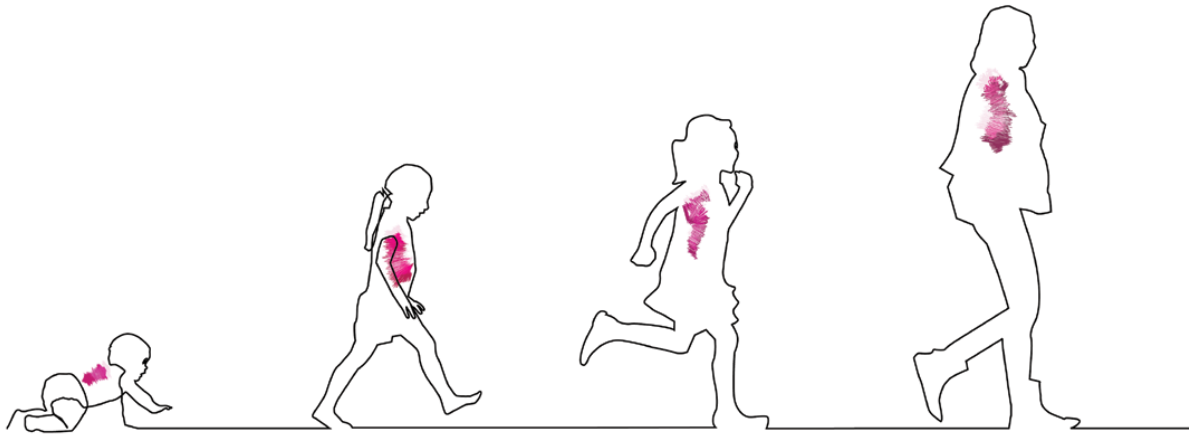
If all goes as planned, Spider will begin a two-week voyage in late December 2014, first launching in a balloon from Antarctica's McMurdo Station and then circumnavigating the continent. Bock hopes a successful Spider mission will lay the technical and observational foundation for future orbital missions dedicated to understanding the origin of the cosmos. —*JSC*



Aging from the inside

by Jessica Stoller-Conrad

Researchers at Caltech peer beneath our wrinkles and gray hair to add to our understanding of aging.



Aging. It's about more than just wrinkles, stiff knees, and hair loss; it's about a process that begins at birth and starts from the inside, affecting how we function at the level of our DNA, our cells, and our tissues. Despite claims made about creams and potions, it's unlikely that science will ever provide us with unending youth. Yet, thanks to improvements in medicine and our understanding of health, humans around the globe are living longer today than ever before. In fact, according to the World Health Organization, in 2011 the average global life expectancy was 70 years, an increase of six years since 1990.

For researchers who study aging, increasing the human life span isn't the only priority. In their studies of how aging affects organisms ranging from yeast to mice to human beings, researchers at Caltech are working to understand the basic, fundamental changes that happen *under* the surface as we age. "Researchers on aging don't really think they're going to find the 'fountain of youth,'" says biochemist Judith Campbell. "Instead, they're looking at ways to try to improve your health span—or, the number of healthy years in the life span."

CLIPPING AND REPLENISHING

Campbell has spent the past three decades at Caltech studying DNA replication—the process necessary to make sure that new cells in your body carry all the same genetic information that the old cells carried. During an embryo's development, cells divide to create organs and tissues; in adults, cell division replaces old, worn-out cells with new ones. Every time one of your cells divides, the double-stranded DNA that makes up that cell's 26 chromosomes unzips into two single strands, each of which then serves as a one-sided template, attracting the molecules needed to build the second, complementary strand.

However, the machinery involved in DNA replication always leaves a little piece of DNA at the end of each strand uncopied—meaning that every time a cell divides, the chromosomes carrying the cell's genetic material get a little bit shorter. To guard against clipping off genes at the end of the chromosome during cell division, the chromosome has protective end caps made up of special DNA sequences called telomeres; during every round of cell division, the telomeres are clipped shorter. After a cell ages—and has divided many times—the telomeres become so short that more divisions and replication would threaten to cut into important gene sequences. At that point, the cell stays alive but ceases to divide, reaching a stage called replicative senescence—a marker of aging in cells.

As it turns out, it was a gene that interacts with these telomeres that led Campbell and her colleagues into aging research. "We were driven to look at aging because the protein produced by one of the genes we were working with at the time, called Dna2, was actually massively concentrated at the telomeres," Campbell says.

Dna2 is a DNA binding protein, Campbell says, but at first she and her team didn't know why it is so strongly attracted to telomeres—or what it does once it reaches them. So they decided to find out, using a tiny, single-celled organism as their guide.

Campbell and her colleagues first encountered Dna2 while working with *Saccharomyces cerevisiae*, or brewer's yeast—the organism best known for turning water and grain into beer. But in addition to its role in crafting fine brews, *Saccharomyces* has also provided an important model for the study of aging, Campbell says.

"In the early 1960s the people studying yeast noticed that even this single-celled fungus showed signs of aging," she says. "Every time that a dividing yeast cell, called the mother cell, grows and divides, it gets older. Then, after about 23 divisions, it goes into replicative senescence."

At least, that's what happens in "normal" yeast cells. But in the 1990s, researchers in Campbell's laboratory noticed that in mutant yeast cells—cells in which the Dna2 gene was absent—the telomeres were shorter than those in a Dna2-laden yeast cell that had been through the same number of divisions. And the mutant cells also entered into replicative senescence after fewer divisions: their aging process seemed to have accelerated.

These findings suggested that, in normal yeast cells at least, Dna2 might have a role in maintaining the length of telomeres. An already-known enzyme called telomerase can slow a cell's aging process by adding a short sequence of DNA to the end of a shortened telomere; this partial restoration of telomere length is especially important in frequently dividing cells, like immune cells and skin cells in humans. Campbell and her colleagues hypoth-

esized that Dna2 might be interacting with telomerase.

Further work has backed up this hypothesis, showing that the telomerase in yeast cells lacking the Dna2 protein was ineffective, unable to add length to the telomeres. In other words, they found that the Dna2 protein was necessary in order for telomerase to function properly.

And that's not only the case in yeast. "We also work on mouse and human cells, and so more recently we've been showing that, in mice, Dna2 does the same things," Campbell says. "I can't tell you if the mice that have a reduced amount of Dna2 age more rapidly, but I can tell you that their telomeres get short."

Dna2 has other tasks in the cell as well; Campbell and her colleagues have recently shown that, in addition to lengthening telomeres, Dna2 plays a role in repairing damaged DNA in yeast, mouse, and human cells.

So, if Dna2 and telomerase work together to replace clipped telomeres, and Dna2 can repair DNA damage, are these two proteins the key to increasing an organism's life span?

They likely have an important role in longevity, says Campbell. But, as she points out, a longer life isn't necessarily a healthier one. Cells that continuously divide, multiply, and never die are dangerous—these are the characteristic traits of cancer. "One of the most important diseases of aging is cancer," she says. "Cancer cells need telomerase, and all tumor cells reactivate telomerase—otherwise, they would only go through a few divisions and you wouldn't get a tumor."

A healthy cell has to strike a delicate balance between clipping its telomeres through cell division and replenishing its telomeres via telomerase and Dna2—in other words, each cell needs to find its balance between aging and cancer. Although Campbell's work began investigating the aging side of this balance in yeast, her lab's focus has now shifted to the role of Dna2 in telomeres—and cancer—in mice.

"I could say that we focus much more now on cancer than on aging, but it's very difficult to dissect those two processes because we're working on machinery that functions in both kinds of biology," Campbell says.

FUSION AND FISSION

While telomeres shrinking on chromosomes are associated with aging, they are not the only age-related DNA changes your cells undergo. Outside a cell's nucleus are free-floating mitochondria—organelles best known as cell "power plants," converting nutrients from the food we eat into usable energy. These organelles contain their own genetic material, called mitochondrial DNA, or mtDNA. And according to biologist David Chan, whose lab at Caltech focuses on the role of mitochondria in health and disease, that genetical material is also involved with aging and, in particular, diseases of aging.

"Mitochondria have their own genome," Chan says. "That genome is very small; it only has 37 genes and only 13 of those are protein-encoding. But all of those 13 proteins are essential to the cells' generation of energy."

For that reason, Chan says, it's crucial that the genes for these 13 important proteins remain relatively free of mutations—acquiring just enough changes to allow evolution to occur but not so many that the cell can no longer function. Indeed, if such negative mutations accumulate, they can have drastic effects on the cell, with those effects being most devastating in muscle cells, in which large numbers of working mitochondria are needed to produce the energy needed for physical activities like walking and running.

"In a young person, all of the muscle cell fibers have varying degrees of respiratory activity from their mitochondria. But then, in an older individual, some muscle fibers start losing their mitochondrial function—and aging people tend to have an increased number of these defective fibers," Chan says. "If you look at the mtDNA in these nonfunctional fibers, there is invariably a mitochondrial genome that has deletions in the DNA sequence—the accumulation of mtDNA mutations increases with age."

These mutations arise as a result of the inevitable interactions between the hundreds or even thousands of mitochondria that are needed to power the routine activities in just one cell, Chan says. "You can have two mitochondria fusing together, becoming one mitochondrion," he says. "And you can also have the opposite process, in which a mitochondrion divides, which is called fission. They constantly come together and separate, come together and separate, as a way to exchange contents."

