# e&s

Engineering & Science


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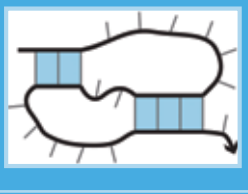

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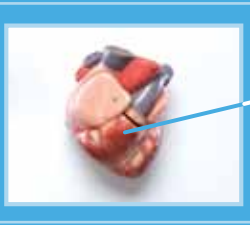

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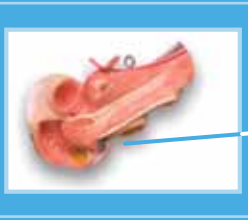

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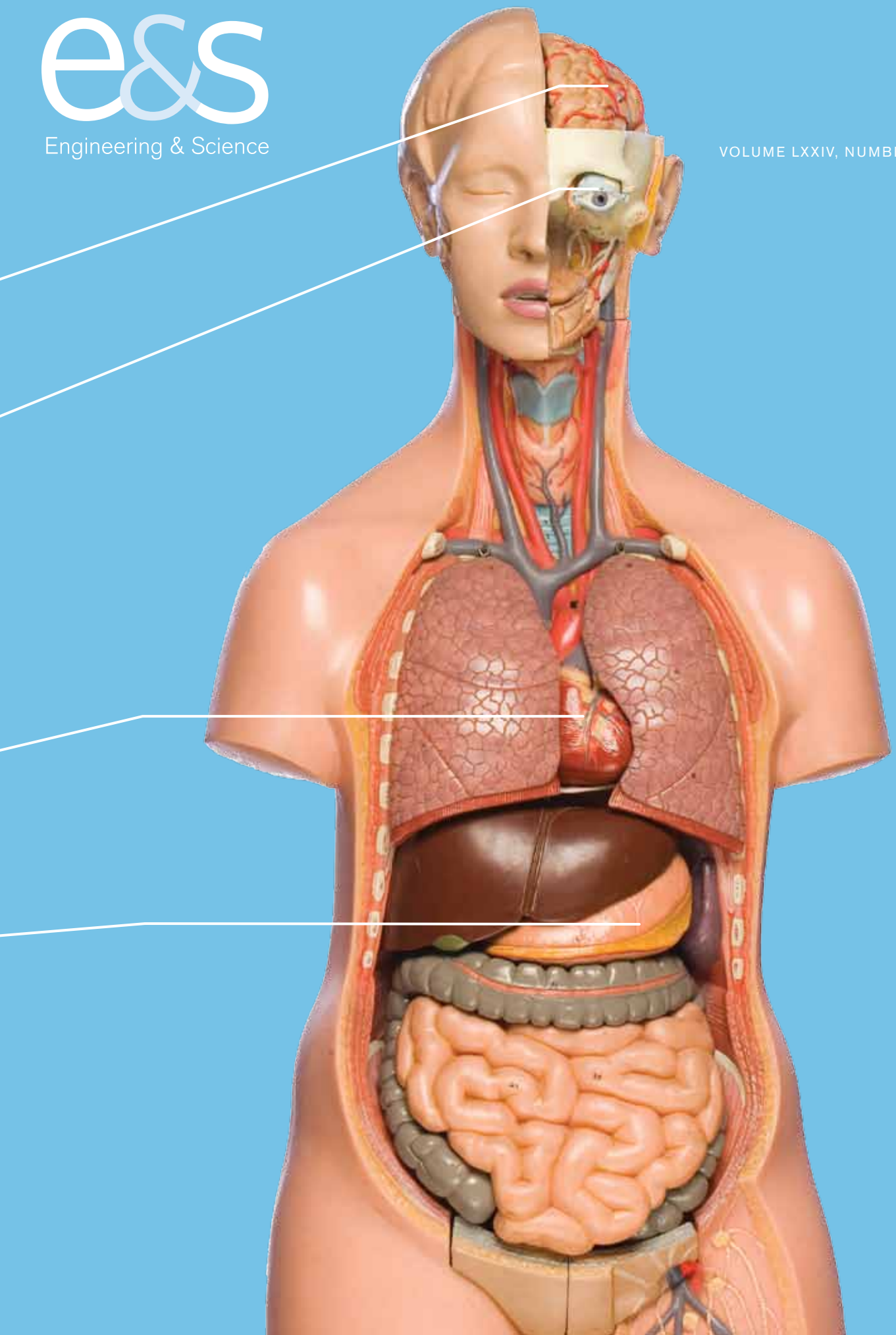

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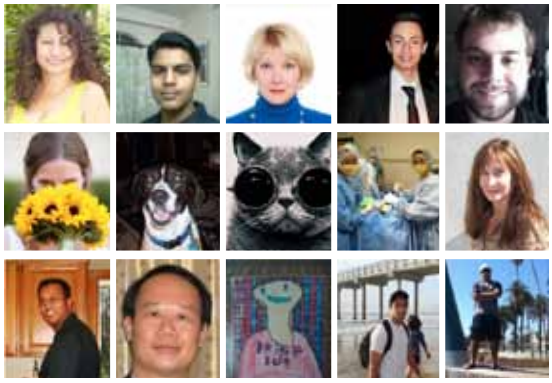

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## FROM THE PRESIDENT

You might not think of Caltech when you think of advances in clinical medicine. But perhaps you should.

No, we're not building a hospital, or opening a medical school. But we *are* establishing enduring partnerships with top facilities in Southern California and beyond.

Though these partnerships—and our ever-sharpening focus on developing solutions to medical, biomedical, and biotechnological problems—we are taking vital research from laboratory benches to patients' bedsides.

But we can't do it alone. Which is why Joel Burdick is working with neurobiologists from UCLA and physicians from the University of Louisville to test his paralysis-reversing electrode array; it's why Yu-Chong Tai is working with ophthalmologists from USC to test the retinal implants he's devised. (Both projects are described in "Connecting the Dots," page 20.) It's why David Tirrell and Julia Kornfield are collaborating with scientists at UC San Francisco on implantable materials meant to heal damaged corneas. ("Some Assembly Required," page 38.)

It's why the Broad Foundation gave Caltech and UCLA $5 million to start a Joint Center for Translational Medicine. And it's why, this summer, an anonymous donor gave $3 million each to Caltech and City of Hope to strengthen scientific collaborations between these institutions.

We know that to accelerate the speed at which game-changing discoveries move from the laboratory to patient care, you need extraordinary people doing extraordinary work. And you need other extraordinary people to fund that research.

Take, for instance, Ben and Donna Rosen. Ben (BS '54) is a Caltech trustee, known for his leadership as a venture capitalist and in the computer industry—and now for his leadership at Caltech. Our three-year-old Donna and Benjamin Rosen Bioengineering Center has already become a hub for collaborations.

Ben and Donna Rosen

There's also the Anna L. Rosen Professorship—named for Ben's mother—which is held by Scott Fraser, whose bioimaging work is described in "Programming Molecular Apps" on page 26, and "Naturally Inspired" on page 34.

Among the more than 50 beneficiaries of the Rosen Graduate Fellowship Fund at Caltech are Hesham Azizgolshani and Derek Rinderknecht, who have helped develop tiny implantable valveless pumps (described in "Naturally Inspired").

Caltech's mission is "to expand human knowledge and benefit society through research integrated with education." In this issue of *E&S*, you'll see just how seriously we take that charge.

Yours in discovery,


e&S

Engineering & Science

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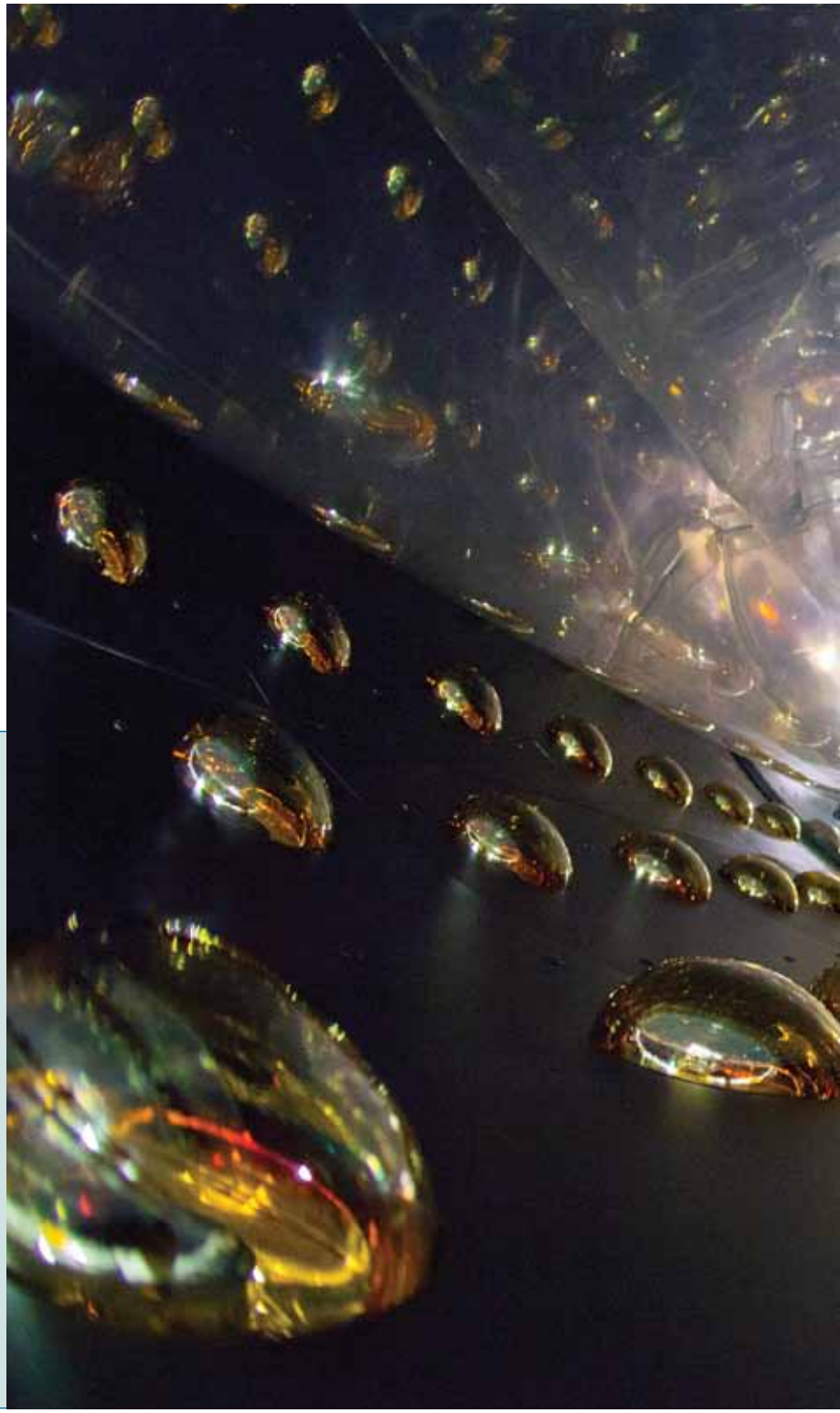
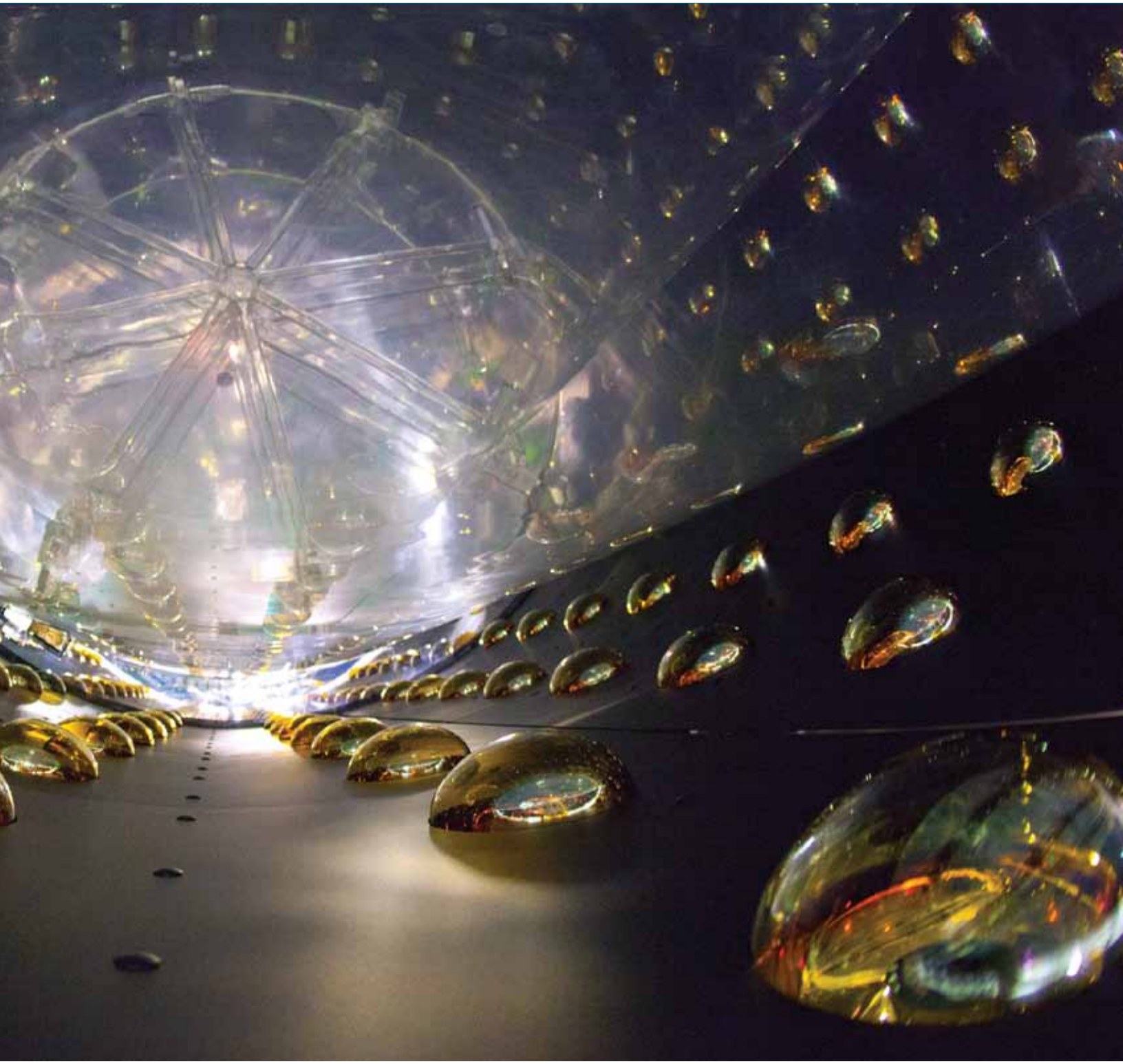
# Random

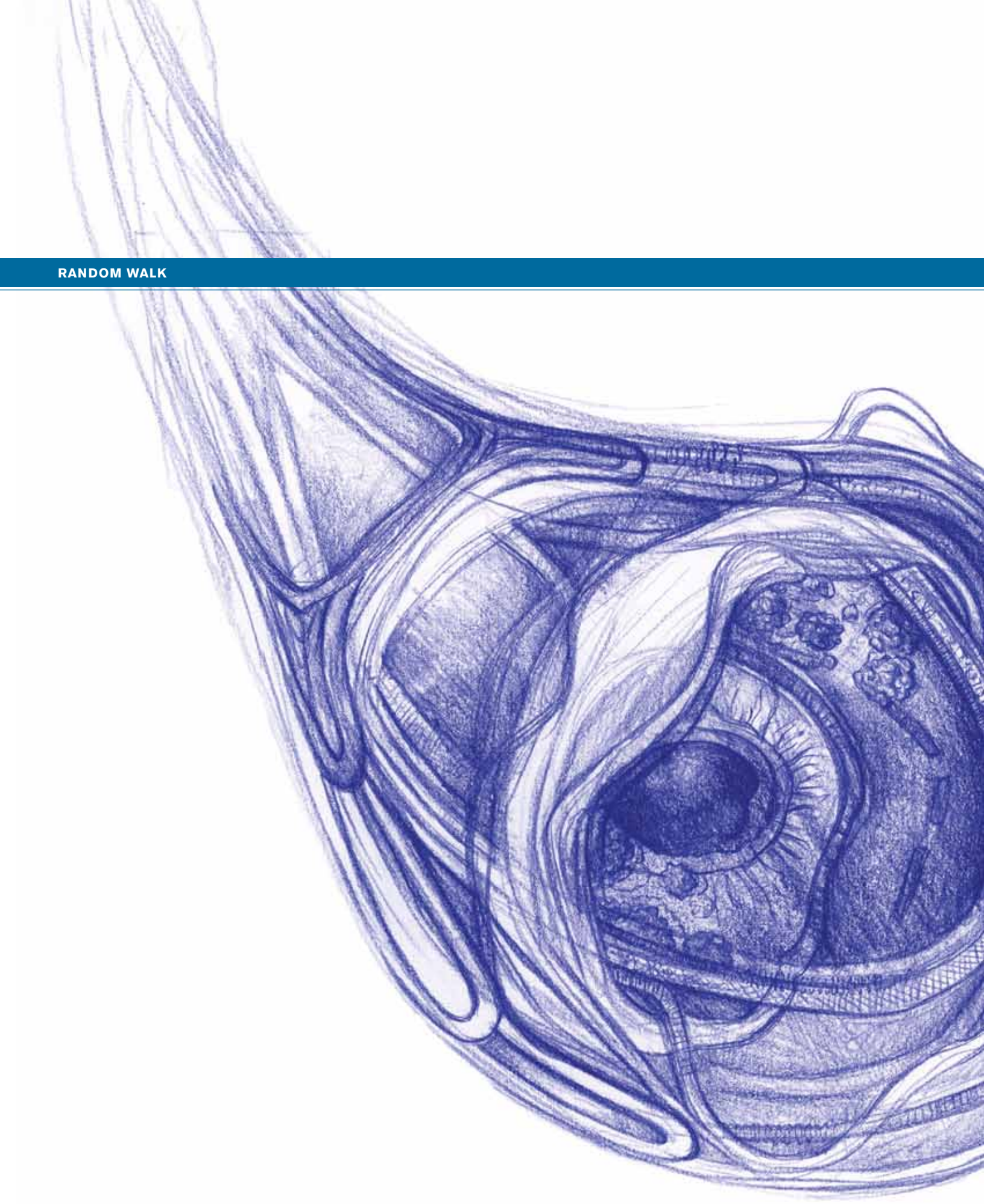


This image is a glimpse into the depths of a neutrino detector that's part of the Daya Bay Neutrino Experiment, buried under the mountains of southern China near Hong Kong. The detector consists of two inner nested transparent acrylic cylinders. Each of the experiment's eight 100-ton detectors is filled with a clear, liquid scintillator that flashes when an antineutrino—a neutrino's antimatter counterpart—zips through and interacts. The alien-looking globules along the inner walls are photomultiplier tubes that amplify and record the signals. The experiment, for which Caltech designed and built the 24 calibration devices, started taking data last August, probing the nature of the neutrino, that elusive particle that flies through the cosmos at nearly the speed of light. Physicists hope the small particles will help reveal answers to big questions—for example, why the universe has more matter than antimatter.

# Walk

THINGS THAT CAUGHT OUR EYE . . .