This give and take between fusion and fission—one aspect of the field called mitochondrial dynamics—can be beneficial for the organelle. "Say there is a mitochondrion with a mutation that prevents it from making an essential protein. After it fuses with a mitochondrion that *can* produce the protein, you get a mixing of gene products—the proteins coded by those genes," Chan says. By conjoining, the mitochondria create a single mitochondrion that has all of the essential proteins—which can then be combined into protein complexes necessary for respiration, he adds.

Chan's laboratory investigated how fusion can benefit mitochondria by studying two genes that control mitochondrial fusion in mice and humans—Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2). In a study published in the journal *Cell* in 2010, Chan and his colleagues showed that the muscle cells of mice with mutations in both Mfn1 and Mfn2 were much smaller than those of normal mice of the same age. Although the animals had the same number of muscle cells, or fibers, the muscles were smaller overall, due to the smaller muscle cells. Furthermore, as the mutant mice grew older, they also experienced an increase in mtDNA mutations compared to normal mice of the same age.

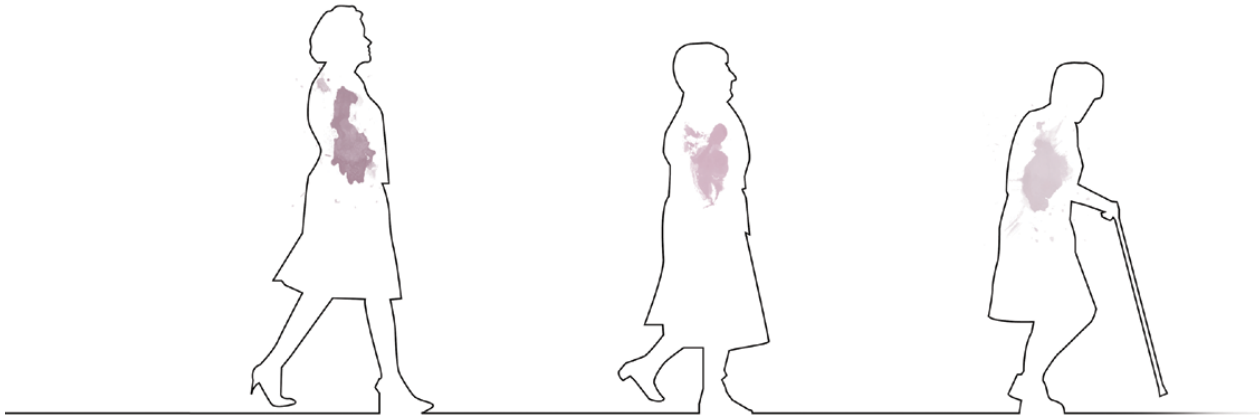
This, says Chan, is a real problem. "We've found that if you simultaneously have more mutations in the mtDNA and a loss of mitochondrial fusion due to a mutation in the mitofusins, there is a synergistic effect and you get much more severe symptoms in the mouse," he says. After all, if mutations in mtDNA genes result in missing essential proteins—and the mitochondrion can't replace these proteins by fusing with a "healthy" mitochondrion—the effects of the mutations will be compounded. "So when there are lots of mutations, mitochondrial fusion seems to be important to mitigate the effects of these mutations," Chan says. "That's how fusion ties into aging."

Chan has also been investigating the role of mitochondrial fusion in Parkinson's disease—a degenerative motor and nervous disorder associated with aging—due to the increased presence of Mfn2 not only in muscle cells, but in the neurons of the brain, nerves, and spinal cord.

Usually affecting people over the age of 50, Parkinson's disease is characterized by a loss of brain neurons that produce dopamine, a neurotransmitter responsible for relaying signals to other nerve cells. As a result, people with Parkinson's often experience symptoms such as trembling hands, slowed movements, emotional changes, and dementia.

The exact causes of Parkinson's disease are not clearly defined, but scientists have found evidence that links the disorder to defects in mitochondrial function, Chan says. For one thing, some inherited forms of Parkinson's disease result from mutations of genes that have a function in the mitochondria. In addition, Chan points to case studies of "young people—some in their 20s—who injected synthetic opiates and developed chronic Parkinsonian-type symptoms. The drugs were later found to be contaminated with a mitochondrial poison," he notes.

With this evidence in hand, Chan and his colleagues have been investigating the role of Mfn2 in the dopaminergic neurons—the main nerve cells affected by Parkinson's—in order to better understand the relationship between mitochondrial fusion and Parkinson's disease. In one part of the study, published in the journal *Human Molecular Genetics* in 2012, the researchers observed both normal mice and mice lacking Mfn2, tracing the spontaneous walking patterns of the mice as they traversed an open space. At



four weeks of age, the Mfn2-less mice traveled only about 68 percent of the distance that normal mice walked; by about 12 weeks, the mice without Mfn2 traveled only approximately a third of the normal distance. These mice also had trouble rearing back on their hind legs and moved more slowly than their normal counterparts.

In other words, says Chan, "when we knock out a gene that's involved in the fusion of mitochondria in the dopaminergic neurons, we get a mouse that has some characteristics of Parkinson's disease. It seems like those neurons are very sensitive to changes in mitochondrial dynamics." Restoring the mitochondria's ability to fuse and divide in damaged cells, then, could be an important aspect of future treatments for Parkinson's disease, he notes.

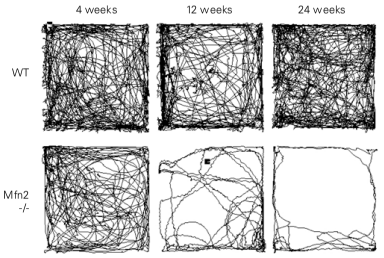
CIRCUIT LIGHTS

Neuroscientist Viviana Gradinaru (BS '05) is seeking to solve the puzzle of Parkinson's disease and the aging brain in a different way: by looking deeply at the brain's neural circuitry.

"Parkinson's is a disease of aging," Gradinaru says. "So if we want to think about increasing longevity, we need to understand what kind of use and abuse the circuits in our aging brains can take, and how we can make them last longer."

One way that Parkinson's researchers currently study these circuits in living human brains is via a therapeutic technique called deep brain stimulation, or DBS, in which physicians or scientists send electrical signals into the brain's motor centers via electrodes. This stimulation has been shown to counteract abnormal brain signals, alleviating the motor symptoms most often associated with Parkinson's disease, such as shaking and hand tremors.

Although used as a therapy for humans, DBS can also be used as a research tool in rodents—allowing researchers to analyze the animal's behavior after stimulating neurons in a certain region of the brain. It's an imperfect tool, however. Because the brain's neurons are so tightly networked and interconnected, the electrodes can "wind up stimulating neurons they're not intended to stimulate," says Gradinaru. This can cause side effects such as mood alterations in human patients and also make it difficult for researchers to be sure they're hitting the specific group of cells they're interested in studying in rodents.



Above: The traced walking patterns of both normal, wildtype mice (WT) and mice lacking Mfn2, a gene necessary for mitochondrial fusion: as they aged, mice without Mfn2 moved more slowly than their aging wildtype counterparts and traveled only a fraction of their walking distance.

All of which is why Gradinaru instead uses a more targeted technique called optogenetics to study how circuits in the brain associate with one another. With this technique, researchers genetically engineer neurons in the brains of rodents to produce a class of proteins, called opsins, which respond to light; neurons producing opsins can then be specifically excited by shining light on them.

By engineering different neurons to produce different opsins, each of which can only be activated by a specific color, or wavelength, of light, Gradinaru is able to use different colors of lasers to activate individual neurons—or networks of neurons—in a living brain in real time. In this way, by stimulating only the targeted neurons and observing their resultant behavior, optogenetics researchers are increasingly able to parse out the specific neurons responsible for specific symptoms in Parkinson's.

Of course, the technique can be applied to other conditions associated with an aging brain. "Optogenetics is being used to study Alzheimer's, Parkinson's, depression, addiction, memory, cognition, and sleep," says Gradinaru. "It can be used with such a wide range of processes because it lets you really focus on any of these circuits, stimulate a small population of neurons, and see what the behavioral and mechanistic outcome is."

In September of last year, Gradinaru received a New Innovator Award from the National Institutes of Health to support her work in the study of circuits involved in Parkinson's—and why the aging brain becomes more susceptible to the disease. "One of the goals of the award is to look at the Parkinson's-related dopaminergic cells over their lifetime," Gradinaru says. "A healthy individual starts with a population of dopaminergic cells that mature and function. But over time, as that individual ages, some of those cells will either die or just won't function as a dopaminergic cell anymore. We want to know how aging contributes to these changes."

One way Gradinaru and her colleagues plan to do this is by using optogenetics to stimulate the same set of dopaminergic neurons in a young brain and in an aging brain, and observing the differences in the animals' behavior. But to be certain they know what's going on, the researchers need to also look at the physical changes that occur in the brain as it ages. They'll be able to do that thanks to a visualization technique Gradinaru helped develop while a research associate at Stanford.

The technique, dubbed CLARITY, renders brain-tissue samples nearly transparent, allowing researchers to visualize those hard-to-see neurons and their connections from deep inside the brain. "The hope is that we can use CLARITY to observe and compare across aging brains and young brains, diseased brains and healthy brains, and get very detailed maps of neuron connectivity," Gradinaru says.

This is important because, as more humans live to very ripe old ages, conditions of aging are being diagnosed at an unprecedented rate—for instance, some researchers believe that over the next two decades the number of Parkinson's diagnoses will double. "The clock is ticking to find a solution," she says.

Although tools like optogenetics and CLARITY help us better understand the aging brain, they are not therapies that can be used in humans now, Gradinaru notes. Still, she says, "while this kind of basic, fundamental research won't directly provide a cure for Parkinson's or a way to halt aging, it's a necessary part of finding better treatments. We can gain a greater understanding of how aging changes specific cells and circuits in the brain."

We aging humans try to hide from the passage of time, but our cells and their genes don't lie—and that honesty provides important information for researchers like Viviana Gradinaru, David Chan, and Judith Campbell.

"Sure, you might be able to develop a cream that makes your wrinkles go away," Campbell says. "But what we're doing through the study of aging is unlocking some of the basic mechanisms of human health. And that's much more important." E&S

Judith Campbell is a professor of chemistry and biology. Her work on telomeres and aging is supported by the National Institutes of Health (NIH) and the Ellison Medical Foundation.

David Chan is a professor of biology at Caltech and an investigator with the Howard Hughes Medical Institute (HHMI). His work on mitochondrial dynamics is funded by NIH and HHMI.

Viviana Gradinaru is an assistant professor of biology. Her work on optogenetics is supported by the Human Frontiers in Science Program, the Beckman Institute, the Mallinckrodt Foundation, the Gordon and Betty Moore Foundation, the Pew Charitable Trust, the CIT-GIST program, the Michael J. Fox Foundation, and the NIH/NINDS New Innovator Award.

A Bacterium's Best Friend

by Katie Neith

It's a common belief that bacteria, in general, are necessary evils—detrimental beings that live alongside us but that we should do our best to avoid. Caltech microbiologist Sarkis Mazmanian, however, is working hard to flip that script; he wants us to recognize that many bacteria are here to help and that we should be embracing them rather than trying to kill them with a barrage of soaps, pills, and sprays.

"I think that we all grew up viewing microbes as insidious little creatures that only want to make us sick—but it's simply untrue," Mazmanian says. "Making us sick doesn't necessarily help bacteria in the long run. What helps microbes most is to create an environment that's hospitable—on the skin or in the gut—for long-term propagation. If I were a bacterium, I would help my host!"

And it would be a selfish move, he points out. That's because the healthier a bacterium's host is, the better the living environment is for that bacterium. Which is why Mazmanian believes that most bacteria have, over evolutionary time, adapted to improve their hosts rather than harm them—an idea he is working to prove through his research.

The idea that our bodies are teeming with propitious microbes has been around for more than 100 years; the term probiotic—referring to a microorganism that may provide health benefits when consumed—was first coined in the 1950s.

If you look across the human population, you'll find that there are close to 10,000 species of bacteria, known as the microbiome, capable of colonizing our bodies; each of us will come in contact with some subset of that group over a lifetime. The number of bacterial pathogens that actually *infect* humans—i.e., cause harm to us—is only about 70.

And yet, Mazmanian says that when he started his work about a decade ago, he was considered to be "completely on the fringes of science" by many of his peers simply for wanting to study organisms that don't necessarily cause disease. Even today, he adds, the vast majority of scientists in the field of host-microbial interactions concentrate solely on the bugs that make us sick.

Fringe or not, however, Mazmanian's point of view has started to gain real momentum. His laboratory was the first to demonstrate that specific gut bacteria from the human microbiome direct the development of the mammalian immune system by enhancing the function of specific immune cells, and provide protection from intestinal diseases by balancing, rather than activating, the immune system. In other words, he says, fundamental aspects of health are absolutely dependent on microbial interactions with—and within—our bodies.

Mazmanian's road to radical thinking in microbiology had a rather inconspicuous start: armed with a love of writing and at the urging of teachers who thought he showed real talent, he entered UCLA as an English major in 1990.

"One of my high school teachers actually went to the trouble, without telling me, of entering a poem I had written in a national poetry contest," he recalls. "And I won first place."

But it was a required biology course—rather than one of his English classes—that caught his attention during his sophomore year in a way that nothing ever had before.

"Perhaps I was more mature than I was in high school, or the stars lined up in a way that made me appreciate it more," says Mazmanian. "But for the first time—and I can say this with a great deal of confidence—I was truly interested in a subject. That was a new feeling for me, to not just learn something but to be captivated by what I was learning. So I took a few more science classes, mostly in microbiology, and I never looked back."

He went on to get bachelor's and PhD degrees in microbiology—both from UCLA.

"I really appreciated how versatile, dynamic, and powerful these little biological machines are, and I've been a microbiologist ever since," says Mazmanian, who joined the Caltech faculty as an assistant professor in 2006 and became a full professor of biology and biological engineering in 2012.

BENEVOLENT BUGS

But Mazmanian hasn't just been *a* microbiologist since his college days; he has quickly become a leader in the field. In 2007 he was awarded a Searle Scholarship, and in 2008 was named one of *Discover* magazine's "20 Best Brains Under 40," which hailed young innovators in science. He was a 2011 recipient of a Burroughs Wellcome Fund award and, in 2012, was named a MacArthur Fellow and awarded a five-year, $500,000 "genius" grant.

Mazmanian's creative and award-garnering work on beneficial bacteria began with a simple notion. Since most symbiotic bacteria live in the intestines, he decided to start looking at the ways they might positively impact a disease in the gut—in this case, Inflammatory Bowel Disease (IBD), which includes such conditions as ulcerative colitis and Crohn's disease, and affects 1.5 million Americans and many more people worldwide. IBD is believed to start when the gut's immune system becomes activated despite the lack of an actual infection, creating chronic inflammation that

Above: A mural, painted in the second floor hallway of the Church Laboratory by a commissioned artist, illustrates segments of the human intestine where bacteria with powerful beneficial effects live.

keeps damaging gastrointestinal tissues, eventually causing such symptoms as bloating, abdominal pain, constipation, bloody diarrhea, and severe weight loss.

Mazmanian theorized that introducing "good" bacteria into a gut under siege might work to balance and thus tame this misguided immune response. So he and his team used mouse models of IBD to identify organisms that interact in a positive way with the immune system. These initial studies identified *Bacteroides fragilis*, a member of the human microbiome that produces a molecule with powerful anti-inflammatory properties, essentially stopping IBD in its tracks.

Not content to tackle only IBD, Mazmanian decided to venture beyond the gut and into the central nervous system.

"Based on both human and mouse studies, we knew that the immunological response driving multiple sclerosis was very similar to the inflammatory cascade that causes IBD," he explains. "And so we wondered if maybe beneficial microbes living in the intestines might be able to have an effect outside of the gut."

Multiple sclerosis (MS) is a neuro-inflammatory disease in which the immune system attacks the protective sheath around nerve cells, causing symptoms from tingling to numbness and even paralysis in extreme cases. As they had done in their IBD experiments, Mazmanian and his team set up cases of MS in mice, introduced *B. fragilis* bacteria into the gut and, sure enough, were able to demonstrate regulation of inflammation in the central nervous system and amelioration of the symptoms associated with MS in mice, most importantly paralysis.

"It was astonishing to see beneficial effects of the gut microbiome in tissues as distant as the brain and spinal cord," says Mazmanian.

Having looked at how gut bacteria can change and shape the immune response both in the gut and in the brain, the team is now considering how those same bacteria might affect the nervous system directly, influencing everything from neurological diseases to common behaviors. After all, Mazmanian says, the kinds of helpful molecules the microbes produced in the IBD and MS experiments are capable of interacting with any kind of cell, whether it's part of the immune system or not.

"As far as a microbe is concerned," he says, "a cell is just a cell."

To see if he could prove that point, Mazmanian began working with Paul Patterson, the Anne P. and Benjamin F. Biaggini Professor of Biological Sciences, Emeritus, a few years ago on a program to study the effect of the bacteria in our bodies on some of the behaviors seen in autism. Why autism? For one thing, Patterson had recently modeled autism in a mouse and reproduced many of the features of the disorder in humans, including the so-called leaky gut issues that many children with autism experience. He and Mazmanian then introduced probiotics—again, *B. fragilis*—into the bellies of the animals to see what influence the bugs might have on the GI problems as well as specific behavioral symptoms.

They recently reported their results in the journal *Cell*, noting that the probiotic-treated mice showed fewer signs of anxiety, were less likely to engage in a repetitive behavior, and were more likely to communicate with other mice than their untreated counterparts. Anxiety, repetitive behavior, and defects in communication are hallmarks of autism. Mazmanian thinks these changes may be thanks to the microbiome's regulation of the release of certain metabolites involved in developmental functions.

"We've been working for several years on exactly what these mechanisms are and how commensal microbes interact with other microbes in the gut, how they interact with the gut's epithelial cells, how they interact with the gut's immune cells, and how they interact with the nervous system, all in the context of autism," he says.