# FLIP IT AND REVERSE IT

A team of Caltech researchers has found what it's calling a "missing link." No, not *that* missing link—a link you probably didn't know was missing in the first place. The group is referring to a bacterium, called *Acetonema longum*, which seems to be the link between bacterial species with two membranes and those with just one.

*A. longum* belongs to a little-known family of bacteria that have two membranes and respond to extreme environmental stresses by forming protective spores, a process known as sporulation. Outside of this small family, the only bacteria known to sporulate are those with a single membrane.

Using a powerful technique called electron cryotomography (ECT), Professor of Biology Grant Jensen and members of his lab captured the first high-resolution images of *A. longum* undergoing sporulation. The results were surprising: "We saw that a piece of the inner membrane actually becomes the new cell's outer membrane," says Jensen, who is also a Howard Hughes Medical Institute investigator.

In the case of a double-membraned bacterium such as *A. longum*, sporulation begins with the inner membrane pinching together asymmetrically, creating a mother cell and a smaller daughter cell, both covered by the outer membrane. Next, the mother cell engulfs the daughter, giving the daughter a second layer of what was originally inner membrane. At this point, the daughter is a spore, surrounded by two membranes within the mother cell. Having done her maternal duty, the mother cell dies away, leaving the spore protected by those two membranes and a protein coat.

When conditions improve and the spore germinates, part of its protective protein coat cracks open and the new cell outgrows its former shell. Unlike a single-membraned bacterium, which would at this point also shed its outer membrane, the double-membraned bacterium retains it.

Jensen's group found that the new outer membrane has the structure and all of the functions of a typical outer membrane, even though it originated as part of the mother cell's inner membrane. This, they say, means that sporulation could have been the mechanism by which the bacterial outer membrane arose.

The whole study started after Jensen spoke with Professor of Environmental Microbiology Jared Leadbetter about the capabilities of ECT, which allows researchers to image biological specimens in a near-native state rather than requiring them to be dehydrated, embedded in plastic, sectioned, and stained. Leadbetter, who has long been interested in the process of sporulation, wondered if the technique might be used to image sporulating cells. Alas, the model organism for studying sporulation, *Bacillus subtilis*, is too thick to be imaged using ECT. But *A. longum* saved the day—in addition to its tendency to sporulate, it's also relatively skinny.

Elitza Tocheva, a postdoc in Jensen's lab, is the lead author of the paper describing the work, which appeared in the September 2 issue of *Cell*. The other authors include postdoc Eric Matson, grad student Dylan Morris, and Farshid Moussavi of Stanford. —*KF* E&S

An artist's representation of the entire sporulation process as a single drawing.

# MOONWARD BOUND

GRAIL, NASA's Gravity Recovery and Interior Laboratory, will answer longstanding questions about the moon and give scientists a better understanding of how Earth and other rocky planets in the solar system formed.

The twin spacecraft lifted off on a single rocket from Cape Canaveral at 9:08 a.m. Florida time on September 10, and they will fly in tandem orbits around the moon to measure its gravity field. GRAIL-A is scheduled to reach the moon on New Year's Eve 2011, while GRAIL-B will arrive New Year's Day 2012. The science-collection phase for GRAIL is expected to last 82 days.

This artist's conception shows the two spacecraft using radio links to each other to measure the distance between themselves while continuously relaying the information back to Earth—a feat they can accomplish even when the moon is between one of them and us. The inset photo was shot on August 23, as technicians were testing the clamshell fairing that protects the copper-foil-covered spacecraft during launch.

JPL manages the GRAIL mission, which is part of NASA's Discovery Program. Lockheed Martin Space Systems in Denver built the spacecraft. — *DN* E&S

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## JACKIE BARTON WINS NATIONAL MEDAL OF SCIENCE

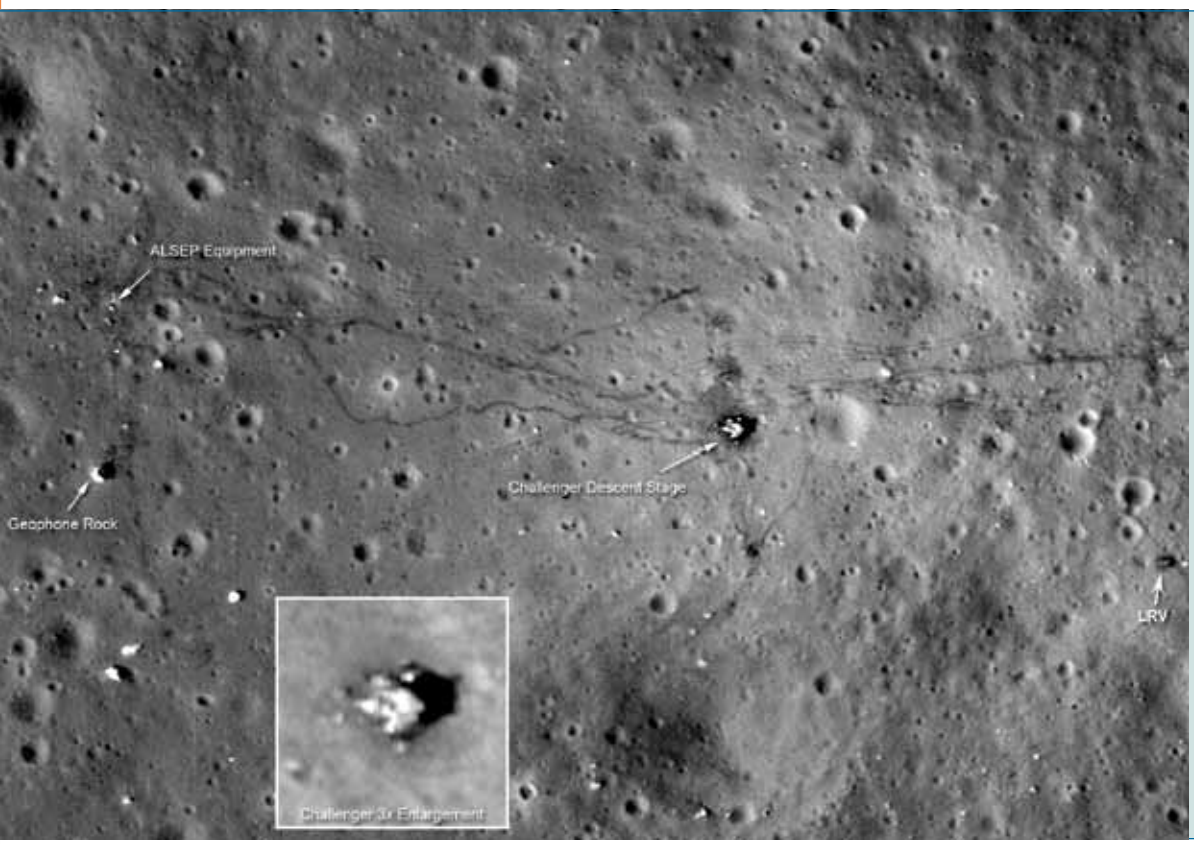
Chemistry professor and division chair Jacqueline K. (Jackie) Barton has good reason to celebrate. She is one of a handful of recipients of this year's National Medal of Science, the highest honor bestowed by the United States government on scientists. The award recognizes her discovery of a new property of the DNA helix—long-range electron transfer.

Over more than 20 years, Barton has pieced together an understanding of how double-helical DNA can behave like a wire, allowing the transfer of electrons across long molecular distances. Her experiments have revealed that a single mismatch in the DNA's nucleic-acid sequence can prevent the transfer from happening. "The DNA's base pairs are something like a stack of pennies," Barton says. "If you interrupt the stack in some way—if you distort even one penny—it interrupts the conductivity of the stack."

Nature might use this conductivity to locate and repair lesions in the DNA, Barton says. There are metal-containing proteins that are believed to be involved in the repair process; in her model, two of these proteins "test the wire" by attaching themselves to the DNA at widely separated points. Then, if one protein successfully sends an electron to the other, the wire is unbroken and the DNA is OK. Mutations in these proteins have been linked to predispositions to colon and breast cancer.

Barton joined the Caltech faculty as a professor of chemistry in 1989. She was named the Arthur and Marian Hanisch Memorial Professor in 1997 and became the chair of the Division of Chemistry and Chemical Engineering in 2009. Barton is also the recipient of the 1985 National Science Foundation Waterman Award, the 1988 American Chemical Society Award in Pure Chemistry, and a 1991 MacArthur Foundation Fellowship.

—*KF* E&S

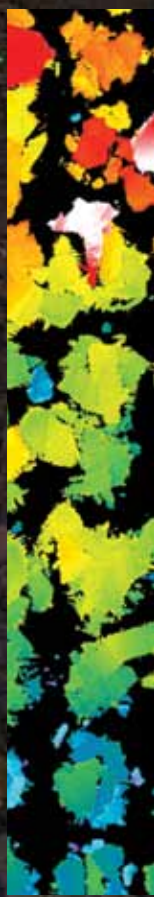


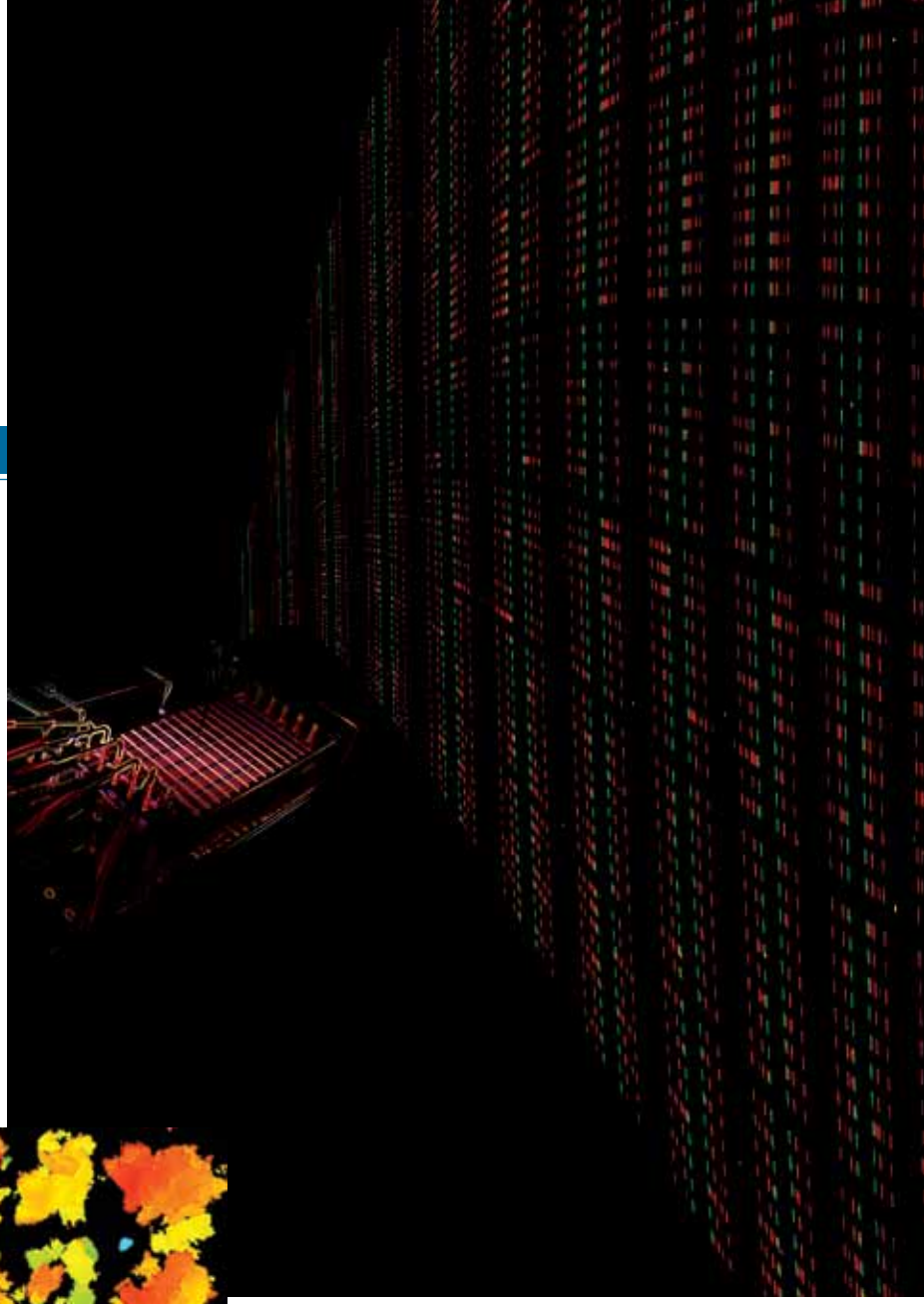

## THE MOON AND FOOTPRINTS

This high-resolution image of the Apollo 17 landing site, taken by the Lunar Reconnaissance Orbiter last September, has a pixel size of 27 by 56 centimeters—almost enough to distinguish the individual footprints left by astronauts Eugene Cernan and Harrison Schmitt (BS '57), who is the only geologist ever to walk on another world. The Apollo Lunar Surface Experiments Package (ALSEP), the descent stage of the lunar module *Challenger*, and the lunar rover (LRV) are all clearly visible, and the foot trails made by the astronauts are easily distinguishable from the dual tracks left by their rover.

# THE ART OF SCIENCE

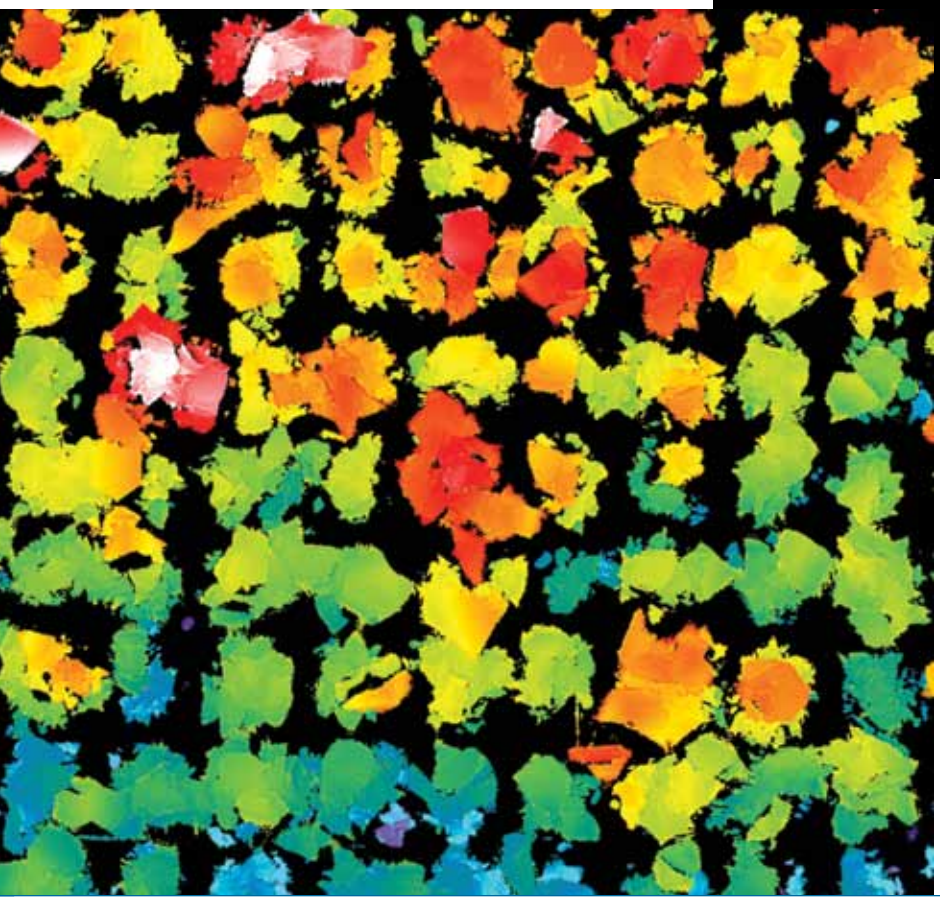
Caltech's third annual Art of Science competition was held last June. Here are some of our favorite images from the show.





FIRST-PRIZE WINNER (left)
ARTIST: Floris Van Breugel (grad student)
TITLE: *Fluorescent Treasures*
Scheelite (blue/white), calcite (red), uranyl ions (green), fluorite (pink), and "desert varnish" (yellow/orange) fluoresce under ultraviolet light in this 20-minute-long time-lapse exposure of tailings at a tungsten mine near Darwin, California.

SECOND-PRIZE WINNER (right)
ARTIST: Young Shik Shin (MS '06, PhD '11)
TITLE: *Single-Cell Barcode Chip*
This image shows 960 sets of protein data from individual cells in a microfluidic device. Each red bar represents a specific cancer-related protein; the green bars are reference proteins. Such analysis can offer information missed by a conventional cell screening in bulk.



THIRD-PRIZE WINNER (left)
ARTISTS: Andrew Leenheer (grad student) and Nick Strandwitz (postdoc)
TITLE: *Crystalrise*
The topography, as measured by confocal reflectance microscopy, of gallium phosphide crystals grown on a silicon microwire array to be used for photoelectro-chemical solar fuels. The rainbow color scale covers 15 microns height.

# DIFFERENT

If there's one thing Ralph Adolphs wants you to understand about autism, it's this: "It's wrong to call many of the people on the autism spectrum *impaired*," says the Caltech neuroscientist. "They're simply different."

These differences are in no way insignificant—they are, after all, why so much effort and passion is being put into understanding autism's most troublesome traits—but neither are they as inevitably devastating as has often been depicted. They are simply differences; intriguing, fleeting glimpses into minds that work in ways most of us don't quite understand, and yet which may ultimately give each and every one of us a little more insight into our own minds, our own selves.

What makes autism so fascinating, Adolphs notes, is what also makes it so difficult to study, to get a good grasp on: the diversity of the population itself. If you've met one person with autism, the saying goes, you've met one person with autism.

Still, there are characteristic tendencies and traits, gifts and gaps. According to psychiatry's diagnostic bible, familiarly known as the *DSM-IV*, autism involves an "impairment" in social interaction and communication, as well as "restricted repetitive . . . patterns of behavior, interests, and activities." What this means to the rest of us is some combination of these: Lousy eye contact. Social awkwardness. Hand flapping. Toe walking. Late-talking babies. Kids who can't seem to get the hang of playing cops and robbers with friends, yet can talk for an hour about Egyptian gods, elevators, or elephants. Adults who speak in flat tones, who come off as rigid, uncomfortable, brilliant.

Or not. The fact that there are few absolutes is part of why the set of disorders—autism, Asperger's, pervasive developmental disorder not otherwise specified (PDD-NOS)—that fall under autism's umbrella are referred to as a spectrum. As with the spectrum of visible light—where red morphs into orange, which morphs into yellow—it is difficult to draw sharp lines between the various diagnoses in the autism spectrum.

And, like the autism spectrum itself, the spectrum of autism research at Caltech also runs a gamut. Adolphs, for example, studies brain differences between adults on the high-functioning portion of the autism spectrum and the general public—the so-called neurotypical population. Neurobiologist John Allman's work on a particular set of neurons is providing insight into a possible basis for some of autism's social quirks. And then there's neurobiologist Paul Patterson, who literally has just finished writing the book on the connection between the immune system and autism, and who is collaborating with biologist Sarkis Mazmanian to explore the connections between gastrointestinal symptoms and the brain in autism spectrum disorders.