The ultimate goal of his research, Mazmanian notes, is the development of therapeutic probiotics—pills containing helpful organisms that would colonize your gut and keep you healthy. Such pills would be used to address more than just IBD or MS or autism; they could, Mazmanian says, be useful in both protecting against and reducing a wide variety of symptoms and conditions associated with the immune, nervous, and metabolic systems.

"We describe our efforts as discovery of 'drugs from bugs,'" he says.

So why not just grab some of the commercially developed probiotics on the market today? While there are certainly plenty to choose from, Mazmanian says, there is little to no evidence that they provide any real benefit when tested in clinical trials. After all, the bacteria in the probiotics available at your local health-food store were chosen for their long shelf life rather than for benefits shown through medical research. And while Mazmanian expects that probiotics based on his studies will be in clinical trials within the next two years, he knows that the natural course of drug development takes time; he says it's likely to be at least a decade before these probiotics to become available at your local pharmacy.

In the meantime, Mazmanian says, the best thing we can do to keep ourselves healthy and to give ourselves the benefits offered by the obliging microbes already in our bodies is to stop using antimicrobial agents and reduce high-fat, high-sugar diets. He points out that in Western societies—where antibiotics, sanitation, and the use of antibacterial products are the norm—rates of IBD, MS, and autism are increasing rapidly. The "cleaner" we live, it seems, the more likely we are to increase our risk of developing these kinds of immunologic and neurologic disorders. He also notes that the "Western diet" alters the microbiome, which may impact the effects of gut bacteria on the immune and nervous systems.

Modern lifestyles include strategies that have led to critical advances in controlling infectious disease. However, "in our efforts to distance ourselves from infection, we've also altered our association with beneficial organisms," Mazmanian says. "I think evidence is mounting that the absence of microbes may well be a risk factor for certain diseases.

A HELPING HAND

Mazmanian's beneficial bacteria aren't just improving health; they're also helping to advance science in Armenia. Or, at least, they're helping to fund that advancement of science. When he isn't testing the effects of beneficial bacteria in the lab or helping the young scientists he mentors develop into independent thinkers—something he calls his "greatest joy"—he is using the funds from his MacArthur grant to help provide aid to the Armenian scientific community.

"When you go to developing countries and see the conditions by which other people are trying to do science, it's night and day compared with the standards we enjoy in the United States," says Mazmanian. "I'm Armenian—if I didn't use the opportunity as a successful scientist to help bourgeoning scientists in Armenia, then I wouldn't be using my very fortunate position to its fullest."

So, beginning in 2008, Mazmanian worked to build a relationship with scientists and university administrators in Armenia. These days, Mazmanian and three additional scientists he's recruited from different U.S. institutions head to the Molecular Biology Institute in Yerevan, Armenia, each fall, where they spend a week teaching 50 to 60 graduate and medical students about the ways humans and microbes affect and shape one another's lives.

"It's really a small contribution in the grand scheme of things, because there's only so much you can do in one week," Mazmanian says. "I leave once the course is over, and for 51 weeks they go back to very poor conditions—it's like a Band-Aid on a festering wound."

The way to really begin to close the wound, he says, would be to build—from the ground up—a research institute in Armenia that is based on the scientific approaches and technologies being used in the United States, Europe, and Japan—the world's leaders in scientific discovery. That, he says, would be a true benefit to the people of Armenia.

"Whether or not this will happen, I'm not sure," says Mazmanian. "But it's my dream. If it comes to pass, I think it could be the most impactful thing I will ever do as a scientist."

He is quick to point out, however, that for any gains he makes in Armenia, he has countless people to thank back in the States. Without the successes of his research lab, none of his extracurricular work would be possible.

"So many students and research fellows have given abundant time, energy, and intellect to help move forward our lab's contribution to science and society," Mazmanian says. "Their hard work has put me in a position to help others."

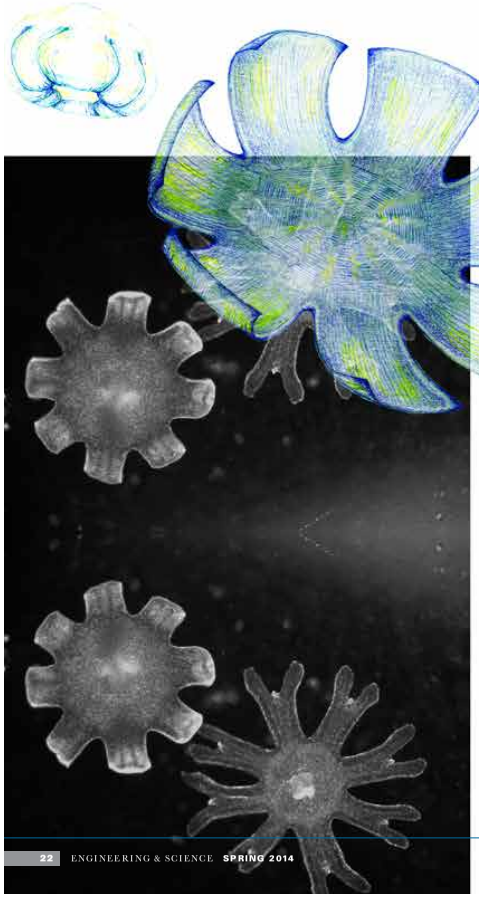
And though he hasn't done creative writing in many years, Mazmanian doesn't hesitate to wax poetic about his and his team's ultimate ambitions to change the public's view of bacteria into a more positive sentiment.

"If our bodies are colonized with microbes not making us sick, there is no room or space for invaders," he stresses. "For example, if you have lush vegetation, weeds don't grow. But if all the plants die off, the weeds come because there is room for them. The microbes that live inside and on us actually help us fight off infections, they improve our immune and nervous systems, and our lives. If we embrace them as old friends and not as new enemies, then we may appreciate and potentially harness the awesome power of bacteria as revolutionary therapies for people suffering from various diseases, both in the U.S. and abroad." E&S

Sarkis Mazmanian is a professor of biology and biological engineering. His research is funded by Caltech, the National Institutes of Health, the Crohn's and Colitis Foundation, the Department of Defense, Autism Speaks, and several other charitable organizations.

MEDUSOID IN MOTION

by Cynthia Eller

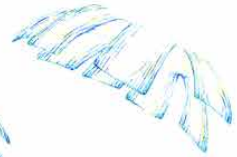


Call it a medusoid—that's what its makers have dubbed it. Or, if you prefer, call it a ratfish, since it was constructed by layering rat muscle tissue atop a silicone substrate. Or perhaps you'd prefer cniborg (rhymes with cyborg, which is what it is, from the phylum Cnidaria); or robojelly, since this star-shaped creature, constructed in the lab of Caltech bioengineer John Dabiri, is both robot and jellyfish.

Whatever you call it, this one-centimeter-diameter creature is worthy of your attention. Although the medusoid is not the first nor the only attempt to culture cells in the lab and attach them to an inorganic substrate, it does something no other such invention has yet been able to accomplish, something truly extraordinary: it swims.

This may not seem amazing to you. Perhaps you yourself can swim. Even a paramecium can swim, with only one cell to its credit. But for the medusoid—which lacks a heart, a brain, or even a central nervous system—it's quite a feat. According to Dabiri, who came up with the idea of bioengineering a cyborg jellyfish, and biologist Janna Nawroth, who designed the creature, making a medusoid that could swim was a three-and-a-half-year labor of love and science.

The medusoid is the product of a collaboration across disciplines, marrying biology to engineering, electrophysiology to fluid dynamics. This description suits Dabiri himself, whose work with jellyfish comes not simply from an interest in marine life, but out of an appreciation for the jellyfish's simple but effective form of propulsion.



"As a kid I was fascinated with rockets and helicopters and airplanes," Dabiri remembers. This enthusiasm for moving and flying things grew into an interest in fluid dynamics, a field of engineering that, in spite of the term *fluid*, applies to both water and air. For Dabiri, fluid mechanics is "a challenging topic but also a really beautiful one. You see these water motions that a jellyfish creates, and it's neat to think that you could describe them with a few equations."

Those motions, or vortices, are the result of the jellyfish's repeated cycles of body contraction and relaxation. What makes jellyfish propulsion fascinating is that the creature continues to propel itself through the water during its relaxation phase (though not quite as far as during its contraction phase). In most animals, this is not the case. Propulsion occurs when the muscles contract, but when they release, propulsion slows down, or even reverses.

In the spring of 2008, after Dabiri had given a lecture at Harvard on the intricacies of jellyfish propulsion, Harvard bioengineer Kit Parker introduced himself to Dabiri, commenting that the videos of juvenile jellyfish propelling themselves through the water had brought to his mind the muscular contraction and relaxation of the heart tissue he was working with in his lab. Parker had by then pioneered a technique through which muscle cells would attach themselves in an organized fashion to fine lines of protein laid down on silicone. This work marked the first time that researchers had been able to grow muscle cells that would not only contract and relax individually, but would act as actual muscle *tissue,* the cells working in concert with one another. Dabiri and Parker realized that Parker's "functionalized" laboratory muscle tissues meant that it was now theoretically possible to build from biological materials, in the lab, something that could potentially swim as a jellyfish does.

The medusoid is the product of a collaboration across disciplines, marrying biology to engineering, electrophysiology to fluid dynamics.

Making this robo-jellyfish, Dabiri knew, "would require a broad range of skills—tissue engineering, electrophysiology, fluid dynamics. But what it required first of all is someone who is persistent."

With those requirements in mind, Dabiri assigned the creation of the medusoid to Nawroth as her doctoral thesis project. Nawroth had originally come to Caltech to study neuroscience, but when her mentor moved to Germany, she started looking for other opportunities. Having been intrigued by the work in Dabiri's lab during an earlier research rotation, Nawroth returned, looking for a meatier project. Dabiri handed her the medusoid challenge.

Over the next several years, Nawroth would move back and forth between Parker's lab at Harvard and Dabiri's lab at Caltech. At Harvard, Nawroth worked on tissue cultures, learning Parker's methods for attaching cells to substrates; at Caltech, she turned to questions of what the appropriate architecture might be for a medusoid. This back-and-forth was helpful, Nawroth says, because Harvard's biologists were, like herself, "much more used to dissecting organisms and analyzing their internal structure." The engineers in Dabiri's lab, on the other hand, were more interested in examining the shape, movement, and fluid interactions of intact jellyfish so as to find the best possible design for an engineered creature that could swim.

From the outset, Dabiri's focus was on function rather than form. "For centuries, there's been an interest in biomimicry," Dabiri explains, "in building something that looks like a biological system. If you're trying to build an airplane and you see a bird, for example, you might start by mimicking its flapping wing design. But the history of aviation shows us that until we decided to use a fixed wing and stick an engine on the back of it, that plane wouldn't go anywhere. So we're realizing that directly copying animals isn't the way to success. Instead, we have to figure

out the underlying physical principles and then bring engineering materials and control systems to bear on them." Which is why Dabiri tasked Nawroth with designing a creature that *moved* efficiently like a jellyfish; what it looked like, he said, didn't matter.

With this broad mandate, Nawroth initially came up with some very *un*-jellyfish-like prototypes, each of which took about a year to design and construct, and each of which, in turn, failed. Ultimately, the design that worked—the medusoid—had a star shape reminiscent of a juvenile jellyfish. But that, says Dabiri, was just coincidence: they were replicating jellyfish propulsion, not jellyfish physiology.

In her first research rotation in Dabiri's lab, Nawroth had experimented on the effects of water temperature on the shape of adult jellyfish. Juvenile jellyfish have star-shaped bodies with gaps between each petal or lobe. As they grow, webbing fills in between the lobes to form the bell, or body, of the jellyfish. According to Nawroth's observations in Dabiri's lab, jellyfish that grow in colder water—which is more viscous—develop webbing more slowly, using "sticky" layers of viscous fluid between the lobes to give them greater traction on the fluid through which they must move.

Below: The bottom strip of images shows a juvenile jellyfish as it contracts and releases its muscles; above those are illustrations of the same process as performed by the medusoid.

Jellyfish in warmer waters grow tissue between the lobes more rapidly, to compensate for traction lost by contact with the less viscous warm water.

Because Dabiri was planning to use mammalian (rat) muscle to power the medusoid, a warmer fluid environment—close to human body temperature—would be needed, and this suggested that the medusoid would require smaller gaps between its lobes. "People always talk about DNA, DNA, DNA," he says. "But in reality, the environment plays a big role in determining the shapes and sizes of organisms. Knowing the environment in advance helps us think more constructively about design."

attempted similar experiments on jellyfish, a tricky business, she reports, since a jellyfish "is evolutionarily so far away from a rat, and many dyes and experimental techniques developed for rodents don't work in jellyfish." Nevertheless, these optical maps confirmed for Nawroth that the wave pattern along the muscles in the lobes of a juvenile jellyfish and those in the heart muscle of a rat were similar enough that the latter cells could indeed stand in for the former.

But what to attach them to? Dabiri and Nawroth knew that whatever they laid the muscle cells on would need to be able to recoil—or flap—with each released contraction of the muscles, just

Nawroth initially came up with some very *un*-jellyfish-like prototypes.

The next step in making a medusoid was to determine whether or not rat heart muscle—the key component in Parker's tissue experiments—shared more than a superficial similarity with the muscles of a juvenile jellyfish. Nawroth began directly examining the propagation of electrical signals through rat muscle tissue using a procedure called optical mapping, in which cells are stained with a dye that is voltage sensitive. As an electrical stimulus passes through the muscle tissue, the color of the dye changes, making it possible to directly visualize the tempo and movement of the electrical charge. Nawroth then

as the mesoglea (the middle, jellylike layer of tissue) in a jellyfish does. They already knew from Parker's work that muscle cells could adhere to silicone if it was properly prepared with lines of protein; fortunately a thin piece of silicone is also suitably elastic for an efficient recoil. And so silicone it was.

With such a lightweight material to control, the researchers knew that they could apply their muscle cells very sparingly. In the end, they needed only a one-cell-thick layer of muscle cells to be able to flap the silicone substrate.

Two challenges remained, both fairly easily solved once Nawroth had put silicone and cells together into a workable design. First, Nawroth needed to figure out how to protect the medusoid's muscle cells—after all, the cells came from rats, where they are ordinarily covered by layers of more muscle, bone, fat, and skin—and how to keep the cells fed. She determined that placing the medusoids in a tank of carbohydrate-rich cell-growth medium would protect the cells, and that the sugar in the growth medium would easily be taken up as food—and thus energy—by the muscle tissue.

"Muscle tissue is more efficient in storing energy than, say, trying to attach a battery to the medusoid," says Dabiri, who explains that this is one of the key advantages of using a biological rather than a synthetic material to mimic jellyfish propulsion. "The medusoid doesn't require a big backpack with a battery on top, because the energy is taken from the solution."

Nawroth's second challenge was to figure out how best to stimulate the medusoid's muscle cells to contract in unison, in a productive pattern. Nawroth provided her medusoid a pacemaker by attaching two U-shaped electrodes to the side of the tank and using them to deliver a pulse of electricity through the water every second. Like the coxswain in a boat commanding the rowers to stroke in unison, the electrodes commanded the medusoid's muscle cells to contract, relax, contract, relax—and thus propel the medusoid through the water.

Set loose in their tank, the 20 or so medusoids Nawroth ultimately created did in fact look strikingly like juvenile jellyfish pulsing through the water. Sadly, within an hour, and as expected, their response to the electric pulsing slowed and eventually stopped; this was due, says Nawroth, "to the physiological stresses and toxic electrochemical products generated by the stimulation over time." Following their successful experiments, Dabiri, Nawroth, and Parker coauthored a paper reporting their findings, titled "A tissue-engineered jellyfish with biomimetic propulsion." It was published in *Nature Biotechnology* in August 2012.

A tiny swimming disk of silicone and rat muscle is exciting all on its own. But that excitement ratchets up a notch or three when you consider that something like a medusoid—a bioengineered, self-sustaining contractor—could one day be used to address human heart malfunctions.

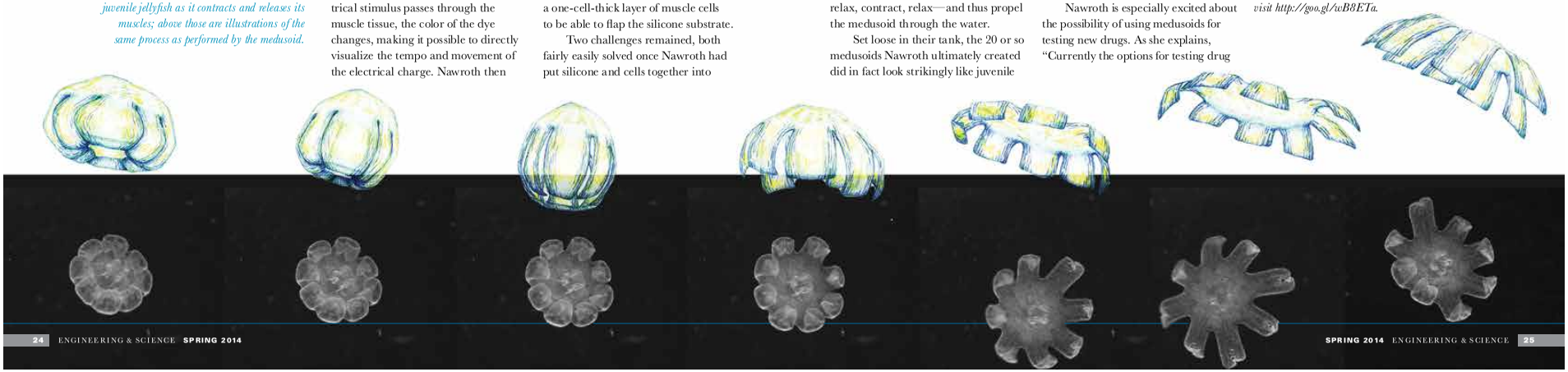
"If you're thinking about building an artificial heart or a valve or an active stent," Dabiri explains, "you want materials that are biocompatible and relatively gentle in handling blood cells. Biologically inspired systems that can deform and generate a gentle flow, as the medusoid does, are things that I think have an interesting future. A heart is an amazing system," says Dabiri, "but there's no reason not to ask how we could improve upon what nature has refined over millions of years."