They and half a dozen or so of their colleagues have come together in a sort of informal Autism Working Group, which meets regularly to talk about their individual findings and to brainstorm together. "People don't think of Caltech when they think about autism research," says Patterson. "But we have a lot going on here; a lot of insight to offer."

## AN INFECTIOUS THEORY

Much of that insight comes from Patterson, who pioneered the study of the connections between the brain and the immune system in autism, schizophrenia, and depression a decade ago.

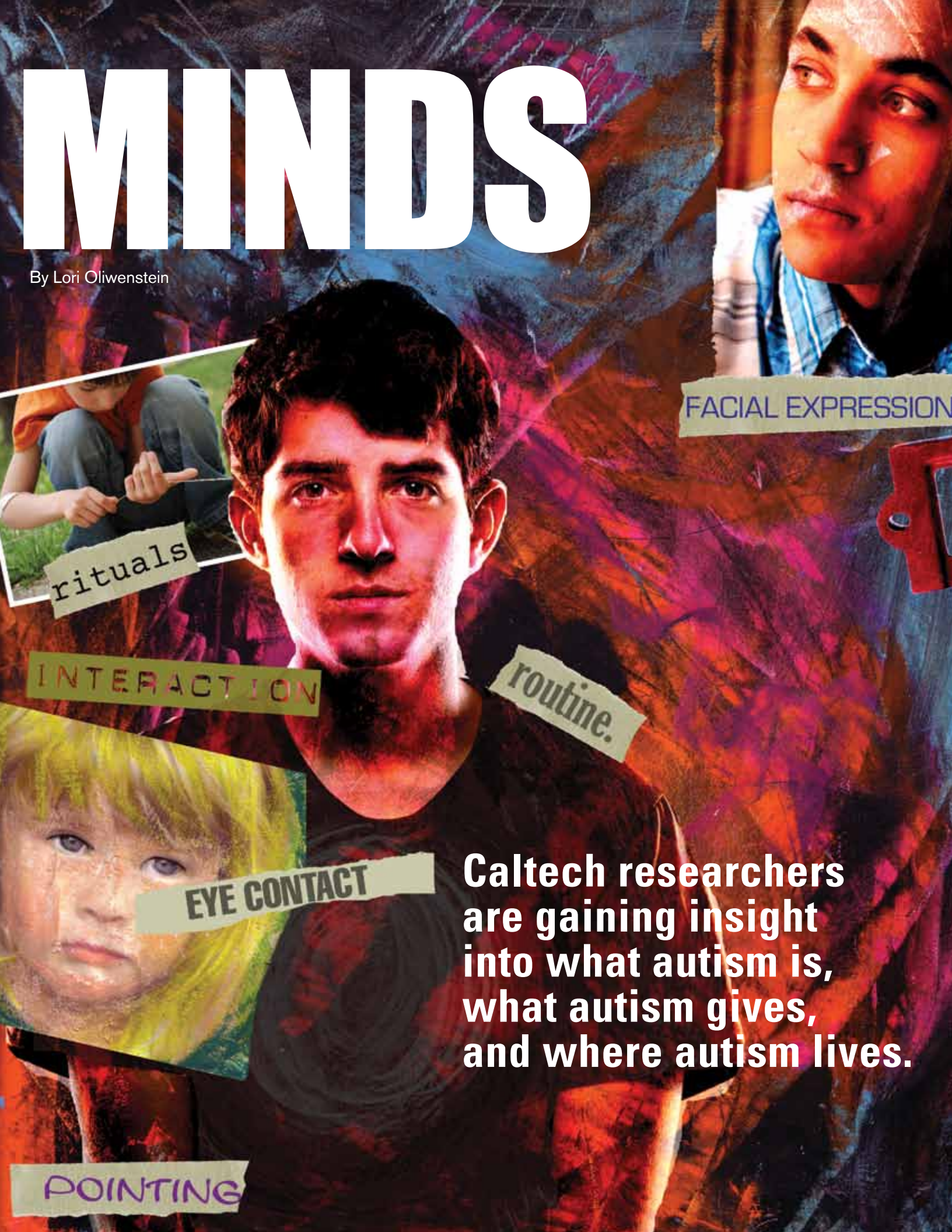
The main focus of that connection? Some kind of viral infection during pregnancy, Patterson explains. Or, rather, the immune response that infection inevitably engenders.

To bolster his argument, Patterson points to a recent study by Hjordis O. Atladottir of Aarhus University, Denmark, and colleagues—"an extraordinary look at over 10,000 autism cases" in the Danish Medical Register, which is a comprehensive database of every Dane's medical encounter from cradle to grave—that showed a strong epidemiological link between autism in a child and a first-trimester viral infection in the mother. "And we've found that if you give a mouse the flu during pregnancy, or activate the mother's immune system directly without a pathogen, the offspring will show a neuropathology characteristic of autism, as well as the three cardinal symptoms of autism."

In mouse terms, that means exhibiting repetitive behavior such as excessive self-grooming and compulsively and furiously burying marbles placed on its bedding. Freaking out, rather than making friends, when faced with an unfamiliar mouse. And communicating much less as a young pup with its mother, or as an adult with other mice. (Mice "talk" to one another at ultrasonic frequencies, requiring a special microphone and recording equipment to make their conversations audible to human ears.)

# MINDS

By Lori Oliwenstein




**Caltech researchers are gaining insight into what autism is, what autism gives, and where autism lives.**


Patterson observed the same neuropathology and behavior in mice who had never had an infection, but were instead given synthetic molecules that mimic the presence of a virus. In other words, Patterson found that simply mounting an immune response may be enough to steer a fetus down a path that could eventually lead to an autism-like condition after birth.

That "may" is key. There is definitely a connection between infections during pregnancy—especially the early months of pregnancy—and increased risk of autism (and, as Patterson has also shown, schizophrenia) in the offspring, he says, but that is not the same as saying it's a direct, 100 percent, if-you-get-sick-while-you're-pregnant-your-baby-will-have-autism correlation.

How does it all work? Patterson thinks cytokines—proteins produced by the body in response to an infection—play a role. In fact, grad student Steve Smith (PhD '08) found that giving pregnant mice one cytokine in particular, called interleukin-6 (IL-6), leads to offspring who exhibit autistic and schizophrenic features. "It was really unexpected that a single injection of a single cytokine would exert such a powerful effect," Patterson notes.

This is an important clue connecting the mother's immune reaction to the fetus's brain development. It's known that the interleukins are inflammation-boosters, and inflammation is all well and good when you need to wake up the immune system and get it to pour white cells into an infected area. But it has its unintended side effects as well; the inflammatory response often takes a scattershot approach, meaning that healthy tissues can also get caught up in the onslaught.

For instance, grad student Elaine Hsiao is finding that IL-6 and other cytokines not only work directly on the fetal brain, but can also alter the function of the placenta, which would have indirect effects on fetal development.

Why does an immune response sometimes result in a developmental disability—and sometimes not? Patterson thinks it could be the timing of the infection, or the genetic makeup of the mother, or her fetus that modulates the outcome.

The questions Patterson is asking about inflammation and the brain might apply to other parts of the body as well. So he and biologist Sarkis Mazmanian are looking at the gastrointestinal problems somewhat commonly found in kids with autism, and how those might be related to the development of autism.

"The evidence that there are gastrointestinal issues in children with autism is pretty good," Patterson notes. "You test it by feeding a child a molecule that gets broken down in the gut; if the gut is leaky—if there is some dysfunction there—then the breakdown product gets into the bloodstream. And research has indeed found that this happens more often in kids with autism than in typical kids."

There's similarly strong evidence, he says, implicating our normally helpful and cooperative intestinal bacteria—as it turns out, the various types of bacteria found in the digestive systems of typical and autism spectrum kids tend to differ.

But while the bowel-bacterium-brain connection is clear, it's still not known just how widespread it is. "Estimates of the percentage of people with autism who are affected by these gastrointestinal differences vary from 20 to 70 percent," Patterson says. "Clearly, the science is lagging; there's still a lot of work to be done."

Which is why the science-and-advocacy group Autism Speaks recently brought Patterson and Mazmanian together with immunologist Paul Ashwood at UC Davis and pediatrician Alessio Fasano from the University of Maryland to explore the gut-brain-immune connections in mice and in kids with autism spectrum disorders.

"You have Sarkis's and Alessio's expertise in the human gastrointestinal system, you have Paul's expertise in children with autism, and then you have our mouse model," says Patterson. "That makes for a pretty exciting consortium. It should allow us to look at autism in new and unprecedented ways."

## LOOKING AND CONNECTING

Ralph Adolphs, too, is looking at autism in new ways—and looking at *looking* in autism as well.

Adolphs, who runs the Autism and Asperger Syndrome Research Program at Caltech, spends most of his time working with high-functioning adults with autism. "We're exploring the social differences people with autism have," says Adolphs. "We're looking at every-

thing from eye-tracking, to reasoning, to complex theory-of-mind stuff, which is about understanding what others feel or think. We hope one day to be able to tell a story about the roles of particular brain areas, and how the white-matter connections between them look abnormal, and how that causes the effects we see."

For example, people with autism look at faces differently—focusing not on the other person's eyes, the way a neurotypical person would, but on the center of the face or on a point beside the face. Several research groups, including Adolphs's lab, have discovered that this is linked to the brain's amygdala, which is known to play roles in face recognition and in the processing of emotions—both our own and others'.

The amygdala is also involved in social interactions, so Adolphs's team is looking at how being aware of other people affects behavior. In one set of experiments, volunteers were asked to make charitable donations (with their own money!) in the presence or absence of an observer. As expected, neurotypical people gave bigger sums when other people were watching. By contrast, the people with high-functioning autism gave the same amount either way. "For most of us, when other people are watching, we act differently," he says. "But we've found that people with autism lack that behavioral change. They don't seem to think about what other people think of them."

But at its root, this seems to be more about what you notice around you, and how you respond to it, rather than a lack of caring. "What's interesting is figuring out what people with autism pay attention to," says Adolphs. "It's not that their amygdala doesn't work, it's that it works differently."

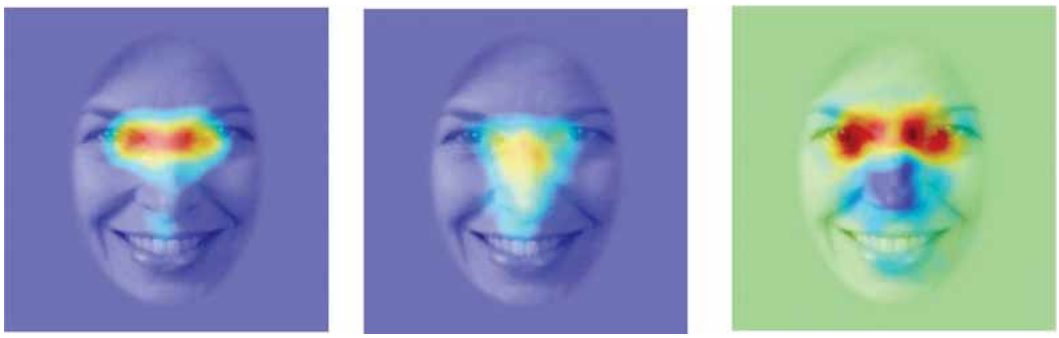
Neurobiologists John Allman and Atiya Hakeem (BS '93) have also been focusing on a component of the brain that may work differently in people with autism. Called the von Economo neurons, these cells are thought to play a key role in your ability to quickly and intuitively assess a situation—say, for example, when you meet someone for the first time, and come to an immediate conclusion about how to respond to their greeting. Those sorts of snap judgments, Allman says, are much more difficult for people with autism, who tend to have trouble realizing that what you say when you first meet a new client is very different from the way you should respond upon first meeting your brother's new girlfriend or your long-lost Aunt Sadie.

And that, he posits, may well be due to abnormalities in the connections these neurons make or where they wind up in the brain. The latter notion has since begun to gain traction elsewhere—a recent study led by Micaela Santos of the Mount Sinai School of Medicine in New York has found that children with autism have an oversupply of von Economo neurons in the fronto-insular cortex relative to another type of neuron. This brain structure is linked not only to your emotional awareness and empathy, but also to your internal awareness—of the state of your digestive system, the sensation of pain, and the like. This fits well with the known tendency of people with autism to be hypersensitive to sound, light, temperature and other stimuli.

The missed or unusual connections both Adolphs and Allman are looking at may be a critical part of the story, Adolphs adds. Indeed, he says, there's a sort of "globally abnormal connectivity in the brains of people with autism."

Which is why Adolphs and Caltech psychology researcher Lynn Paul have been studying a group of people born without a corpus callosum—the bundle of nerve fibers that connects the brain's two hemispheres. Intriguingly, a full third of such people also meet the diagnostic criteria for having an autism spectrum disorder.

The team recently found that despite the missing 200 million or so connections between neurons that the corpus callosum normally provides, these folks' left and right hemispheres still manage to carry on communications with one another. "This finding really amazed us," says Adolphs, "and it shows that you can generate remarkably normal functional networks that communicate between different parts of the brain even when the wiring is all scrambled. There must be some fundamental principle about how the brain orga-



These eye-tracking studies show how we "read" other people's faces. Left: Neurotypical people look at the eyes. Middle: People with autism tend to focus on or around the bridge of the nose. Right: Superposing the two, with red being the neurotypical folks and blue being people with autism.

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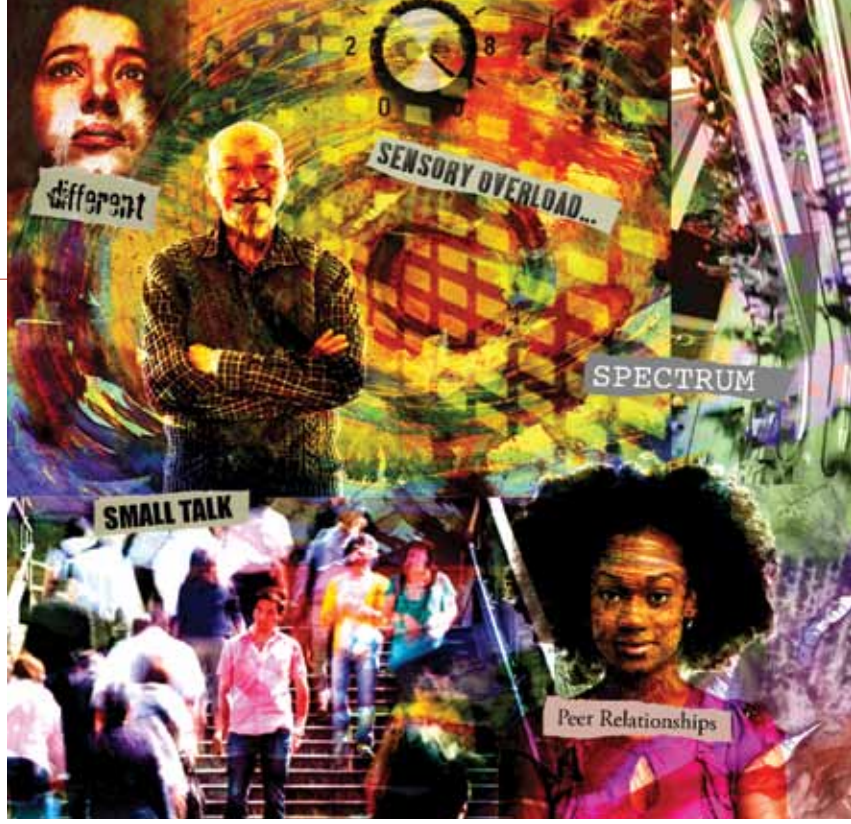



nizes itself functionally during development, such that it can do so even when the corpus callosum is entirely missing."

Although the corpus callosum study looked at a specialized population, most of Adolphs's other findings have come about thanks to the cooperation of some 40 adult volunteers with diagnoses of high-functioning autism, Asperger's, or PDD-NOS.

Why study high-functioning adults? Adolphs admits that at least some of the impetus is purely practical. It's much easier to get adults to sit through long hours of testing and MRI scanning than it is to get any child—with or without autism—to do the same. But the payoff is worth it. Those hours they've spent lying motionless in the MRI mean that Adolphs knows these people inside and out.

And there are other draws as well. For one thing, the overwhelming majority of autism research is done on children and is about children. "You hear a great deal about children with autism, but not so much about adults," Adolphs says. "In fact, although autism starts to be noticed in childhood, it's not a childhood disorder. Instead, it's a disorder of development, and those children who have autism become adults with autism, and eventually elderly adults with autism. We know extremely little about how autism interacts with the aging process, for instance."

Indeed, he notes, while some of autism's symptoms are most apparent in childhood—delayed speech, for instance—others don't make themselves known until later in life and are a direct result of the atypical development that came before. "Autism affects development," Adolphs says, "and in turn, development affects autism. And so we want to look at the interaction of autism with the entire developmental lifespan."

They also want to look at the way autism interacts to create not only deficits, but benefits. "One of the things we're getting with such detailed assessments is a profile of peaks and valleys of ability," says Adolphs. "People with autism have strengths and they have weaknesses, just as we all do."

Mapping these peaks and valleys will not only help academics like Adolphs and his Caltech colleagues learn the ins and outs of autism, it will help society as a whole understand how best to help people with autism exploit their strengths and work around their weaknesses.

And lest anyone think these lessons apply only to those with a diagnosis that falls clearly onto the autism spectrum, Adolphs has a few words of caution. "Autism is just one extreme of this broad spectrum of individual differences that stretch across the general population," he says. For instance, in a 2008 paper published in *Current Biology*, Adolphs and colleagues showed that the parents of children with autism—who were not themselves autistic—frequently respond to faces in a manner similar to children with autism, spending more time looking at other people's mouths than at their eyes.

"It turns out that what we're learning about autism," Adolphs notes, "may be relevant to almost anyone who is a little bit different, who does things differently."