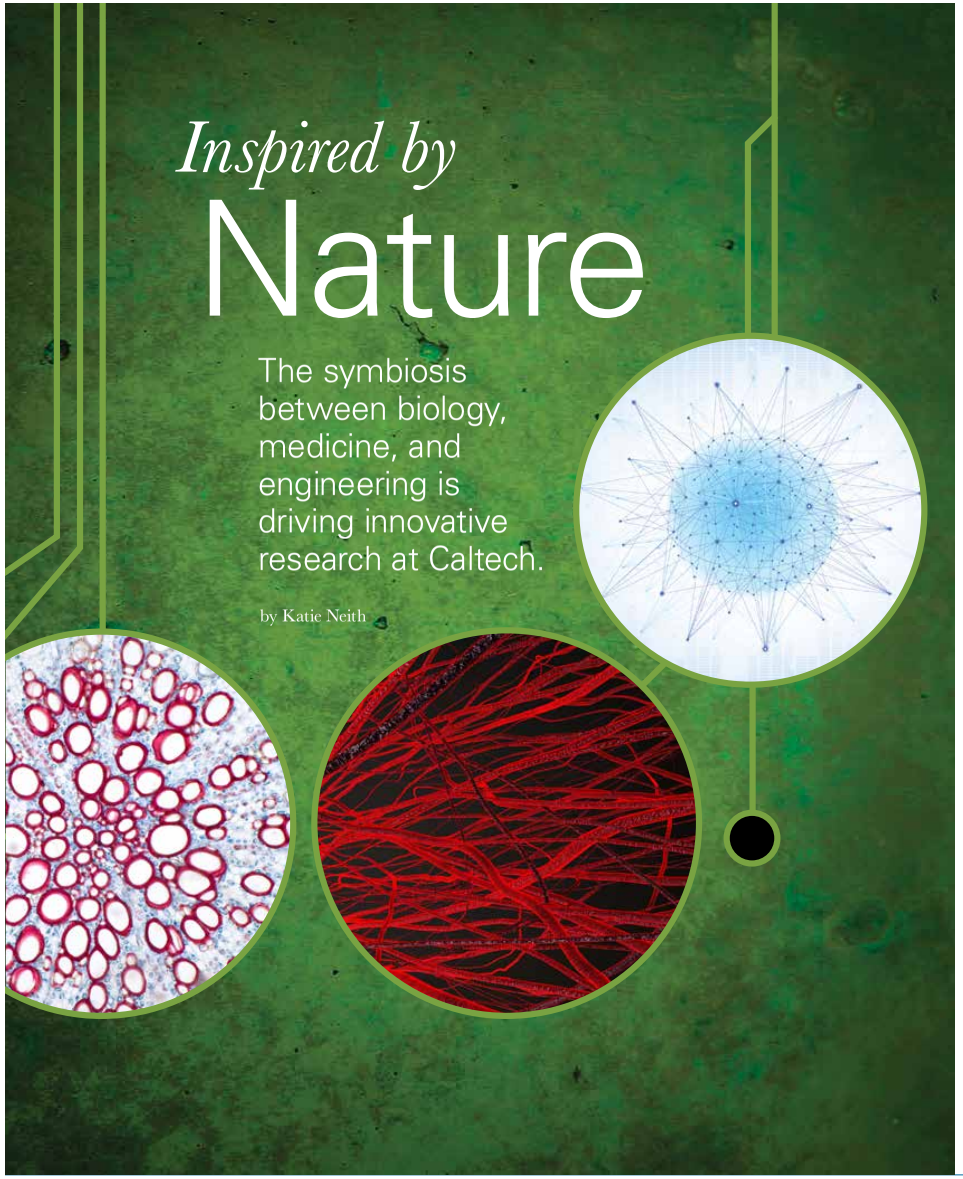
Nawroth is especially excited about the possibility of using medusoids for testing new drugs. As she explains, "Currently the options for testing drug efficacy and biosafety are pretty limited. To test biosafety, you have a cell culture, and you just put the drug on it and see if the cells survive. If the drug passes that test, you go to an animal model to test efficacy. But this is very costly and not always informative about the effect the drug will have in humans. So one idea is to build medusoids from human-derived cardiac muscle and then test the effect of cardiac drugs on the swimming of these specialized medusoids. This would serve as a proxy for cardiac muscle health and contractile strength."

The work on medusoids also contributes to basic science and engineering. "By getting closer to these engineered systems that incorporate both muscle tissue and biological control, we're able to ask more precise questions about the evolution of design," Dabiri says. "It helps us better understand the biology, and it also helps us to build better technologies." E&S

John Dabiri is a professor of aeronautics and bioengineering; Janna Nawroth, who received her PhD in biology from Caltech in 2013, is now a postdoctoral fellow with the Disease Biophysics Group at Harvard's School of Engineering and Applied Sciences. *Their work on the medusoid was funded by the National Science Foundation, the National Institutes of Health, and the Office of Naval Research. Jellyfish were provided by the New England Aquarium and the Cabrillo Marine Aquarium.*

To see a video of the medusoid in motion, visit http://goo.gl/wB8ETa.





Inspired by Nature

The symbiosis between biology, medicine, and engineering is driving innovative research at Caltech.

by Katie Neith

Learning how to program biological molecules as if they were computers in order to build molecular machines with the ability to process information, make decisions, take actions, learn, and evolve.

Gathering the information gleaned from more than three decades of battling HIV in order to engineer antibodies that can outsmart the virus's attempts to evade destruction.

Detailing the biophysics and biochemistry of the zebrafish heart in order to create man-made artificial pumps that one day might help human hearts beat a little more steadily.

Building an understanding of the basics of a phenomenon so that you can pursue the best and most practical way to apply those findings—often within the same research group or collaboration—is the crux of bioengineering at Caltech. Instead of handing knowledge off, Caltech's scientists and engineers use what they've learned to solve the problems they are most interested in.

To acknowledge and formalize its commitment to this kind of continuity and collaboration, last fall the Institute combined the disciplines of biology and biological engineering into the Division of Biology and Biological Engineering (BBE). It was a move that created an academic division unlike any other among its peer institutions, and the first time a Caltech division has been renamed since 1970. Simultaneously, the Division of Engineering and Applied Science (EAS) announced it would be providing a more solid platform for the in-depth exploration of bench-to-bedside medicine by dedicating an entirely new department to medical engineering (MedE).

"We've been doing bioengineering work at Caltech for a long time, but we've never organized it in such a way that the connection between the science and the engineering was so clear," notes Caltech vice provost Mory Gharib, whose own research focuses on what he calls bioinspired engineering. "Now we're set up so that we can not only develop the scientific understanding of biological engineering and then apply it, but we can also translate it to a clinical setting. This, I believe, is creating a model for the rest of the country. Instead of putting researchers in boxes, we are trying to nurture them in a collaborative, fluid way."

BUILDING FROM BASICS

The study of nature—of what goes on in the living world around us as well as the one inside our own bodies—is among the oldest fields of human inquiry. Scientists working in biology have long examined plants, animals, and other organisms to determine how they are structured, as well as to better understand how they function and how they evolve.

But even before we were able to understand our surroundings, we worked to improve them, to solve the various problems we encountered by using the raw materials around us to develop tools, machines, and other technological solutions. It's a most basic of human endeavors; a pursuit we refer to today as engineering.

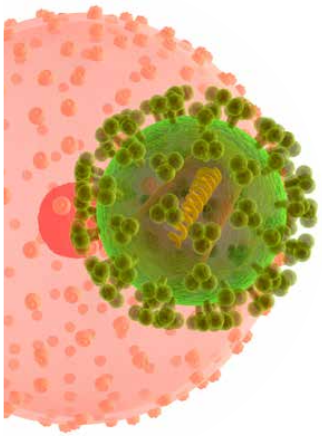
Those two approaches—that of basic science and that of engineering—tend to address similar questions and problems from different angles, says Gharib. As, he adds, do biological and medical engineering, as exemplified by the fundamental approaches taken by researchers in BBE and MedE, respectively. "In trying to understand how biology works and then building upon that to get to the point where it can contribute to the field, biological engineering is bottom-up. Medical engineering, on the other hand, is top-down. We look at the problems that are currently challenging to the field and try to come up with devices and techniques to help clinicians do their job better or make breakthroughs. Essentially, we're looking at the same wall from two different sides."

This kind of dedicated focus on bioengineering, no matter which side of the wall a researcher is on, Gharib notes, "will not only help coordinate scientific work at Caltech but will also give outsiders a more accurate impression of how we at Caltech are taking a multifaceted approach to the challenges of this field across disciplines."

According to BBE chair Stephen Mayo, who guided BBE through its reorganization, melding biological engineering with the fundamental science of biology is a unique way of approaching this area of research. "Although other schools have biological engineering programs within their schools of engineering," he notes, "none has a college or school in which biological engineering is integrated directly with biology, so that they can enhance each other—allowing those people who are doing engineering to interact more closely with those who are doing fundamental work and obtaining basic knowledge."

Caltech's Division of Biology was originally founded in 1928 by Nobel Prize–winning geneticist Thomas Hunt Morgan. As part of its transformation into BBE, it has added 11 faculty members who also work within other Caltech divisions; their research areas include genetic engineering, translational medicine, synthetic biology, and molecular programming.

"The formation of BBE is a reflection of the diversity and breadth of activities in engineering and the biological sciences at Caltech—from the structure and function of proteins at the atomic level to developing nanoprobe electrodes that can simultaneously measure the activity of thousands of neurons in the brain," says Mayo. "Putting these activities into one division increases the potential and the pace for providing transformative solutions to some of the biggest problems in science, medicine, and health."



Biologist Pamela Bjorkman is working to engineer antibodies that function more effectively against HIV, seen above (in green) infecting a cell.

EAS's new MedE department, spearheaded by EAS chair Ares Rosakis and a core group of faculty, joins six other departments in the division, each of which is grounded in a specific engineering discipline. "We have been engaged in medical engineering for several decades, but are now formalizing our commitment to this area by focusing more resources on finding fresh avenues for developing diagnostic tools, medical devices, and treatment options, in an approach sometimes known as translational, or 'bench-to-bedside,' medicine," says Rosakis. "The evolution of MedE reflects the desire of many faculty members and of local research hospitals and medical foundations to engage jointly in engineering-centric technology-development efforts for medical applications."

To that end, MedE is already partnering with the Keck School of Medicine of USC, UCLA's David Geffen School of Medicine, City of Hope, the UCSF School of Medicine, and Huntington Memorial Hospital, among others. Alongside the newly established BBE division, MedE positions Caltech to become an even more dynamic force in the field of bioengineering, says Rosakis.

"Caltech really has an opportunity here," says Yu-Chong Tai, the inaugural executive officer for MedE. "While there are more than 60 accredited biomedical engineering programs in the United States, and there are about 100 biomedical programs at various universities and institutes, Caltech is engaged in a very unique pursuit. The work we want to do relies on deep engineering, which is our strength at Caltech. That's why our intention is to build the Caltech medical engineering department in a way that is rooted in really first-class engineering, moving from that base toward medical applications."

Not every aspect of bioengineering at Caltech is undergoing an evolution, however: the Institute's Donna and Benjamin M. Rosen Bioengineering Center, founded in 2008 through an $18 million gift from the Benjamin M. Rosen Family Foundation, will remain an intellectual hub for bio- and medical engineering resources and activities, and will continue to be jointly administered by BBE, EAS, and the Division of Chemistry and Chemical Engineering.

"The Rosen Center acts as a kind of glue that ensures that the broad bio-related engineering activities on campus have a central point of coordination and support," Mayo says.

TRANSFORMATIVE SOLUTIONS

For bioengineer Lulu Qian, this renewed recognition of the importance of her field for Caltech plays out every day in her lab, where she and her team apply engineering's computer programming principles to biological molecules like DNA and RNA. Qian, who became one of the first new members of BBE when she joined the Caltech faculty last year as an assistant professor, is bringing to this problem both the biological knowledge and the computational expertise she gained when she spent time as a Caltech postdoc working with Shuki Bruck, the Gordon and Betty Moore Professor of Computation and Neural Systems and Electrical Engineering.

"Nature has been very successful in evolving and selecting the most efficient and powerful biological systems made of simple individual molecules," says Qian. "If we want to use the full potential of molecules to create complex and programmable systems, we'll need to borrow biology's own information-processing principles."

For example, Qian and her lab members, inspired by learning and memory-forming rules in the brain, are working to create synthetic DNA neural networks that can learn from their biochemical environment and recall patterns of biochemical signals. Such circuitry could, in the future, lead to molecular robots that respond intelligently to unexpected events they encounter during autonomous operations such as delivering drugs in the body. Inspired by collective behaviors such as foraging in ants and swarming in termites, Qian's group is working to build molecular robots that may have simple functions as individuals but are able to perform remarkably complex tasks when in groups.

"I take inspiration from biology and apply the conceptual frameworks and tools of computer science to molecular engineering," says Qian. "My research aims to extend computer science with new molecular substrates, and to create new frontiers in chemistry and the biomedical sciences."

While Qian is applying what she's learned from biology to her engineering pursuits, biologist Pamela Bjorkman is attacking from another angle—applying engineering principles to the development of innovative ways to counter the human immunodeficiency virus (HIV), the infectious agent that causes acquired immunodeficiency syndrome, or AIDS. A worldwide scourge, AIDS has killed an estimated 35 million people, according to the World Health Organization. Another 34 million are believed to be living with HIV.

Specifically, Bjorkman and her team are trying to create—or, rather, engineer—antibodies that can work more effectively against HIV, which is difficult for the human immune system to clear from the body once it has been infected. There's only one clear target on the virus for antibodies to go after—spikelike proteins that stick out of the outer coat of the virus.

The problem is that HIV-1 can easily evade these antispike antibodies because its spike proteins—which are used to bind to receptors on the host cells it wants to infect—are able to rapidly mutate so that the antibodies are no longer able to recognize or glom onto the spikes.

It's that evasive technique that Bjorkman and her team are trying to counter in the lab. "We are using structure-based protein design methods to engineer antibodies that can fight back against some of the common routes of HIV mutation," says Bjorkman.

The production of ever-changing types of antibodies in response to an infection is a remarkable example of real-time evolution, Bjorkman says. The immune system begins churning out huge numbers of antibodies when it detects a pathogen in the body; the ones that bind best to that pathogen are then made in large quantities. By studying the natural antibodies produced by an infected host, she hopes to learn what makes certain antibodies—in particular those targeting HIV—effective, and to then take the optimal properties found in various anti-HIV antibodies in order to engineer new versions specifically created to have many of those advantageous properties.

"It's this ability to draw on both the quantitative and engineering aspects of biology that puts those of us in the Caltech community in a unique position to conduct both fundamental and applied research," Bjorkman says. "And that's what will ultimately help us to make real improvements in human health."

ADDRESSING SOCIETAL NEEDS

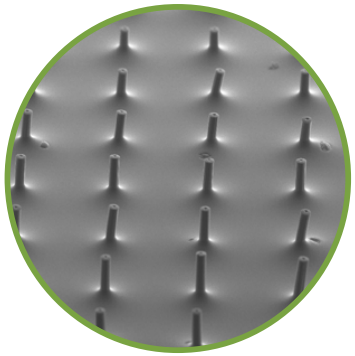
The researchers who make up the MedE department—brought together from a broad range of engineering and science specialties both within EAS and outside it—are, for their part, focusing on improving human health though interdisciplinary collaboration in those critical areas of medicine and engineering that can positively effect well-being, says electrical engineer Hyuck Choo, who is part of the new department.

"The outcomes of biomedical engineering research impact our lives directly and can greatly improve the span and quality of human lives," says Choo, who is working on building implantable sensors to improve the management of glaucoma and diabetes. "Our society is aging and, as a result, the medical care burden on our society will continue to increase. It's a great responsibility and also opportunity at the same time. Because it is a large-scale societal burden that we have no other choice but to deal with, you can easily foretell that new, useful medical engineering technologies will create economic engines for our society."

The nanoscale biomedical implants that Choo is engineering in his lab will provide pressure readouts for people with glaucoma, an eye disorder associated with increased fluid pressure in the eye that can lead to optic-nerve damage, including blindness. He is also working on glucose-monitoring sensors that can be implanted in diabetes patients to help them know how to regulate their glucose levels, which is key to managing the disease. In addition, his lab works on developing imaging techniques that give both literal and figurative insights into human diseases; the team is also involved in building nanoscale power generators for its and others' implantable medical electronic devices, all of which require robust power sources in small spaces.

Choo says that, as an engineer, he finds it fascinating to learn more about how our bodies work and why they sometimes malfunction, and to consider how he and others might use engineering technologies to solve health problems and improve our functioning.

"Frequently, while studying how our bodies work, I find a lot of similarities between independently human-engineered devices and their naturally evolved counterparts, which are often



Mory Gharib was inspired by the thorns of cacti when developing microneedles for drug delivery (above, right). Lulu Qian is exploring how knowledge of biological systems can help her create synthetic DNA neural networks (next page, left).

better designed and optimized than human devices," he says.

BLURRING THE LINES

Several faculty members are so deeply embedded in both the biological and the engineering worlds that they are part of both the renamed BBE division and the new MedE department.

Mory Gharib is one of those with a joint appointment. Gharib and his research team work to better understand how our most important physiological machines—such as our hearts and our eyes—actually work. He uses these insights to design and build devices for drug delivery and other medical applications.

Take, for example, zebrafish. Gharib and his team have been looking at how the hearts of these small vertebrates work, using advanced imaging techniques to understand the physics and chemistry of the mechanisms responsible for what he calls "these amazing machines that work on all scales." By deciphering the science and engineering principles underlying those mechanisms, he has been able to build small pumps that might one day be used for cardiovascular medical applications.

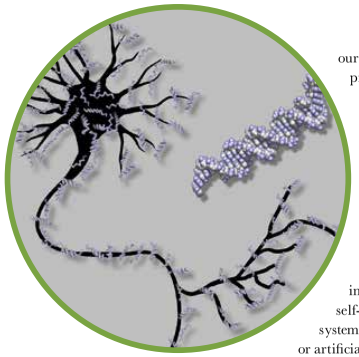
But his biology-derived motivation doesn't stop there. Gharib has designed visualization systems based on spider eyes, is investigating carbon nanotubes for their ability to be super hydrophobic (meaning they stay very clean because nothing attaches or sticks to them, including microbes), and has engineered microneedles based on the design of the thorns found on cacti, that are now being used for drug delivery.