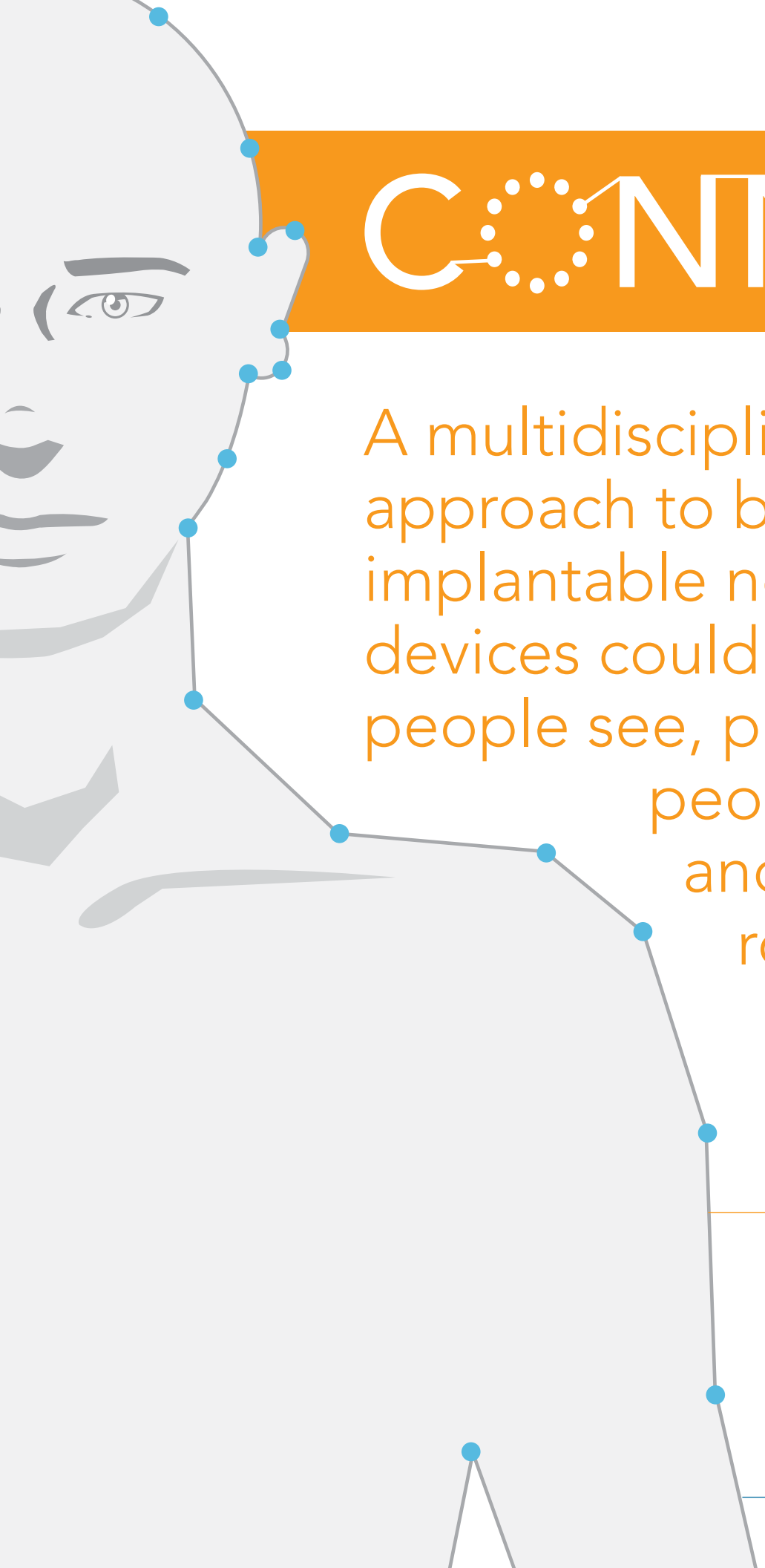
That means you over there in the corner, who hates large parties and small talk. And you, the person who plugs your ears at a concert, because you feel physically assaulted by the noise. And you, spending hours upon hours fixing up old computers, or old cars, or organizing your model-train collection.

Not diseased. Not impaired. Just different. Just like you and me. E&S

***Paul Patterson is the Anne P. and Benjamin R. Biaggini Professor of Biological Sciences at Caltech. His research on autism and schizophrenia is funded by Autism Speaks, the International Rett Syndrome Foundation, the National Institute of Mental Health (NIMH), the U.S.-Israel Binational Science Foundation, the Simons Foundation, the McGrath Foundation, the Weston Havens Foundation, the Della Martin Foundation, the Department of Defense, and the Caltech Innovation Initiative. His book,* Infectious Behavior: Brain-Immune Connections in Autism, Schizophrenia, and Depression*, was published in September by the MIT Press.***

***Ralph Adolphs is the Bren Professor of Psychology and Neuroscience and professor of biology, as well as director of the Caltech Brain Imaging Center. His research is supported by grants from Autism Speaks, NIMH, and the Simons Foundation.***

***John Allman is the Frank P. Hixon Professor of Neurobiology. His research is funded by the James S. McDonnell Foundation, NIMH, and the Simons Foundation. He and neuropsychiatrist Peter Williamson are the coauthors of* The Human Illnesses: Neuropsychiatric Disorders and the Nature of the Human Brain*, published in January 2011, by the Oxford University Press.***



# CONNECTI

## A multidisciplinary approach to building implantable neural devices could help blind people see, paralyzed people stand, and even endow robotic limbs with a sense of touch.

By Katie Neith

# NG THE DOTS

Like the fiber-optic network beneath a teeming metropolis, a labyrinth of neurons sends signals up, down, and across your body. This marvelously complex system helps us to see stunning sunsets, hear brilliant symphonies, and achieve athletic feats—things that most people take for granted until there is a break in the matrix. Accidents, injuries, and degenerative disease can easily render the eyes sightless, the ears deaf, and limbs paralyzed by disconnecting neural pathways. At Caltech, researchers are working on innovative ways to restore nerve functions via implantable devices.

## HITTING A NERVE

Information flows through nerve cells, or neurons, in the form of electrical impulses that travel from one end of the cell to the other. In some cases, this is quite a journey—for example, the sciatic nerve is a single set of cells that sends signals from the spinal cord all the way to your feet.

"If neurons can propagate electrical pulses a long distance in the body, then we can interfere with those electrical pulses and/or restore the right electrical pulses," explains engineer Yu-Chong Tai, who specializes in making micro- and nano-devices. "We can help the nerve to operate properly, possibly even better than before. And we do this by making electrodes."

Just as a current moving through a coil of wire can generate a current in a second coil, an electrode can induce a current within a neuron. If the electrode is properly positioned on the far side of the broken pathway, it can jolt the neuron back into activity, helping a paralyzed person's legs decide, for example, that it's time to stand. Explains Tai, "The 'start' signal from the brain has stopped, but we provide the signal with the implant."

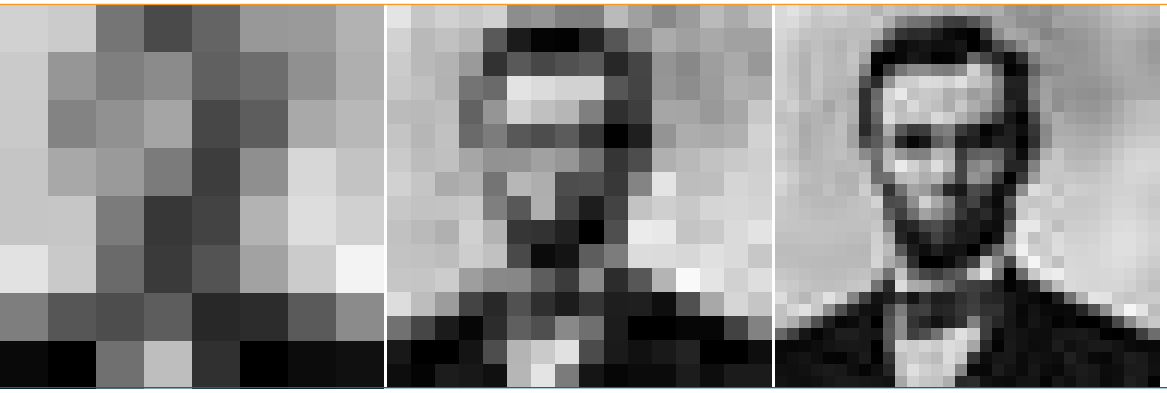
## THE BODY ELECTRIC

Tai entered the field after a chance meeting with an ophthalmologist from the Doheny Eye Institute at the University of Southern California, who had an idea for a retinal implant but needed an engineer to help with the technology.

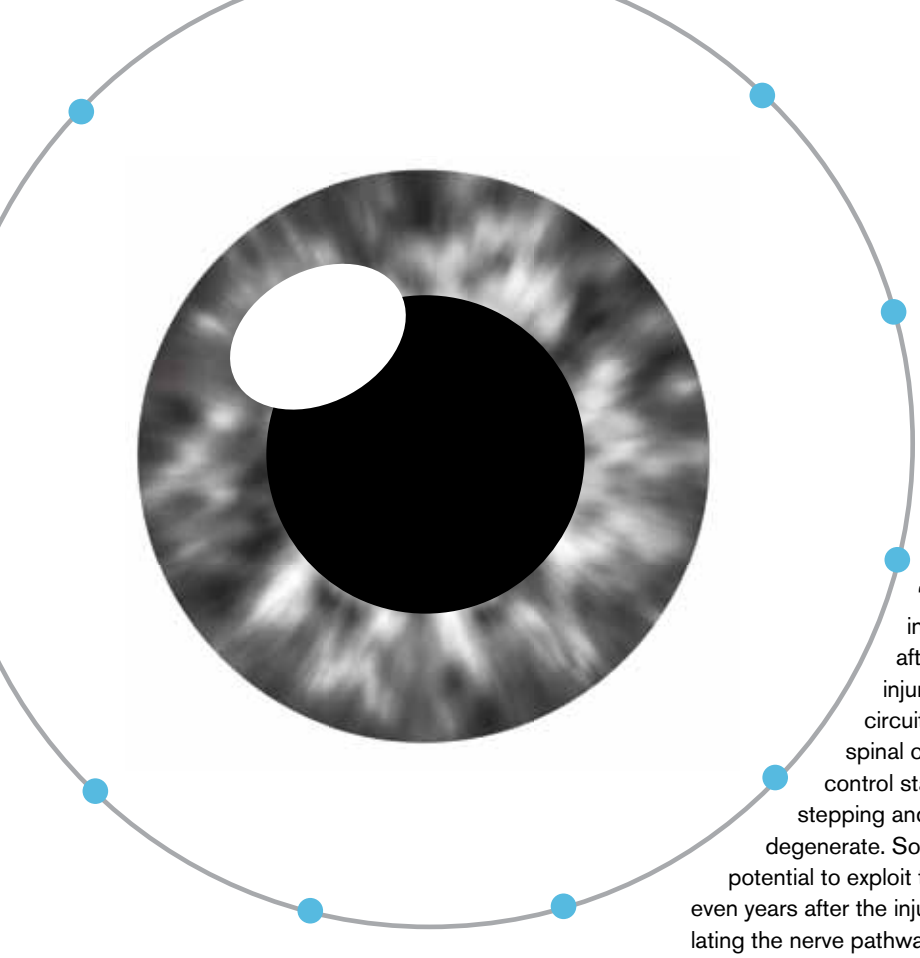
"I'm a small-device person, so when we started to brainstorm, you can imagine that we came up with many ideas," says Tai of the beginning of his partnership with Mark Humayun. "Since then, we've been working on retinal implants nonstop."

That was eight years ago. Now, their second-generation implant, the Argus II, has been approved for commercial use, receiving patent number 8,000,000—a milestone for the patent office that netted the device a mention on National Public Radio's *Morning Edition.*

Designed for people with degenerative eye diseases such as macular degeneration, the implant is emplaced inside the eye, up against the retina. The implant's electrodes are thus in direct contact with the ganglion cells, which lie on the retina's inner surface and collectively form the optic nerve. The user wears a pair of glasses equipped with a video camera plugged in to a tiny computer that fits in the user's pocket. The processed images are sent wirelessly to a receiver chip implanted behind the conjunctiva, which is the mucous membrane surrounding the eye. The signals then travel by a thin intraocular cable to the ganglion cells in the retina. From there, they take the normal route to the visual cortex at the



As Yu-Chong Tai says, 16 pixels (opposite page) is not much resolution for seeing the world. But as the resolution increases from 64 pixels (far left) to 256 pixels (center) to 1,024 pixels (left), a familiar face emerges.



back of the brain. Despite the lengthy explanation, this process happens so quickly that users are able detect light, identify objects, and even perceive motion in real time.

"When I started working on retinal implants, we were working on a 16-electrode device," says Tai. "You can imagine a 16-pixel camera—that's not much resolution for seeing the world. The latest implant has 60 electrodes, and we are working on 256-electrode devices. In less than a year, we'll be working on thousand-electrode devices."

These prostheses have been implanted in less than 20 people so far, but they've been very successful. "We think the direction we are going is absolutely correct," says Tai. "It's not just a science story. We all think we will produce a device that will benefit mankind."

Retinal implants aren't the only such hardware to have gone from the bench to the bedside with the help of Caltech faculty. Tai and bioengineer Joel Burdick have lent their talents to a neuroprosthesis in the spine of Rob Summers, a now-25-year-old college baseball star who was paralyzed by a hit-and-run driver in 2006.

One in every 50 Americans suffers from some form of paralysis. However, says Burdick, "an amazing fact is that after spinal-cord injury, there is circuitry in the lower spinal cord that can control standing and stepping and that doesn't degenerate. So we have the potential to exploit this circuitry, even years after the injury, by stimulating the nerve pathways that are still intact." Burdick, who is also a mechanical engineer, has been helping to develop a device for doing just that as part of a research team that includes neurobiologists from UCLA and neurosurgeons from the University of Louisville, where Summers received his implant. The electrode array is implanted in the small of the patient's back, in the same area where pregnant women get epidural anesthesia during childbirth.

"By basically beaming energy in there, we try to raise the level of excitability of the existing neurons," explains Burdick. "This does at least two things, and probably a lot more: it replaces the descending input from the brain and tells the circuitry to 'go,' and it excites certain parts of the spinal cord that help process the sensory information needed to tell muscles how to do their job."

After two years of using the array, Summers can now stand, balance, and step when the device is turned on. (According to the terms of the FDA's testing protocol, the device can only be used during designated exercise periods.) However, Summers has also gained improved control of his bladder and bowels even when the device is off—a "surprise" outcome, Burdick says, which if replicated in other patients would be a huge quality-of-life improvement.

The implant uses an off-the-shelf electrode array approved by the FDA for treating back pain. Meanwhile, Tai has been developing a more advanced device from scratch using microelectrodes instead of the standard-sized ones, hoping that putting more power into fewer neurons will give better results. But due to tough FDA regulations that classify all long-term electronic implants at the highest level of risk, his device still has a number of years before it will be ready for human trials.

## THINK AND DO

A short walk away from Tai's lab, neuroscientist Richard Andersen (not to be confused with actor Richard Anderson, of *Six Million Dollar Man* and *Bionic Woman* fame) leads a research group focusing on "the idea that paralyzed people or people with amputations could control a wheelchair or a robotic limb via a neural implant," he says. "It's kind of sci-fi sounding, but it actually works."

Back in the late '80s, Andersen, an early pioneer of cortical-function studies, discovered that a part of the brain called the posterior parietal cortex (PPC) that was known to be involved in spatial awareness also fed the *intention* of movement to the motor cortex. In other words, the PPC helps us plan how to pick up a pen, or type a certain word on a keyboard. His lab, in collaboration with a company called Microprobe (whose main line of work is building testing devices to listen in on electronic components), has designed a microelectrode implant that eavesdrops on the PPC and decodes the subject's intent by using algorithms gleaned

from the lab's research. With such an implant, a severely paralyzed person could, in theory, move their wheelchair forward just by thinking about it. "The initial application would be for typing or possibly operating an iPad or other tablet-type computer," says Andersen. "With all the tablet applications that exist today, one might be able to do quite a lot without being able to move."

His lab is also involved in a sprawling collaboration, directed by the Defense Advanced Research Projects Agency and the Applied Physics Laboratory at Johns Hopkins, that is attempting to build a robotic arm—from shoulder to fingertips—that has all the freedom of movement of the human variety. His lab is working on two brain implants: one controls grasping, and the other, the movements of the hand as a whole. In addition, they are developing a feedback loop to the brain so that activating sensors on the robot's fingertips will lead to electrical stimulation of the somatosensory cortex, the part of the brain responsible for the feeling of touch. This feedback will give the hand more finesse by telling the brain whether the object being grasped is hard or soft, whether it is slipping through the hand or is firmly grasped, and how to manipulate the object with dexterity. Clinical trials are planned in collaboration with Huntington Hospital, just three miles west of campus.

## GRAY MATTERS

While neural devices have been shown to work well, their longevity remains a challenge. It is particularly hard to keep brain implants working for more than a year or so.

"The brain is a lot like the ocean—it's very corrosive," says Andersen, pointing out that finding and/or developing better materials will be part of improving the technology.

Tai and Burdick agree. "We are constantly looking for materials that our bodies like, or at least react neutrally to," says Tai.

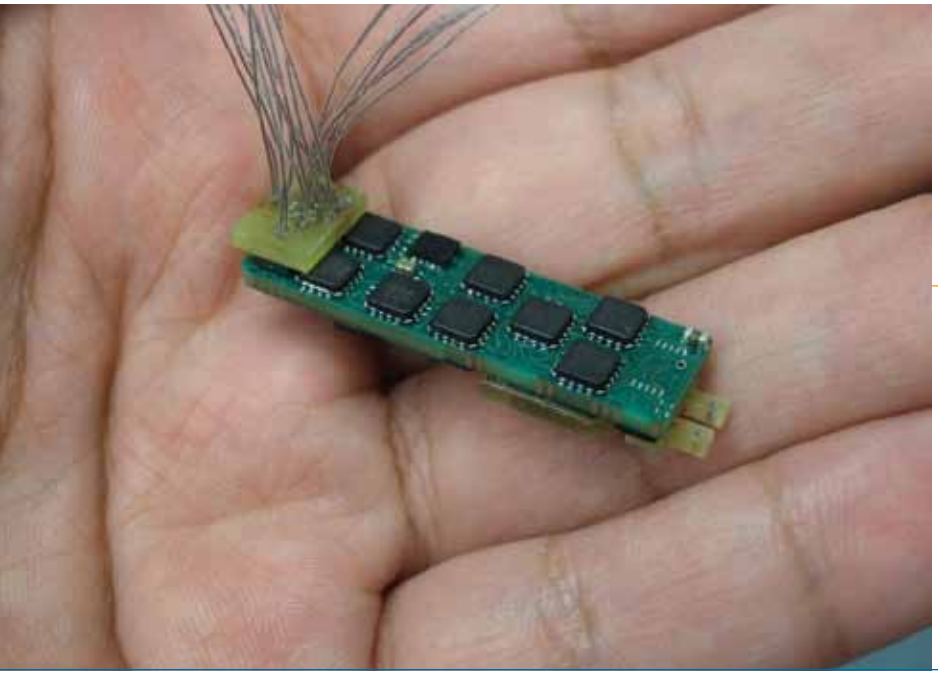
Beyond biocompatibility, the components need to be flexible, so that they can bend and stretch with the body. In addition, the implants need to be engineered to fit within tiny spaces: behind the eye, perhaps, or between vertebrae—without moving the body's own parts out of position. Andersen is also exploring the idea of making the implants wireless. With no connections penetrating the skin, there's no path for infection.

"The challenge there is that you have to broadcast a very large amount of information and you don't want to heat the tissue up, so you need special electronics of very low power but very high bandwidth," he says.

Figuring out a general method for tailoring the therapy to the patient is also a high priority. "We have a large number of electrodes, and we can change the voltage and frequency on every one," Burdick says of the spinal-cord implant. For example, the array placed in Summers has 16 electrodes, each of which stimulates a handful of neurons. But the spinal cord is so densely packed that only a few of the neurons in contact with the array will belong to the correct circuit, and even those few will generally require different levels of stimulation. "We have an enormous number of parameters to work with to figure out the best combination of stimuli for each person."

All of these projects are collaborative efforts, both on a Caltech scale and a national scale. The research requires expertise from many fields—from the engineers and scientists who build the devices to the medical doctors who oversee the human trials and help translate the technology into general use.

"Neural implants are complicated and involve so many different backgrounds—you cannot be a lone wolf," says Tai.



Tai's prototype spinal-cord implant has successfully helped paralyzed rats to stand. Researchers hope to have a human-scale device ready for trials in a few years.