"There are medical needs that we are trying to respond to," says Gharib. "There are some areas where no one else is doing research because they don't believe a solution is possible. Those are the problems we like to attack and where we believe bioengineering can provide an answer."

Bioengineer Changhuei Yang is also a member of both BBE and MedE.

"There is a lot of cross-talk and cross-fertilization between the two," he says. "I participate in both options because a lot of my research crosses that diffuse boundary."

Yang's research focus is on optical imaging techniques that have biomedical applications. One example he points to is a suite of microscopy technologies he has developed,



which—designed for a wide field of view—can have a direct impact on digital pathology, giving pathologists accurate and efficient ways to digitize pathology slides. As it turns out, Yang says, these same technologies are useful for laboratory biologists as well, because they allow the scientists to track cell cultures over long periods of time.

"Bioscience research is actually a very good staging ground for the eventual translation of technologies into the medical arena," he says. "Our eventual research goal is to translate this technology into medical applications such as incisionless surgery, deep brain stimulation, and targeted optically activated drug therapy."

Lulu Qian says Caltech's increasing emphasis on bioengineering highlights two general directions for research at the intersection of bio-medicine and engineering.

"In my view, the importance of bioengineering derives from two related facts," says Qian. "First, bioengineering helps us bring engineering approaches from the macroscopic scale down to the microscopic scale, and creates real-world applications in areas such as biology, materials science, and medicine by improving our capability for precisely manipulating matter at the finest level. Second, by building artificial molecular systems, bioengineering helps us to better understand the brilliance of nature, the powerful principles it exploits, and the incredible potential of self-organized biochemical systems—whether natural or artificial."

The consensus, it seems, is that a robust focus on bioengineering will benefit both Caltech and society as a whole.

"Before, it was a hodgepodge, and no one was sure which area to focus on, but now we've given importance to both—to biological engineering and to medical engineering, says Gharib. "The outside world will see it as something that is being taken seriously at Caltech. We are not just sending rovers to Mars, we are also responding to the immediate needs of society." E&S

Pamela Bjorkman is the Max Delbrück Professor of Biology at Caltech and an investigator with the Howard Hughes Medical Institute. Her work on HIV antibodies is supported by the Bill and Melinda Gates Foundation, and the National Institute of Allergy And Infectious Diseases.

Hyuck Choo is an assistant professor of electrical engineering.

Morteza Gharib (PhD '83) is a vice provost at Caltech and the Hans W. Liepmann Professor of Aeronautics and Bioinspired Engineering.

Stephen Mayo (PhD '88) is Bren Professor of Biology and Chemistry and William K. Bowes Jr. Leadership Chair of the Division of Biology and Biological Engineering.

Lulu Qian is an assistant professor of bioengineering. Her work in synthetic molecular systems is funded by the Burroughs Wellcome Fund, the Okawa Foundation, and the National Science Foundation.
Ares Rosakis is Theodore von Kármán Professor of Aeronautics and Mechanical Engineering and Otis Booth Leadership Chair of the Division of Engineering and Applied Science.

Yu-Chong Tai is Anna L. Rosen Professor of Electrical Engineering and Mechanical Engineering and executive officer for medical engineering.

Changhuei Yang is professor of electrical engineering and bioengineering. His work on optical imaging is funded by the National Institutes of Health and Clearbridge BioPhotonics.

The Newest Nobelist

Martin Karplus (PhD '54, Distinguished Alumnus '86)

Martin Karplus was one of three scientists awarded the 2013 Nobel Prize in Chemistry for pioneering work on computer programs that simulate complex chemical processes and that have revolutionized research in areas from drug discovery to solar energy.

The Royal Swedish Academy of Sciences awarded the prize of 8 million crowns ($1.25 million) to Karplus, Michael Levitt, and Arieh Warshel, noting that their work had transformed the modeling of chemical reactions and moved it into the computer age.

Born in Austria in 1930, Karplus was a child when his family, fleeing the country's Nazi occupation, emigrated to the United States. He received a BA from Harvard University in 1950 and a PhD in chemistry in 1954 from Caltech, where he worked with two-time Nobel laureate Linus Pauling.

"Pauling would often drop notes on little yellow sheets saying, 'Wouldn't it be interesting to do so-and-so?'" Karplus recalls. "He wouldn't necessarily expect you to do them. You could throw them away or keep them to work on. A number of people built their careers on his ideas."

After leaving Caltech, Karplus went on to investigate complex chemical reactions, which were generally understood only down to the molecular level and were often modeled using plastic balls and sticks. To learn what happens at the atomic scale, Karplus knew, would require computers capable of performing mathematically intense quantum-theoretical simulations. Karplus, Levitt, and Warshel helped to create a bridge from those primitive models to computer simulations, offering researchers tools to gain a complete view of chemical interactions at all levels.

"This year's recipients have done important computational and mechanistic work on protein and enzyme catalysis," says Rudy Marcus, the John G. Kirkwood and Arthur Amos Noyes Professor of Chemistry at Caltech and the 1992 recipient of the Nobel Prize in Chemistry. "That Karplus was a student of Pauling brings the prize this year close to home."

Karplus is the Theodore William Richards Professor of Chemistry, Emeritus, at Harvard, and director of the Biophysical Chemistry Laboratory, a joint laboratory of the French National Center for Scientific Research and the University of Strasbourg, France.

Alumni stories provided by the Caltech Alumni Association. For more about these stories and to read about other alumni in the news, go to alumni.caltech.edu.

Reading the Leaves

C. Kevin Boyce (BS '95)

Stanford paleobotanist and 2013 MacArthur Fellow C. Kevin Boyce answers a few questions about his work, his Caltech education, and what a 100-million-year-old leaf can tell us about the world today.

What is a paleobotanist? Very different people work on the front line of fossil records. Some analyze vertebrates, such as dinosaurs. Paleobotanists like me study how plants are formed. Taken together, all of our work creates a picture of Earth's environment from a different time.

How did your time at Caltech lead you to this line of research? What I do isn't the type of biology pursued at Caltech, but it was important for me to be there. I studied cell morphology in Eric Davidson's lab; Joe Kirschvink in geobiology helped to spark my interest in Earth's biodiversity. I also majored in literature. George Pigman's classes on Chaucer interested me in historical texts—which are similar to fossils, in a way.

How do you approach your work with fossils? Any examination of fossil records has to start with our understanding of modern ecology. You look at a fossil of a leaf and think, "Okay, that looks like a leaf. I understand that." But as you examine the details more closely—and plant fossils can offer a great deal of detail, down to cellular anatomy—you discover that there are a number of differences within the structure. This leaf may not, in fact, operate like leaves today in terms of its construction or biological processes.

What significant changes in plants have you been able to see? Today, most of the vegetation on our planet comprises flowering plants, with reproductive characteristics that typically include flowers, seeds, or fruit. But more than 100 million years ago, these types of plants didn't exist. So how is it that they came to take over? Through my work, I've demonstrated that as temperatures rose during prehistoric eras, flowering plants evolved a high vein density, which allowed them to cycle water at faster rates than their previously dominant competitors.

What can these plants teach us about today's world? They can help us understand the origins of our food supply—which is dominated by crops that are all basically flowering plants.

One focus of my research is how primary production, the process by which living compounds are synthesized from carbon dioxide, has changed over time. We know that today, carbon dioxide is increasing in the atmosphere. Generally, if you give plants more carbon dioxide, they'll perform more photosynthesis and grow faster. That effect is easy to study over a couple of years. But what would happen if you were looking at increased levels of carbon dioxide across very large scales and over revolutionary time periods?

Understanding how past ecologies adapted and changed may yield us valuable clues into our ecology today—and into how, if presented with new changes to the environment, it might adapt again.

LIFE STORIES We asked alumni to tell us their life stories in 10 words or less.

ChemE—
springboard for
gourmet **cooking**
and fine **wine**
making.

Met at Ruddock. **Married**
at Dabney Hall. **Still** in love.

Christian gay scientist seeks
ENERGY IN BIOLOGY for nation.

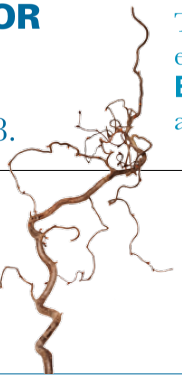
After Caltech,
everything else
was **EASIER**.

PHYSICS, then
DANCE, then
each **SPEAKING**
to the other.

Veni, Vidi, Interrogavi.
I came, I saw, I questioned.

Altadena barrio boy
became **SCIENTIST**,
FOLKDANCER, and
HUSBAND at Caltech.

Holocaust **SURVIVOR**
1939, Caltech **PhD**
physics 1963, NASA
ASTRONAUT 1978.



Two point five
eight nine five
BILLION seconds
and counting.

A **RANDOM**
walk through life
punctuated by
periods of **CHAOS**.

THINK BIG,
drive change, love
kids, go birding.