## KEEPING AN ELECTRICAL EYE ON THE FUTURE

Just upstairs from Yu-Chong Tai, Azita Emami has a toyshop of her own where she, too, is toiling away on the next generation of eye implants. A part of the Caltech-USC collaboration that built the 60-pixel Argus II, her lab has recently developed a stimulator chip for a future self-contained retinal prosthesis.

"The main focus is to put the chip, and the electrodes and coils that Tai is making, into an integrated package," says Emami. "The ophthalmologist can put the whole device in the eye, and once it's healed there is much less risk for infection."

The chip would supplant the external, pocket-sized computer that currently processes the video-camera images and sends the digital information to the implanted electrodes.

"For a person to read, or even have functional sight for everyday tasks, you need many, many points of stimulation in the retina—over 1,000 at the least," she explains. "This requires extremely low power consumption if you want to put everything inside the eye."

This is where Emami and her graduate students come in. As masters of microelectronics, they have devised a tiny, tiny nanochip capable of delivering more efficient stimulation from far less power than the current model.

The chip, which gets its juice from an inductance coil, uses less than one-tenth as much power as the Argus II, even though it powers nearly 20 times as many electrodes, says Emami. "The power consumption has been reduced to levels that we think will work inside the eye."

The team hopes to test the entire intraocular prosthesis within the next two years. —*KN* E&S

***Azita Emami-Neyestanak is an assistant professor of electrical engineering.***
***Her work is supported by the National Science Foundation.***

### A BIONIC FUTURE?

The researchers look forward to seeing their work move out of the laboratory and into people's lives.

Andersen envisions his communication prosthesis initially helping people with severe paralysis or with conditions such as Lou Gehrig's disease, but his long-term goal is to enable amputees to operate prosthetic limbs with the instinctive ease of their natural ones. He also imagines endowing stroke patients with the ability to rewire damaged parts of the brain in order to recover lost functions. To that end, his lab is examining whether targeted stimulation of the healthy neural circuitry that remains can accelerate the relearning needed for brain repair.

While Burdick and Tai are building the next generation of smaller, more powerful spinal-cord implants, Burdick is anticipating wider clinical trials of the first-generation one.

"In five years, hopefully we will be in clinical trials for one or two generations of newer technology for human use," he says. However, he is quick to point out that this is not a cure for paralysis. "We call it a therapy, intended to improve life quality, but not to fully restore locomotion at this point," explains Burdick. "In the long run, a biologic approach will be the right solution, whether it's stem cells, genetic engineering, or tissue implants. But even then, it's naïve to think that someone who's just experienced a major injury will go in to the operating room, have some of their spinal cord snipped out, receive an injection of some stem cells, and get up off the table and walk away. So we think our strategy will be useful in rehabilitation, even when biological solutions are in place."

For all three men, helping people overcome disabilities is a big part of what pushes them forward.

"There are interesting technical challenges as an engineer, and really gratifying opportunities to see positive results with human patients," says Burdick. Adds Andersen, "The medical component of these projects is incredible. You can actually see something work, and show why it is so important."

"A lot of my engineering research ends in a paper, and I never know if or when it will become useful," says Tai. "But with neural implants, I clearly feel that my research will not be in vain. The experience is wonderful in the sense that the project is never-ending. We can always keep improving, to make better devices that help more and more people. For those who can't walk or see, we have to be the marathon runners." E&S

***Yu-Chong Tai is a professor of electrical engineering and mechanical engineering.***
***His work is funded by the National Science Foundation and the National Institutes of Health (NIH).***

***Joel Burdick is a professor of mechanical engineering and bioengineering.***
***His work is funded by the NIH, the Telemedicine and Advanced Technology Research Center, and the Christopher and Dana Reeve Foundation.***

***Richard Andersen is the James G. Boswell Professor of Neuroscience.***
***His work is funded by the NIH, the Boswell Foundation, the Gordon and Betty Moore Foundation, and the Swartz Foundation; the robotic limb project is funded by the Defense Advanced Research Projects Agency.***

## ROBOTS IN DISGUISE

Joel Burdick likes to call himself an "old robot guy," even though he's not old and his extensive background in robotics is still being put to good use. In fact, when he's not busy working on computational models for neural implants, he and a team of undergrads from his robotics lab are building physical-therapy equipment for Rob Summers, the first recipient of the spinal-cord implant Burdick helped design.

"I'm building Rob a series of increasingly sophisticated devices that he can use in his apartment," says Burdick. "It's a prototype phase, so that if our therapy continues to be successful in more patients, we'll have them available."

Burdick's team is developing a home version of the "stand frame," which supports a patient in an upright position as the person learns to stand and walk again. "This device is often used in spinal-cord injuries," says Burdick. "But a home version needs to be more automated, to ensure safety without the help of a technician. It has different straps and adjustments to stabilize Rob so that he can manage all the parameters of his training by himself.

"Physical therapy is expensive, and insurance companies only pay so much," Burdick explains. "If you can lower the cost so people can continue therapy over a long period of time, it's a win for everybody. Rob is continuing to improve after 18 months of rehab, so clearly there is a benefit to extensive PT."

Burdick built his first stand frame out of plastic pipes in his garage this spring. The next generation will be built out of aluminum and may include an elliptical trainer, so that Summers can practice his walking motions. Burdick also plans to go a few steps beyond, building a frame with sensors on it. One set of sensors would measure how much force Summers puts on the frame, while a set under his feet would determine how much weight is being supported by his body. In addition, a set of motion sensors would track his whole body in real time to document his training sessions and monitor his progress. All this information could then be emailed to his doctors and therapists after each session.

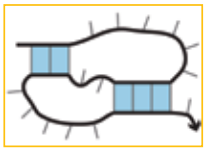
"If you can have quantitative information from the robotic devices about how the PT is working, it's useful for the therapists, doctors, and insurance companies, but also for the scientists so we can test hypotheses," says Burdick. "Plus I'm an old robot guy, so it keeps me excited." —*KN* E&S

Rob Summers works out in a standard physical-therapy-type stand frame at the University of Louisville's Human Locomotion Research Center at the Frazier Rehab Institute as a camera crew from ESPN shoots a story about his progress. Summers is talking to Louisville professors Claudia Angeli and Susan Harkema (in red), who are at the computer consoles, while Caltech's Joel Burdick (to Harkema's right) looks on.

# PROGRAMMING MOLECULAR APPS

By Marcus Y. Woo

## By learning how to program molecules to do everything from assembling a nanorobot to fighting cancer, we may be embarking on the next technological revolution.



Computers haven't taken over—yet. There are no Hals or homicidal cyborgs on Harleys, but computers still pervade every facet of our daily lives. As adding machines and vacuum tubes gave way to electronic transistors in the 1940s and 1950s, and as room-sized computers gave way to laptops several decades later, computer technology has been evolving faster than anyone ever anticipated. From cell phones to coffee makers, nearly every electronic device is now equipped with a silicon chip.

These chips not only allow people to program their latest smart phone, they can embed autonomous decision-making—some might even say intelligence—into what's otherwise a dumb machine. "When you attach a computer to something, it becomes much more powerful," says computer scientist Paul Rothemund (BS '94). But while the computer revolution continues, Rothemund is among a group of scientists and engineers who think we're on the verge of yet another revolution.

That next step? *Molecular* programming. Instead of telling electrons how to call Mom, brew an espresso, or solve a complex equation, these researchers hope to tell molecules how to diagnose diabetes, assemble into a nanobot, or attack a cancer cell. Such molecules might not only seek out the cancerous cell, but based on their evaluation of the cell type, its environment, and the cancer's state of progression, they would release the appropriate drug at the proper dose and time.

"It's hard to tell where things are going to go," says engineer Richard Murray (BS '85), who along with Rothemund is part of Caltech's Molecular Programming Project, or MPP. "But I suspect we'll use molecular programming the way we now think of electronics." Like computer programming, molecular programming is an engineering endeavor, he adds. If the field advances as rapidly as Murray, Rothemund, and their colleagues hope it will, in a few decades molecular programming could be as ubiquitous as the electronic kind, changing not just how we live, but how we understand the world and life itself.

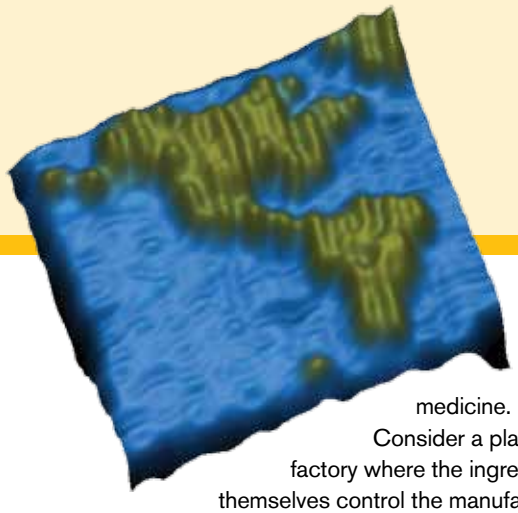
### FROM BINARY TO BASIC

Fortunately, a powerful computing language already exists in the form of DNA molecules, which encode all the information any organism needs to develop, grow, and reproduce, whether it's a bacterium, an elephant, or a towering redwood. This information is spelled out by sequences of four chemical "bases" (commonly called A, T, C, and G) that act as the letters of the DNA alphabet. The letters follow strict rules—A is paired with T, and C with G—so the sequence of letters in a strand determines the sequence of letters in the strand that will bind to it. Couple this intrinsic logic to the ability to write any sequence of letters you want into a DNA strand—now a routine part of bioengineering—and you're on your way to writing a molecular program.

DNA and its cousin, RNA, are easily made in labs and are integral to biology. If you want to learn how proteins function, or inject molecules into the body to combat cancer, then it only makes sense to consider DNA.

The potential for molecular programming, however, goes far beyond

Left: *City of Life*, by Ann Erpino (http://www.annerpino.com/). Copyright 2006. Reprinted with permission.



To the left: This map of North and South America, made using DNA origami, is only about 100 nanometers wide. The image was taken using an atomic-force microscope, which works by dragging a needle across the object, measuring the bumps of every atom.

To the right: Woo and Rothemund have developed a jigsaw-puzzle-like way to assemble DNA tiles. Here, four tiles bearing the raised letters A, B, C, and D bind only if the shapes of their edges match. Top: a diagram of the scheme. Bottom: an atomic-force microscope image of the actual tiles.

medicine.

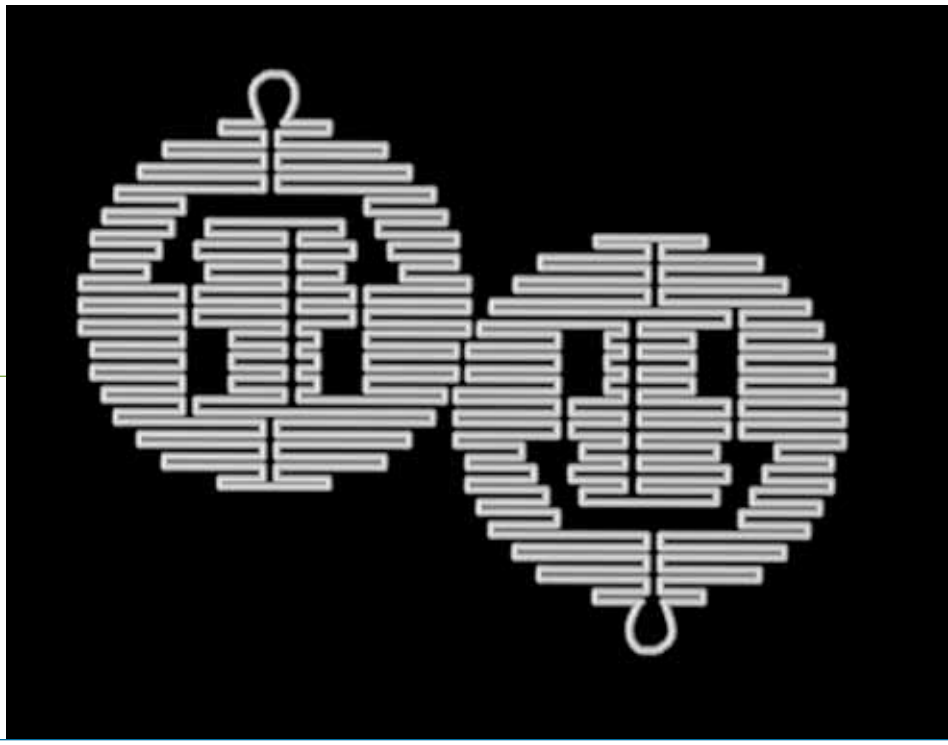
Consider a plastics factory where the ingredients themselves control the manufacturing process through built-in feedback loops, rather than relying on humans (or even computers) to mix the right amounts of chemicals A and B to get the maximum production of C. Programmable molecules could assemble themselves into entirely new kinds of composite materials, or even complicated structures. Maybe one day our cell phones (or whatever communication devices we'll have in the future) will be *grown*, molecule by molecule. Perhaps more fundamentally, molecular programming is already providing tools for studying biology like never before.

The MPP researchers envision a world where molecular programming is accessible to all regardless of technical training. Just as anyone can teach themselves how to write software or design a web page, someone in the future might just as easily write a molecular program. "In a hundred years, someone who has no clue about biology might make a huge contribution to medicine by writing something on the level of an iPhone app," says information scientist Shuki Bruck, another member of the MPP team.

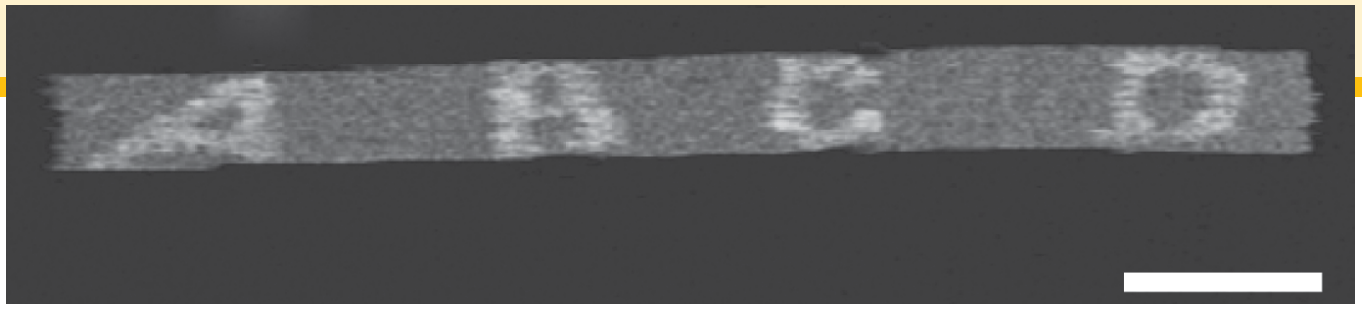
"The difference between the MPP and what other people are doing with nanotechnology and biotechnology is that we're trying to think in terms of information science," Murray explains. "What are the different levels of abstraction we can use to describe the system?" For example, a specific combination of DNA strands that behaves in a certain way can be thought of as an independent component—a black box with a well-defined function. Engineers can mix and match these boxes to create larger, more complex components that will eventually lead to a level of abstraction on a par with the high-level programming languages we now have in computer science. "If you sit down and use Microsoft Word, you don't have to think about what the individual transistors are doing," Murray says. "You think on the level of writing a macro to do something you want to do."

The key is to be able to program molecules without having to wade knee-deep into the intricacies of molecular biology. Writing out the strings of bases needed for individual DNA strands to perform specific tasks is the equivalent of hand-coding applets in binary. The MPP is creating the molecular equivalent of machine language—developing the first low-level assembly languages and the compilers that read them—that will enable the next generation of molecular software developers to write the equivalent of BASIC and FORTRAN.

The MPP "is a quintessential engineering activity, in that we're trying to understand how you design things in a systematic way," says Murray, whose expertise is in feedback and control systems. Since feedback is also crucial to biology—it's how your body regulates your blood-sugar levels, for instance—he's applying control-system principles to molecular programming. In fact, Eric Klavins of the University of Washington, another member of the MPP and a former postdoc of Murray's, has built networks of genes that behave in a homeostatic manner. In other words, just as the amount of glucose in your blood remains within certain limits, regardless of whether you're lifting weights or watching TV, these networks adjust the production rate of a given substance depending on how much of it is being consumed.



Each sheet of DNA origami "paper" is a closed loop of DNA called a plasmid. Any two-dimensional shape you like can be made by folding the loop back and forth on itself.

Woo and Rothemund, *Nature Chemistry*, vol. 3, pp. 620–627. Published online July 10, 2011. Copyright © 2011, Nature Publishing Group.

## FROM ORIGAMI TO NANOBOTS

Paul Rothemund is perhaps best known for his tiny smiley faces. In 2006, he pioneered DNA origami—a method for folding strands of DNA into any two-dimensional shape, including smiley faces just 100 nanometers across and 2 nanometers thick. (He has also made a DNA map of North and South America, spelled out the letters "DNA" in DNA, and formed DNA snowflakes.) Each shape consists of a long strand of DNA folded at intervals so that it runs back and forth in a series of parallel line segments that fill in the shape. The lines are held in place by "staples," about 200 of them—short strands of DNA that bind to the long strand as it folds, guiding the adjoining segments into their proper positions. Researchers around the world now use DNA origami to build everything from tiny boxes to nanoscale transistors.

Just as the wingspan of a folded crane is limited by the size of the sheet of paper, the size of a single piece of DNA origami is limited by the length of the strand being folded. Strands longer than the ones Rothemund is using have proven hard to come by, so over the last two years, Rothemund and grad student Sungwook Woo have worked out new techniques for assembling origami building blocks into larger structures. The standard high-school biology view of a DNA molecule is as a twisted ladder, with the rungs consisting of pairs of bases that cling to each other. However, each rung also sticks strongly to the rungs above and below it through a so-called stacking interaction—in fact, this interaction appears to be the main force holding the ladder together.

If you put a hinge between two rungs and fold the ladder in half, the rungs next to the hinge will be "hanging in the breeze, without a partner to stick to on one side," says Rothemund. This blunt end, as it's called, will readily stick to any other blunt end. "You can visualize the blunt end as the flat, sawed-off end of a log," Rothemund continues, noting that the origami blocks—or, more accurately, two-dimensional tiles—look like tiny log-cabin walls. By including logs that ended in floppy, nonadhesive loops of DNA as well as sticky blunt ends, the researchers created a binary system: "0" for non-sticky and "1" for sticky. Woo and Rothemund demonstrated that these tiles bound preferentially to other tiles whose edges encoded the same binary sequence, meaning that such tiles could be strung together in any order one might care to program. "A lot of people, including us, have made DNA shapes with blunt ends that cause the shapes to stick together into random clumps—piles of junk," Rothemund says. "But if you are careful, you can harness the power of blunt-end stacking interactions—converting something that used to be considered a 'bug' into a 'feature.'"

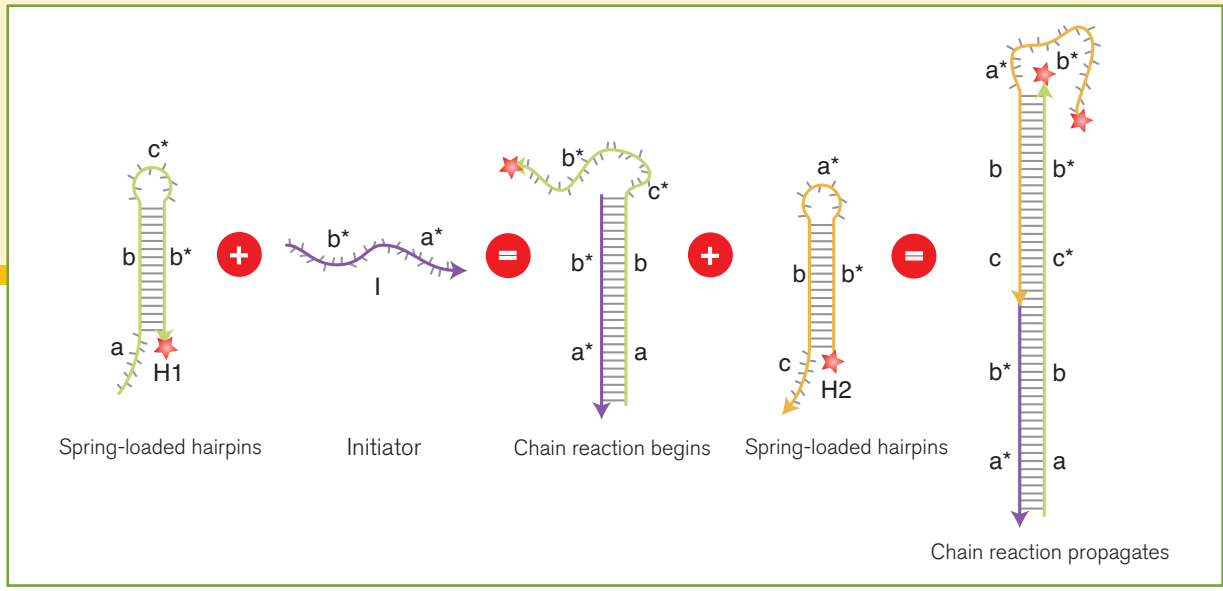
The binary-sequence tiles were rectangular, with straight edges. But Woo and Rothemund also created a set of shape-recognizing tiles with jagged edges: all of the logs had sticky ends, but the logs themselves were of varying lengths. And behold, properly matched edges clicked into place like the pieces of a jigsaw puzzle.

This particular set of jigsaw tiles had 16 possible edge shapes; 16-bit binary tiles would have thousands of easily distinguishable edge patterns. But merely having 16 possible edges to play with would enable people to make much more complex devices than can be made through origami, including simple logic circuits rather than the single transistors that have been made so far.

In addition to enabling larger structures, these techniques could ease us past a sticking point on the way to a full-on, sci-fi, self-assembling nanobot: the problem of moving parts. "A human-scale analogy would be to take all the parts for a car, paint them with glue, throw them in a bag, shake it, and have a working car pop out," Rothemund says. But DNA base-pair binding makes for a very powerful molecular adhesive—your car's motor wouldn't run and the wheels wouldn't turn. Even the wipers would be stuck to the windshield. "We think that we will be able to design stacking bonds in which the parts of a nanomachine will be able to self-assemble and then slide freely past each other," he continues. "The parts won't look exactly like interlocking log walls, but they will work on the same basic principle."

## FROM NANOBOTS TO CELL PHONES

In order to make these parts self-assemble, however, each one has to know exactly




where it's going and how it fits into the grand design. And this is a problem: say you had several thousand unique shapes at your disposal—that's still not enough to orchestrate the spontaneous coalescence of a piece of human-scale technology.

"If we wanted to self-assemble a cell phone, origami won't do it," says Erik Winfree (PhD '98), a computer scientist and director of the MPP. "But algorithmic processes could." For the last 15 years, first as a grad student and now as a faculty member, Winfree has been working on ways to embed algorithms, the abstract ideas at the heart of computer programs, into the DNA itself. "You design a set of molecules that fit together according to a certain logic, and by controlling which molecule fits at which location, you can program the growth of a whole structure," he explains. Then all you need to do is pour the molecules into a beaker, stir briskly, and voilà! The algorithm executes itself. If you are clever enough writing the rules, you can create very complex structures with just a few different molecular bricks.

But why work molecule by molecule? "To build things that are more structured than current technology allows," Winfree says. "If you can build things out of bricks that are a few nanometers in size, you can do a lot more in the same space." Compare a whale and a submarine, he explains. Both are about the same size, and both propel themselves underwater. A submarine is made up of relatively large pieces—steel panels and pipes, screws and bolts. But a whale's internal structure extends all the way down to the arrangement of the individual protein molecules in its cells. In other words, a chunk of whale has a lot more going on than an equal-sized chunk of submarine.

Another advantage of molecular self-assembly is the potential for cheap manufacturing. It costs billions of dollars to build a factory that makes silicon chips. "Biology has always been the opposite of that," Winfree says. "If you have a few seeds, they'll just grow. Mold will grow in your refrigerator even though you didn't want it to." DNA self-assembly mimics how biological organisms grow, cell by cell, protein by protein, and as a result, it's much cheaper than conventional manufacturing. Using molecular programming to "grow" a cell phone would be more akin to kitchen chemistry than to an expensive, factory-based process, he says. (He also adds that we're a long way from growing anything as big and complicated as a cell phone.) "Our lab," Winfree says, "is very simple. Most of our procedures involve ordering a few DNA strands, mixing them together, and letting the molecules do the hard work."

## FROM CELL PHONES TO THE BRAIN

"In a really fundamental sense, algorithmic self-assembly *is* a form of computation," says Rothemund. "In fact, it is far *more* powerful than circuits." But these hardworking molecules can also be made to "compute" in the traditional fashion: Winfree and his colleagues are building DNA circuits, replacing handfuls of transistors with test tubes full of molecules. In a digital logic gate, electrons either flow or they don't. In a DNA-based logic gate, the DNA strands either bind or they don't. Early this year, Winfree and postdoc Lulu Qian created, from scratch, the largest and most complex DNA circuit ever made. It used a set of standardized components—a crucial requirement for developing higher-level molecular programming languages, as well as for scaling up the circuits themselves.

This circuit consists of 74 kinds of DNA molecules, and can calculate the square root of any integer up to 15—or, for the technically inclined, any four-bit number. (The circuit does round the result down to the nearest whole number, however, as dealing with a decimal point is a bit beyond its capacity at the moment.)

The original dream for DNA computing was to solve big, complex problems. "That hasn't panned out," Winfree says. DNA computing just isn't efficient enough; calculating that square root took 10 hours. "Nevertheless, a tiny bit of computing goes a long way in the molecular world," remarks Rothemund. "Molecular computers, no matter how simple, can be used to control other molecular phenomena." No silicon computer has this power, but it's DNA's natural role. "The whole process of embryonic development is controlled by a molecular computer performing logical operations—'If *X* then *Y*, but only if *A* hasn't happened.' And even though

A single strand of RNA can fold onto itself to form a hairpin molecule. A fluorescent molecule, labeled H1, is attached to such a hairpin. When an RNA initiator comes along, it binds to the hairpin and pops it open. The resulting molecule attaches to yet another hairpin, which carries another fluorescent molecule (H2). The chain reaction continues, producing a long molecule with many glowing attachments to form a really bright marker.

it doesn't solve anything we'd recognize as a computationally difficult problem, its computation serves to make a very complicated object."

Still, if doing sixth-grade math isn't enough for you, Qian, Winfree, and Shuki Bruck have created the first-ever DNA circuit that has *brainlike* behavior. That's right—using the same methods employed to design the square-root calculator, they have made a neural network that plays a mind-reading game. To play, you first think of a scientist. Then you answer one or more of four previously defined yes-or-no questions—for example, "Was the scientist British?"—by dropping the DNA strands corresponding to those answers into the test tube. Now you shake the test tube vigorously, and if the facts you provided match any of the four scientists programmed into the network's memory, the test tube lights up with a color-coded fluorescent signal. The network also tells you if it doesn't know the answer. It even tells you *why* it doesn't know: whether the scientist you picked is not in its memory, or whether you didn't give it enough clues for it to narrow its choice to just one person.

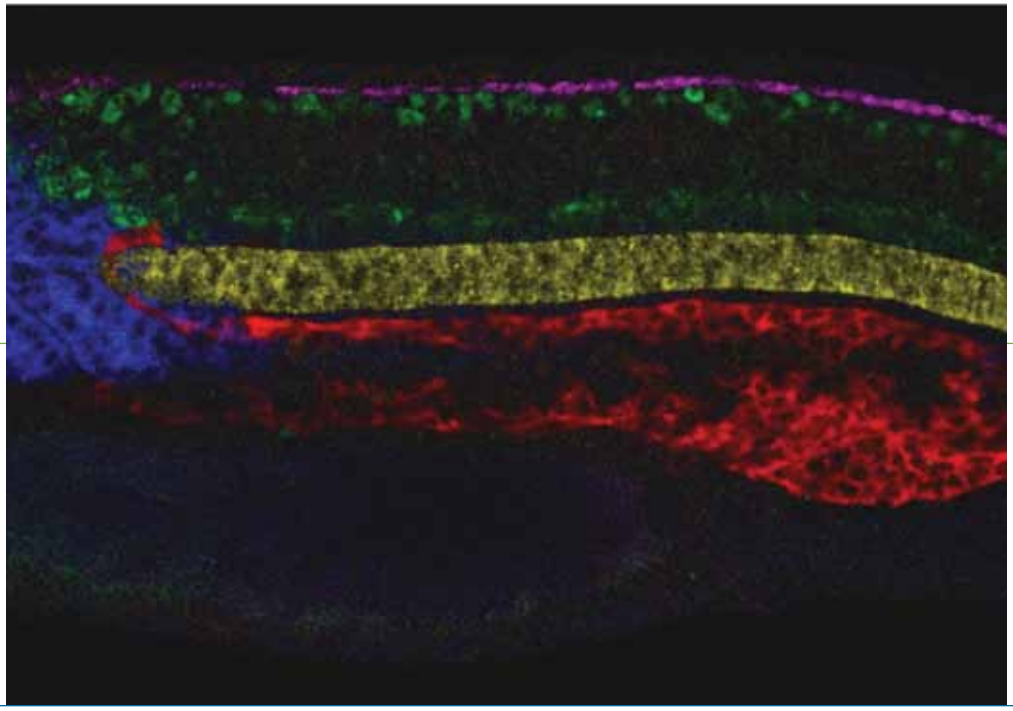
Taking an incomplete pattern and figuring out what it might mean has been one of the hallmarks of a living brain. Maybe it's not just silicon chips that we have to worry about becoming self-aware and taking over the world. We might have to watch out for those molecules, too.

## FROM THE BRAIN TO THE ORGANISM

While his colleagues were concerned with computational power, bioengineer Niles Pierce was all about motive power. In 2004, he and grad student Robert Dirks (PhD '05) came up with a way to make DNA "fuel" in the form of spring-loaded hairpins of single-stranded DNA that could pop open on cue. Four years later, Pierce and postdoc Peng Yin demonstrated that a properly scripted set of cues can nudge molecular machines into performing a surprising variety of feats. One of their creations was a molecular "tree" that grew dendritically from seed to leaf; another was a DNA "walker" that strolled along a DNA track. "In theory, DNA motors could provide us a different way to build things," says Pierce. "Rather than just letting things stick together, if pieces can be moved around *actively*, by DNA walkers, it may be possible to build complex objects much more quickly and efficiently."

Meanwhile, Pierce has begun applying what he had learned from engineering molecular machinery to developing molecular instruments—tools he hopes will revolutionize biological research. "There are profound questions hanging over the heads of biologists about how development works, about how diseases work," he says. "Biologists will be able to make faster progress with more powerful experimental techniques."

Answering many of these questions requires finding out when and where genes are switched on in different cells. For the last 40 years, biologists have been using a method called in situ hybridization, or ISH for short, to pinpoint the locations of messenger RNA (mRNA) molecules that serve as proxies for their activated genes. (RNA, the chemical first cousin to DNA, encodes information in an almost identical set of bases, and mRNAs deliver the DNA's protein-making instructions to the cell's protein factories, the ribosomes.) After flooding a thinly sliced tissue sample or a Petri dish full of cells with an RNA probe designed to bind to the mRNA of interest, the unbound probe molecules are rinsed away. A fluorescent "tag" on the probe then lets you image the mRNA targets under a microscope.



This image shows the fluorescent amplification technique being used in a zebrafish embryo, illuminating five different kinds of mRNA with five different colors.

To the right: A "smart drug" might one day consist of a molecular robot that recognizes malignant cells by their surface proteins. After docking with the marker protein, the robot could crawl along the cell's membrane, slicing it open and destroying the cell.

But when you try ISH on a vertebrate embryo, which are the ones of most interest to scientists studying human development and diseases, you need to boost the fluorescence in order to see it. Biologists add an enzyme that deposits extra tag molecules near the probe, amplifying the fluorescence. To see two mRNAs at once, you repeat the process with the same enzyme and a different dye.

This is a big problem, Pierce says. "It's cumbersome, and an impediment to studying genetic circuits, where biologists want to look at many genes interacting with each other." With the standard approach—first dyeing one mRNA red, say, and then another one green—it takes about five days to do three colors.

But if the fluorescent amplifiers were programmable, they could operate independently, seeking out their various mRNAs at the same time. Pierce realized that the spring-loaded hairpins that powered the walker could run an amplifier as well. With each type of hairpin carrying a different dye molecule, the only limit to the number of colors would be the number of dyes that can be distinguished through the microscope.

After five years of hard work, Pierce and his coworkers, including grad student Harry Choi (PhD '10) and biology professor Scott Fraser, successfully tested fluorescent ISH, or FISH—on, appropriately enough, zebrafish embryos—by targeting five species of mRNA simultaneously. The method passed with, well, flying colors. "These amplifiers, which started as a proof-of-principle exercise in molecular programming, are now a research tool at Caltech," Pierce says; while Fraser continues with the zebrafish studies, biologists Marianne Bronner, Dianne Newman, and Eric Davidson are using the technique to study genetic circuits in birds, bacteria, and sea urchins respectively. And the method is catching on elsewhere—the Pierce lab is providing probes and hairpins, as well as technical support, to biologists around the world.

While the researchers are continuing to enhance this technique—for example, figuring out how to zoom in and achieve molecule-scale resolution in order to map mRNA locations quantitatively—they're also pondering other types of molecular instruments. One possibility, Pierce says, is to design tools that would turn gene B on (or off) depending on whether gene A is already on or off. "This would provide unprecedented tools for studying genetic circuits at specific times and locations within developing embryos," he says. Being able to program conditional gene activation (or silencing) would also have medical potential, he adds.

"These are all dreams right now," Pierce says. But he hopes that in the next 10 to 15 years molecular instruments will become indispensible for research. "The possibilities," he says, "are essentially endless."

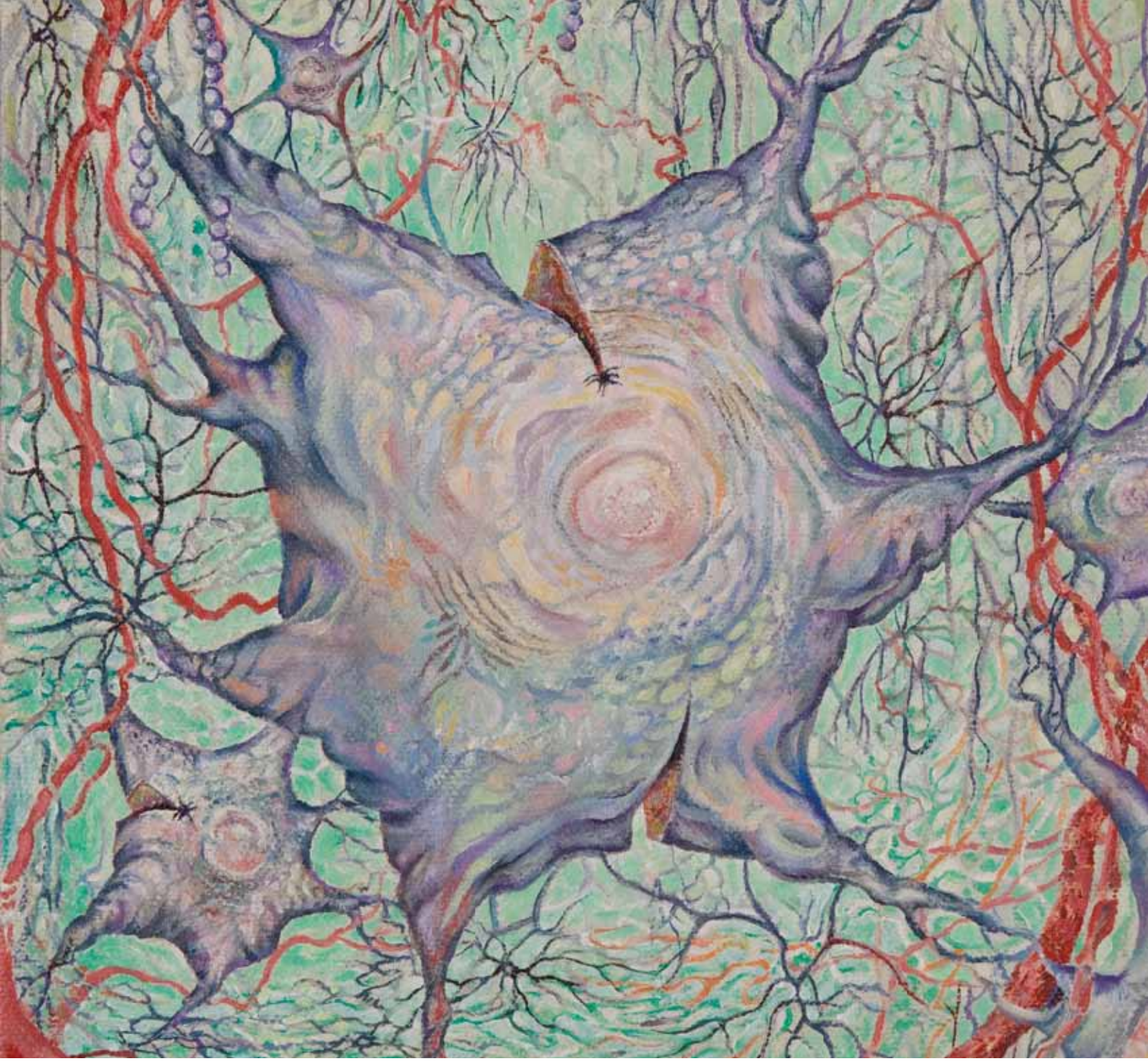
## FROM THE ORGANISM BACK TO BASICS

Although the MPP is informed by the computer revolution, it's rooted in aspirations to understand how life works. "Understanding biological systems is the most important challenge for the next 100 years," says Bruck, whose background is electrical engineering, but who now focuses his research on computing with biological circuits. "If you compare our world to anything else in the universe, based on what we know so far, we have life here and not anywhere else. That's the most precious thing we have here, and we still don't understand it."

For a computer scientist like Winfree, the MPP is about the idea that information is the essence of nature, that life is driven by the programming power of DNA. "The universe just happens to be that way," he says. "Biology has exploited that inherent essence of nature to do what biology wants to do: to reproduce, to evolve, to build really complex animals, and to build brains." The ambitions behind molecular programming go beyond a descriptive understanding of biology, as researchers strive for deeper insight into what life is at its most fundamental level. "Technological developments have historically led to new concepts, and the languages needed to express them," says Winfree. "And these new languages change how we look at the world and reason about it."

Just as miners and engineers tinkering with pumps led to the development of the steam engine, which in turn led to the discovery of the laws of thermodynamics and eventually to the development of statistical mechanics—which is now used to analyze everything from galactic evolution to stock-market rallies—the languages that might spring from molecular programming could give us the conceptual tools needed to think about complex biological systems in a whole new way.

The Industrial Revolution and the Computer Age came about by accident and happenstance, but Rothemund hopes that the Molecular Era will occur by design. "The fact that we have started to recognize the features of such revolutions gives society tolerance for us to play around and see if we can build another one," he says. "This kind of forethought is, I think, a hallmark of our age. Research grants and start-up companies have regularized, ritualized, and mechanized innovation. The MPP, for example, is supported by a very forward-looking program run by the National Science Foundation called Expeditions in Computing. It's really amazing to me that we can come up



*Process of Elimination*, by Ann Erpino (http://www.annerpino.com/). Copyright 2007. Reprinted with permission.

with a futuristic, almost science-fiction vision, organize around it, and have society buy into it." E&S

***Paul Rothemund (BS '94)** is a senior research associate in bioengineering, computer science, and computational and neural systems. Richard Murray (BS '85) is the Everhart Professor of Control and Dynamical Systems and Bioengineering. Jehoshua "Shuki" Bruck is the Moore Professor of Computation and Neural Systems and Electrical Engineering. Erik Winfree (PhD '98) is a professor of computer science, computation and neural systems, and bioengineering. Niles Pierce is a professor of applied and computational mathematics and bioengineering and executive officer for bioengineering.*

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# Naturally Inspired

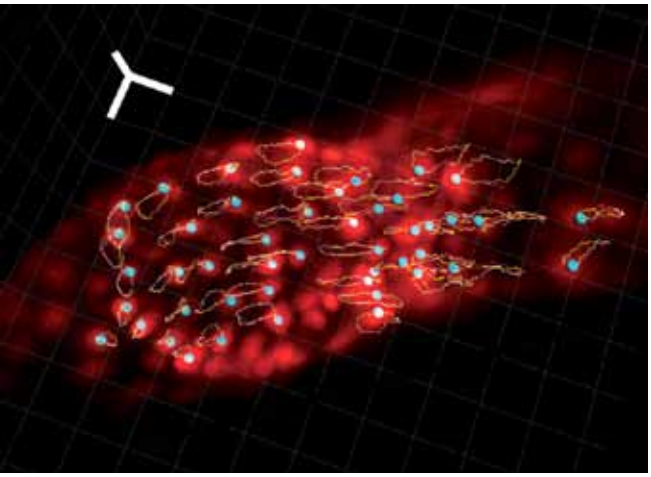
By Kimm Fesenmaier

In the Charyk Lab of Bioinspired Design, even an embryonic zebrafish heart can be an engineering muse. Here, Caltech engineers continue the time-honored tradition of teasing apart nature's tricks and borrowing the best bits.

When Mory Gharib (PhD '83) studies zebrafish, he sees straight to the heart of the matter. Literally. Since zebrafish embryos are almost transparent, it's quite possible to peer right through them. But when Gharib and his group started studying *Danio rerio* about a decade ago, they had a feeling there was more to its tiny pulsing heart than meets the eye.

Since then they've picked apart the properties of the fish's embryonic heart, and are now applying what they've learned to attack problems as diverse as ringing in the ears and overheated electronics. They've even developed the first pump built entirely from biological building blocks.

The striped, pinkie-sized zebrafish has become a mainstay for developmental biologists—it was one of the first animals to have its entire genome sequenced; it reproduces in large numbers and has a short life cycle; and since its see-through embryo develops outside the mother, the changes it undergoes as it matures are easy to follow. Gharib was introduced to this



An unlikely muse: The embryonic zebrafish heart is little more than a tiny tube of cells, but it gets the job done. This three-dimensional reconstruction shows fluorescently labeled heart-muscle cells and traces their movements over the course of two cardiac cycles. The Y-shaped scale bar indicates 20 microns in each direction.

A. Forouhar, et. al., *Science*, vol. 312, pp. 751–753.


little marvel by biologist Scott Fraser, director of the Rosen Bioengineering Center, whose confocal microscopy lab Gahrib uses. "We now have a very fruitful collaboration between the two groups," Gharib says.

Gharib is an aeronautical engineer, not a developmental biologist, so he's interested in species like the zebrafish for other reasons. He likes to steal their tricks, one-up them by enhancing what Mother Nature has accomplished, and find new applications where the tricks could come in handy.

"We can actually be more clever than nature," Gharib says. "We can get inspired by nature and use engineering to come up with better functions. Just look at 747s—they fly from LAX to La Guardia much more efficiently than any bird could." That's why Gharib runs the Charyk Laboratory for Bioinspired Design.

In the case of the zebrafish, the group homed in on a very early stage of the species' development, when its heart is little more than a short tube of cells. By studying the patterns of flow created in and by the tube, Gharib and his team determined that the action wasn't driven by peristalsis, as had widely been assumed. Peristalsis uses a traveling wave of contraction to move the fluid along—think squeezing a toothpaste tube from the bottom up to push the contents onto your brush. Instead, they found a much simpler mechanism, first described in 1954 by German cardiologist Gerhart Liebau and which the Gharib lab has dubbed "the impedance pump."

All you need for an impedance pump is a flexible, fluid-filled tube connected at both ends to less flexible tubes—even tubes made of the same material will suffice, as long as the walls are thick enough to make them substantially stiffer. The key is to make the transition abrupt, because the point where the wall suddenly becomes rigid acts as a reflector, bouncing the pressure wave back into the flexible section of the tube. By compressing the flexible section in just the right (off-center) location at just the right rhythm, the reflected and newly generated waves interfere constructively to create a pressure gradient that drives a flow through the system.

Though the pump is simple, its fluid dynamics are complex. Thus the researchers in Gharib's lab built scaled-up pumps in order to tinker with their parameters and to discover the ins and outs of their function. The first mechanical pumps were centimeters in diameter—small, but still a hundred times larger than the zebrafish's tiny heart tube. Since then, they've been scaled back down. Some models were simple tubes, made with a two-centimeter length of latex tubing and a couple of glass capillaries. Others were more sophisticated, constructed from micromachined metals or silicone and built to lie flat on a tabletop.

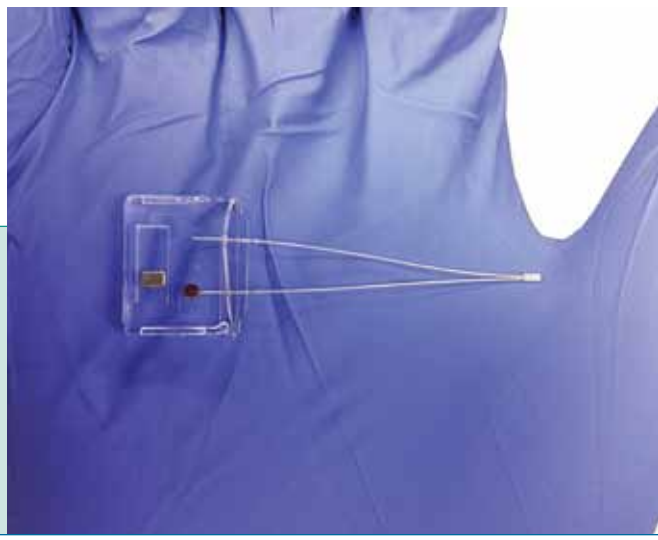
Since impedance pumps don't have valves, there are very few moving parts to break down. Some of the group's creations have managed to go through more than 200 million cycles, which is to say two weeks of continuous duty, without any degradation of performance.

The impedance pump's elegant simplicity is seductive. Clearly, it can operate on a very small scale—nature only needs a handful of cells to make one. "With something like peristalsis, you need to coordinate the motion of many different cells all contracting in succession. But with an impedance pump, all you need is a simple band that's continually beating at one frequency," says Derek Rinderknecht (PhD '08), senior research scientist in aerospace and a member of the Gharib lab. "This allows you to have a very simple way of moving fluid around at a very early stage in the fish's development."

The pumps are also astonishingly efficient. "Taking advantage of resonance allows you to have a much higher output for any given input," Rinderknecht says. "That means less energy is required."

Armed with a solid understanding of the physics at play, the researchers were ready to put their new tricks to work. "We knew we had a 'platform technology' that could hold value for many different areas of medicine," Gharib says. "These pumps could be useful pretty much anywhere you need localized, controlled delivery."

The inner ear, for example. A tiny, implantable pump could deliver a



A prototype impedance pump for treating chronic ringing in the ears nestles in Rinderknecht's gloved palm.

Right: In these frames from a video, water droplets do skateboarding tricks on a carbon-nanotube-coated surface.

Left: Grad student Hesham Azizgolshani watches the workings of a pump he made from biological building blocks.

steady, long-term trickle of medicine to help treat a variety of hearing disorders, and the Gharib team has partnered with pharmaceutical giant Sanofi to develop just such a device.

The pilot version is designed to alleviate ringing in the ears. Chronic tinnitus, to use the medical term, affects at least 20 million Americans, according to the National Institutes of Health. It's also becoming a common disability in the military, where loud explosions in close proximity are unfortunately a part of life. Drugs, devices to mask the "sound" of tinnitus, and neural stimulation have all been tried as remedies, with varying levels of success, but there is currently no cure. Part of the problem lies in the fact that tinnitus can spring from several causes. Some cases appear to originate in the inner ear; others in the nerves and brain regions associated with it.

Rinderknecht is building an impedance pump that could be implanted in the mastoid bone, close to whichever tissues are affected. "The tinnitus project has been a good chance to go from a pump that works on a bench top to an implantable, proof-of-concept device," Rinderknecht says. "That's where we're heading right now. We're starting to lay the groundwork for eventually, hopefully, moving into some sort of clinical setting." The prototype version has just been completed, and now awaits testing.

The Gharib group has also found nonmedical applications. In the hot field of electronic cooling, for example, many researchers are looking for low-power ways to dissipate or redistribute the heat generated by the processors, circuits, and other components of our ever-shrinking electronics. The lab is now developing a circuit-board overlay, thin as a credit card, that would circulate a fluid over the board's electronic hot spots, carrying heat away to cooler areas.

"For electronic cooling, the unsteady flow that these pumps create could be a good thing," Rinderknecht says. "It can be used to move heat more uniformly into the fluid. It's almost like sloshing the contents of a cup in order to mix them up."

While these ventures may be efforts to one-up Mother Nature, another project could be described as an attempt to tune up Mother Nature—to fix something biological that isn't working properly. Toward that end, grad student Hesham Azizgolshani has actually built a "living" impedance pump using heart cells and intestinal tissue from rats. He strips the intestinal cells from the tissue, leaving a tubular scaffold that he repopulates with heart-muscle cells.

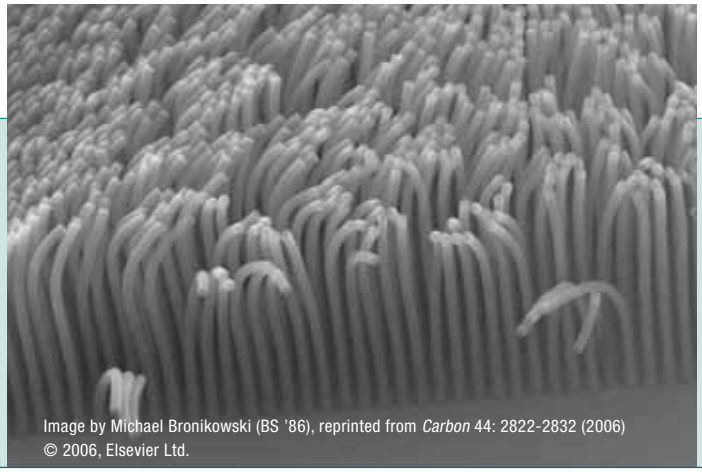
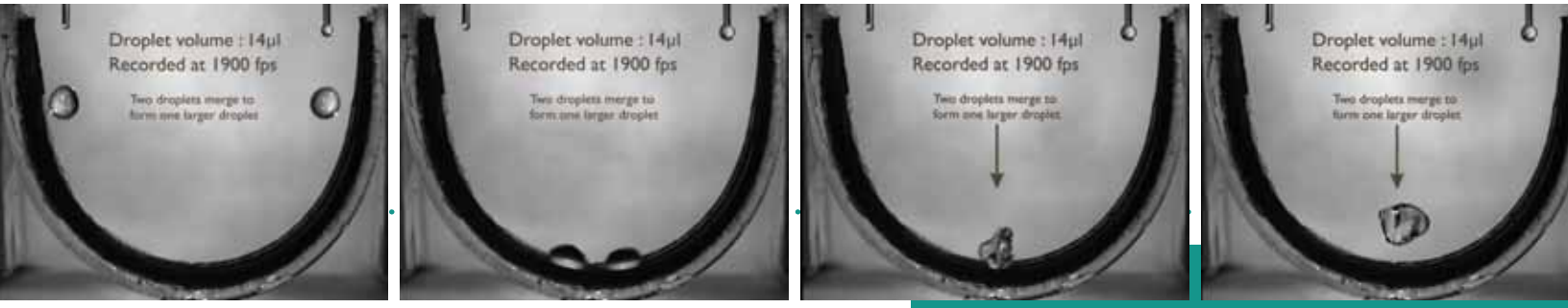


Image by Michael Bronikowski (BS '86), reprinted from *Carbon* 44: 2822-2832 (2006)


Right: An electron-microscope image of a carbon-nanotube array. Each tube is about 40-millionths of a meter long.

Far right: Manipulating the nanotubes' degree of hydrophobicity can create gradients across the array that will drive a fluid sample placed in the center into different wells for analysis. This chip is called "the Zen garden."




"We wanted to show that it's possible to make a pump fully out of biological materials," Azizgolshani says.

He plays a piece of video captured by a high-speed camera mounted on a stereomicroscope. Sure enough, the pump is pulsing, driven by the compression of a ring of cells around the tube. But this isn't enough, he says. "I can't just claim that I have made a pump. I have to verify and characterize its function."

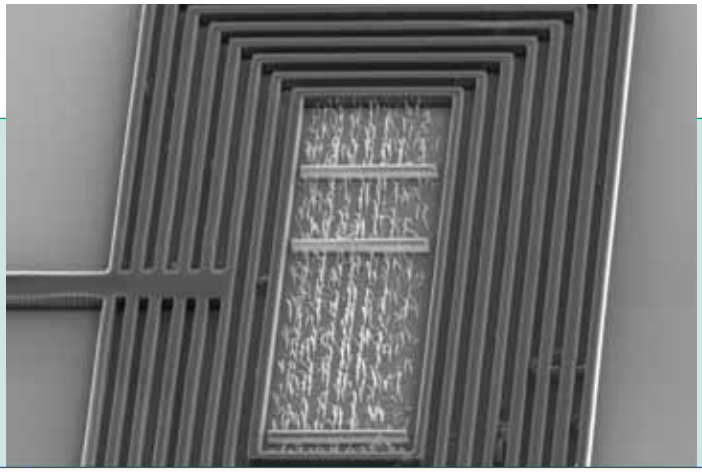
He starts a second video; this one features silver-coated glass particles suspended in the fluid within the tube. The particles slosh back and forth, so it's hard to tell if they are actually *flowing*. But when Azizgolshani plays the video in fast forward, a net left-to-right flow is apparent.

"We started from a biological system, we learned from it, and after we felt we were confident and comfortable in our understanding, we decided it was time to try to make our own biological pump," Azizgolshani says. "I think one of the beauties of this project is that we are closing that circle."

Currently, this pump is only a proof of concept. In his best effort so far, Azizgolshani has managed to keep a pump going in a bioreactor for two weeks. But eventually, durable, long-lasting pumps made from a patient's own cells could be implanted into human veins. This would assist diabetics, for example, who often suffer from poor circulation, and who would benefit greatly from "booster pumps" that would help move blood back to the heart from the peripheries.

"Instead of trying to get the body to accept our man-made materials, which can easily be rejected, the goal is to use the biological materials that are available to us," Azizgolshani says. "The possibilities are limitless." E&S

***Morteza "Mory" Gharib** is the Liepmann Professor of Aeronautics and professor of bioinspired engineering. He joined the faculty at Caltech in 1992, and he currently serves as one of the Institute's vice provosts.* ***The Caltech-Sanofi nanopump project is funded by a Sponsored Research Agreement under the Caltech-Sanofi Alliance Framework. The nanotube work is supported by the Charyk Foundation and the Fletcher Jones Foundation.***



## SUPER-HYDRO-PHOBIC-LOTUS-ACTING-NANO-TUBULES

Zebrafish aren't Gharib's only muses. There's also the lotus leaf, which is exceptionally good at repelling water. Many of Gharib's students are working with carbon nanotubes, minuscule rolled-up graphite lattices that look, at the atomic level, like hollow bundles of molecular chicken wire. The superlatives fly when scientists talk about these tubes—it's not uncommon to hear them described as the strongest material ever made, or the most promising. But the descriptor grad student Adrianus Aria (MS '08) has focused on is "most hydrophobic."

Some arrays of carbon nanotubes are more water-repellant than others, and Aria has found out why. It's all in how you grow them—if their surfaces get slightly oxidized, the oxygen atoms attract water molecules. So Aria developed a recipe for cooking the arrays in a vacuum chamber to get rid of any stray oxygen atoms. The result? Superhydrophobic nanotubes.

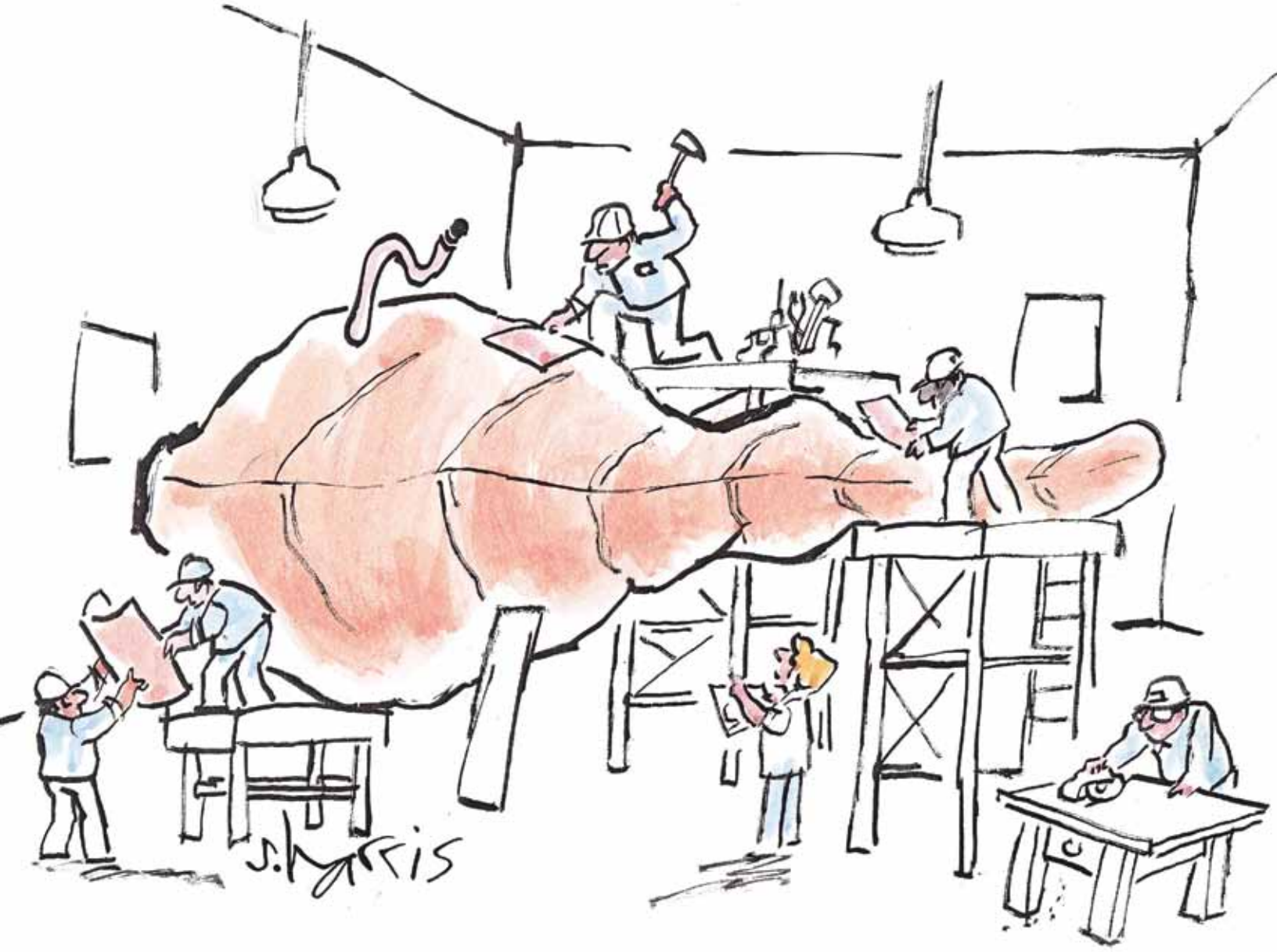
Like the flower itself, the lotus effect lasts only a few days. But if Aria can figure out a way to make the effect more or less permanent, the potential applications are enormous. A ship with a nanotube-coated hull, for example, would knife through the water with almost no drag at all, consuming far less fuel and perhaps carrying much more cargo.

Aria can also make the nanotubes *less* hydrophobic, by treating them with ultraviolet light in the presence of air. "That means I can control the wetting properties," he says. That could come in very handy if, for example, you want to package a water-soluble drug in a waterproof container in order to ensure delivery to the target organ.

A video of water droplets bouncing off Aria's nanotube arrays or rolling down their hydrophobic surfaces—during one segment, it's hard not to envision skateboard champs in a half-pipe—recently showed up on YouTube. Within about two months, it had garnered 400,000 hits. Gharib smiles as he plays it. "Sometimes we just like to have fun, too."

# Some Assembly

By Kathy Svitil




We're a long way from transplantable organs grown to order, but Caltech chemists are developing some of the tools we will need to make that happen.

# Required

DAVID TIRRELL

At any given moment, more than 100,000 people in the United States are awaiting organ transplants. Although thousands of transplants are performed each year, thousands of other people die because there just aren't enough donated organs. One solution? *Making organs*, from scratch. Imagine a big assembly line, churning out kidney after kidney after kidney.

Science fiction? Of course. But through the development of synthetic tissuelike biomaterials, "artificial" proteins with programmable properties, and methods for the pinpoint placement of cells, Caltech chemists are inching us closer to the elusive goal of made-to-order organs.

In truth, artificial organs have been in use for decades. Back in 1982, for example, the first Jarvik-7 replaced the ailing heart of a Seattle dentist, who lived for 112 days (albeit hooked up to machines); artificial ears, a.k.a. cochlear implants, are now commonplace. But the ersatz organs available today are far from perfect substitutes—quite understandably, because human tissues are exceedingly complex, with a daunting variety of strategically placed cells and a complicated infrastructure of nerves and blood vessels. This architecture has, so far, proven impossible to duplicate; indeed, the bladder—essentially a balloon of soft, stretchy tissue—remains the only *living* lab-grown replacement organ yet developed.

A crucial first step in building artificial organs that are more lifelike is creating lifelike artificial tissues. At Caltech, such materials are the purview of chemist David Tirrell. Admittedly, Tirrell's work is not focused explicitly on making such tissues, and he offers no claims that it ever will: "It may be that in 100 years, something we're involved in now may lead to artificial tissue," he cautions.

What he *does* do is far more basic: He invents proteins made with amino acids not found in nature that function in ways that normal proteins do not. In these artificial proteins, as in natural ones, the sequence of amino acids within the molecule determines how it contorts itself into a three-dimensional shape, and that shape in turn determines the protein's function. But the sequence of a protein also determines how it behaves en masse, when surrounded by countless numbers of its fellows.

And that behavior matters if you're trying to build an artificial tissue, which needs to include not just the cells but the scaffold on which they hang. That framework—constructed mainly out of protein molecules—is called the extracellular matrix, or ECM. Tirrell builds artificial ECMs to order, controlling their properties by monkeying with the genetic blueprints of their constituent proteins.

When you design these genes, he says, "you have to think not only about the protein itself but about the behavior of the material that results—is it stiff, is it loose, what other properties does it have?" For example, say you want to build an artificial tissue composed of liver cells, or from the insulin-producing beta cells of the pancreas. An ECM—artificial or otherwise—is an elastic, but solid, gel. When the ECM grows up with the organ, getting the cells inside it is not a problem because they are already there, but otherwise "it's hard to get cells into an elastic solid," Tirrell says. "If you design your gel so that it's initially a liquid, you can distribute the cells within it." Then, once the cells are properly distributed—which can be as simple as stirring the mixture—you add another protein to the gel to make it harden like Jell-O in a refrigerator.

Tirrell, working with bioengineering grad student Alborz Mahdavi and and with H. Teresa Ku of the City of Hope, recently spiked one of his ECMs with pancreatic stem cells. Nestled within the matrix, the cells flourished—and, Ku says, differentiated into endocrine cells, as hoped. "We are planning to transplant the cell colonies into mice in the near future to see whether these cells will secrete insulin and correct diabetes in a mouse model," she says.

The usual way to build a "simple" artificial organ starts with a prefab scaffolding constructed of a porous, biocompatible material such as a water-swollen gel—or "hydrogel"—made from polyethylene glycol. (PEG, as it is known in the outside world, is a common ingredient in skin cream, shampoo, and toothpaste.) The gel is molded into the rough shape of the organ and seeded with cells. The challenge, of course, is steering all of the various cell types to their proper locations—including the cells that form blood vessels. Without blood flow, after all, any tissue will die.

A method developed by grad students Udi and Ophir Vermesh (both PhD '11) and their colleagues in the laboratory of chemist Jim Heath may meet this challenge. By pressing a silicone template containing microfluidic channels against a microscope slide, a gridwork of anchor points is created on the glass. Each anchor can be tailored to adhere to one specific cell type, allowing individual cells to be placed in prescribed locations just a few millionths of a meter apart. "We then encase the patterned cells in a hydrogel matrix and stack these hydrogel sheets to form 3-D tissue constructs," explains

JULIA KORNFIELD

Ophir, who is now in his fourth year of medical school at UCLA as part of a joint MD/PhD program.

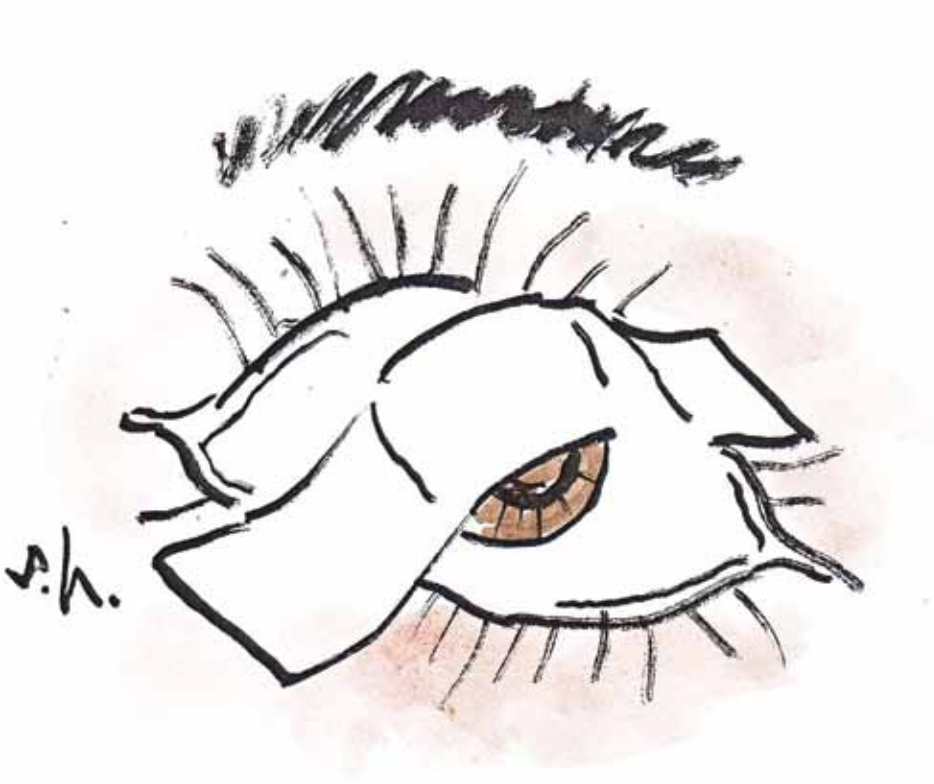
The team tested the process by building very rudimentary islets of Langerhans—as the insulin-producing parts of the pancreas are known—by setting out neat rows of insulin-secreting beta cells alternating with equally neat rows of non-insulin-secreting alpha cells. These cells were actually much better organized than absolutely necessary: in rats and mice, the beta cells form clusters encircled by the alpha cells, whereas in humans the alpha and beta cells are just sort of scattered willy-nilly, surrounded by blood vessels. And although random clumps of cells aren't prohibitively difficult to make, making blood vessels is another issue. To do so, you'd have to snake tunnels, constructed out of the appropriate cells, through your matrix, which means accurately creating and lining up *holes* in the stacked 2-D sheets. "We're still trying to figure that part out," Vermesh admits.

The experiment was merely intended to demonstrate the ability to control where specific cells went, so "we didn't place much emphasis on incorporating ECM proteins into our hydrogels," Vermesh says. "But the types of proteins found in an ECM play an important role in keeping cells alive in real tissues. So while these cells survived for a time, I would expect they would need those ECM proteins in their immediate surroundings, especially in an implantable device."

ECM proteins are also key to a different implantable material that Tirrell, chemist Robert Grubbs, chemical engineer Julia Kornfield (BS '83, MS '85), and collaborators at UC San Francisco have developed for healing damaged corneas.

The cornea is the eye's half-millimeter-thick outer "skin." It's a complex sandwich whose filling contains three collagen-rich layers, where long fibrils of collagen are placed so precisely that the resulting structure is as transparent as a perfect piece of glass.

If these fibrils' orientation gets disrupted by a scratch or infection, the glass can turn cloudy, resulting in corneal blindness—some 2,000,000 cases worldwide. (Cataracts, the most common cause of blindness, are caused by cloudiness of the lens—the light-focusing crystal located deeper within



the eye.) "We want to understand how we can guide wound healing so that it does *not* lead to scarring and blindness," Kornfield says.

Corneal scarring results from the body's overly enthusiastic effort to slap a Band-Aid on a wound. Your system's first responders at the scene of any injury are the constantly circulating platelets in the bloodstream. They set up a triage center by forming a makeshift ECM, upon which the other incoming cells on the emergency team alight so they can fix things. Soon, fresh collagen fibers are being plastered down, mending the damaged area. "The healing response is designed to close a wound as quickly as possible," Kornfield says. "It doesn't have to be pretty, just get it closed."

And, indeed, the result is *not* pretty, because the patch's fibers lack the regimented organization of their neighbors. Instead, they are strewn haphazardly, like a microscopic crazy quilt. And instead of transmitting light unscathed, the patch scatters it. The cornea takes on a milky hue, and vision is obscured.

"What we need to do," Kornfield says, "is tell the system how to come in and clean up the mess without making a mess." The way to do that, she and her colleagues have found, is with an implant somewhat akin to a contact lens, but made of Tirrell's specially crafted gel. In addition to the ECM proteins that form the gel itself, the implant contains signaling molecules that slow the triage process and buy valuable time for the body to lay down collagen fibers the *right* way. "We need to get in there within a few hours to prevent the wrong stuff from laying down," she continues.

"We're very enthusiastic about the cornea work," Kornfield says, "but my hope is that we can create a gel that could prevent *any* kind of scar," anywhere in the body.

The idea is not far-fetched, she argues. Because it has to be transparent, "the precision with which the cornea has to be built is extreme," she says. "If we understood *that*, and could keep that process from going wrong, it would be easier to promote healing without scarring in other tissues, including the skin." Surgical incisions could someday be closed without a trace—but also wounds caused by accidents, say, or even burns.

> Although random clumps of cells aren't prohibitively difficult to make, making blood vessels is another issue. To do so, you'd have to snake tunnels, constructed out of the appropriate cells, through your matrix, which means accurately creating and lining up *holes* in the stacked 2-D sheets.

This type of carefully orchestrated repair would likely take longer than the natural healing process, but, Kornfield says, the results "would be *perfect*"—and that, she adds, is worth the wait. E&S

***David Tirrell is the Ross McCollum–William H. Corcoran Professor and professor of chemistry and chemical engineering. Research on artificial ECM proteins has been funded by the National Institutes of Health and by Caltech's Jacobs Institute for Molecular Engineering for Medicine.***

***Jim Heath is the Elizabeth W. Gilloon Professor and professor of chemistry. The cell-patterning project was funded by the National Cancer Institute, the Ivy Foundation, and the Grand Duchy of Luxembourg.***

***Nobel Laureate Robert Grubbs is the Victor and Elizabeth Atkins Professor of Chemistry.***

***Julia Kornfield is a professor of chemical engineering. Her research on corneal wound healing is also sponsored by the Jacobs Institute for Molecular Engineering for Medicine.***

# CALTECH ALUMNI SHINE IN TR

## Whether it's understanding transplant rejection or building a better prosthesis, Caltech alu

By Katharine Gammon



### 2010
HEATHER AGNEW
PhD 2010, Chemistry

Heather Agnew, now a principal research investigator at Integrated Diagnostics, designs binding molecules that detect specific disease-related proteins and allow doctors to discover them earlier. At Caltech, she was awarded the Lemelson-MIT Caltech Student Prize for making heat-stable antigen-detecting compounds that could one day replace tests based on Tyler's methods and make cheap, reliable diagnostic kits available to the Third World.



### 1929
ALBERT TYLER
PhD 1929, Biology

Albert Tyler earned the first doctorate ever to be granted in the Division of Biology. He stayed on as a member of the faculty, where his studies of embryonic differentiation in sea urchins helped transform classical embryology into modern developmental science. He helped introduce biochemical methods into the field, developing techniques to detect cellular antigens that underlie many of the diagnostic methods used today. He died in 1968.



### 1983
MORTEZA GHARIB
PhD 1983, Aeronautics

Caltech professor Mory Gharib looks at everything from space to cells and finds a way to improve the human condition. His work, which includes studying the dynamics of heart valves and creating valveless pumps, sits on the cusp of biology and engineering. Gharib finds inspiration in the natural world, designing sustainable biomedical devices and harvesting sustainable energy within the body to run them.



### 1983
JULIA KORNFIELD
BS 1983, Chemistry; MS 1985, Chemical Engineering

An undergraduate research fellowship on nerve cells got Julie Kornfield hooked on biotech. Now a Caltech professor, she studies how polymers can be exploited—in and out of the human body. One of her projects focuses on giving cataract patients better vision through laser-adjustable lens implants; another is helping to build artificial tissues with real cells. Kornfield was the first alumna to gain tenure at the Institute.



### 1974
DAVID HO
BS 1974, Biology

David Ho changed gears as he entered his graduate studies and was drawn toward medicine. Ho's AIDS research caused him to be named Man of the Year for 1996 by TIME magazine. He pioneered treating HIV-infected patients with protease inhibitors, and championed the use of combination anti-retroviral therapy early in the disease's course. Ho is currently a professor at Rockefeller University in New York.

# ANSLATIONAL MEDICINE

mni have made an impact in translational medicine. Here are some of the highlights:

## 1941

WILLIAM CORCORAN

BS 1941, Chemistry; MS 1942, PhD 1948, Chemical Engineering

Bill Corcoran had interests everywhere—he played all the intramural sports, wrote for the *California Tech*, and even worked on the firing mechanism for the atomic bomb during the Manhattan Project. After World War II, he returned to his studies and earned one of the first doctorates given in chemical engineering at Caltech. As a Caltech professor, he studied the fluid mechanics of heart valves by shooting laser beams through them to accurately measure the flow. He also helped develop better disposable hospital equipment. Corcoran died in 1982.

## 1956

WILLIAM HILDEMANN

PhD 1956, Biology

After serving in World War II, Bill Hildemann came to Caltech to study with legendary immunologist Ray Owens, who was working on the problem of tissue rejection. Hildemann discovered the role of antibodies in this process, laying the groundwork for successful organ transplants between unrelated donors and recipients. He died in 1983.

## 1956

LEONARD A. HERZENBERG

PhD 1956, Biochemistry

In 1970, Len Herzenberg developed the fluorescence-activated cell sorter—a device that revolutionized immunology and cancer biology and is the basis for the purification of adult stem cells. Herzenberg continues to work on FACS development with his wife, Leonore (Lee)—whom he met while she was a research assistant for Albert Tyler.

## 1960

LEROY HOOD

BS 1960, Biology; PhD 1968, Biochemistry

The future got a boost from Lee Hood. While a Caltech professor, he and his colleagues pioneered four instruments—the DNA sequencer and synthesizer, and the protein synthesizer and sequencer—which comprise the technological foundation for contemporary molecular biology. Hood now heads the Institute for Systems Biology in Seattle, where he is pioneering a transition from reactive medicine to an approach that's proactive—as well as predictive, preventive, personalized, and participatory.

WE ASKED CALTECH ALUMS TO TELL US THEIR FAVORITE CLASSROOM OR LABORATORY MEMORY. HERE'S WHAT THEY HAD TO SAY:

# Meeting Einstein.

*Linus Pauling's Chem 1 lecture where he held a chunk of sodium over what he led us to believe was a bucket of water. Students in the front row were especially fearful.*

It was a quantum mechanics class and the previous professor had left all the blackboards full. Dr. Leighton [BS '41, MS '44, PhD '47] walked in and spent a minute or two absorbing this mass of chalk, which was physical chemistry (quantum mechanics for chemists). He then announced that we were going to make a "few" changes of notation, and proceeded to give the hour lecture using the other guy's boards, finishing, on time, at the last equation. I discovered that it was just as unclear in P-chem notation as physics. I flunked the course.

I was one of six students enrolled in Richard Feynman's Quantum Electrodynamics course. The final exam was simultaneously frightful and delightful: a solo oral examination standing at Feynman's office blackboard. He convinced me that I understood far more than I realized.

*I was neck and neck with Les Ingber [BS '62] regarding breakage in Chem I lab. However, when he dropped a balance, I gave up.*

Friday afternoon seminar in which von Kármán and Hsue-Shen Tsien [PhD '39] would argue about rocketry theory.

**To read more favorite memories, visit http://EandS.caltech.edu/endnotes/memories**

# SB

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