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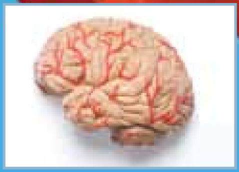

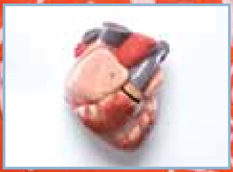

Minding Brains ▪ Mending Retinas ▪ Pumping Blood

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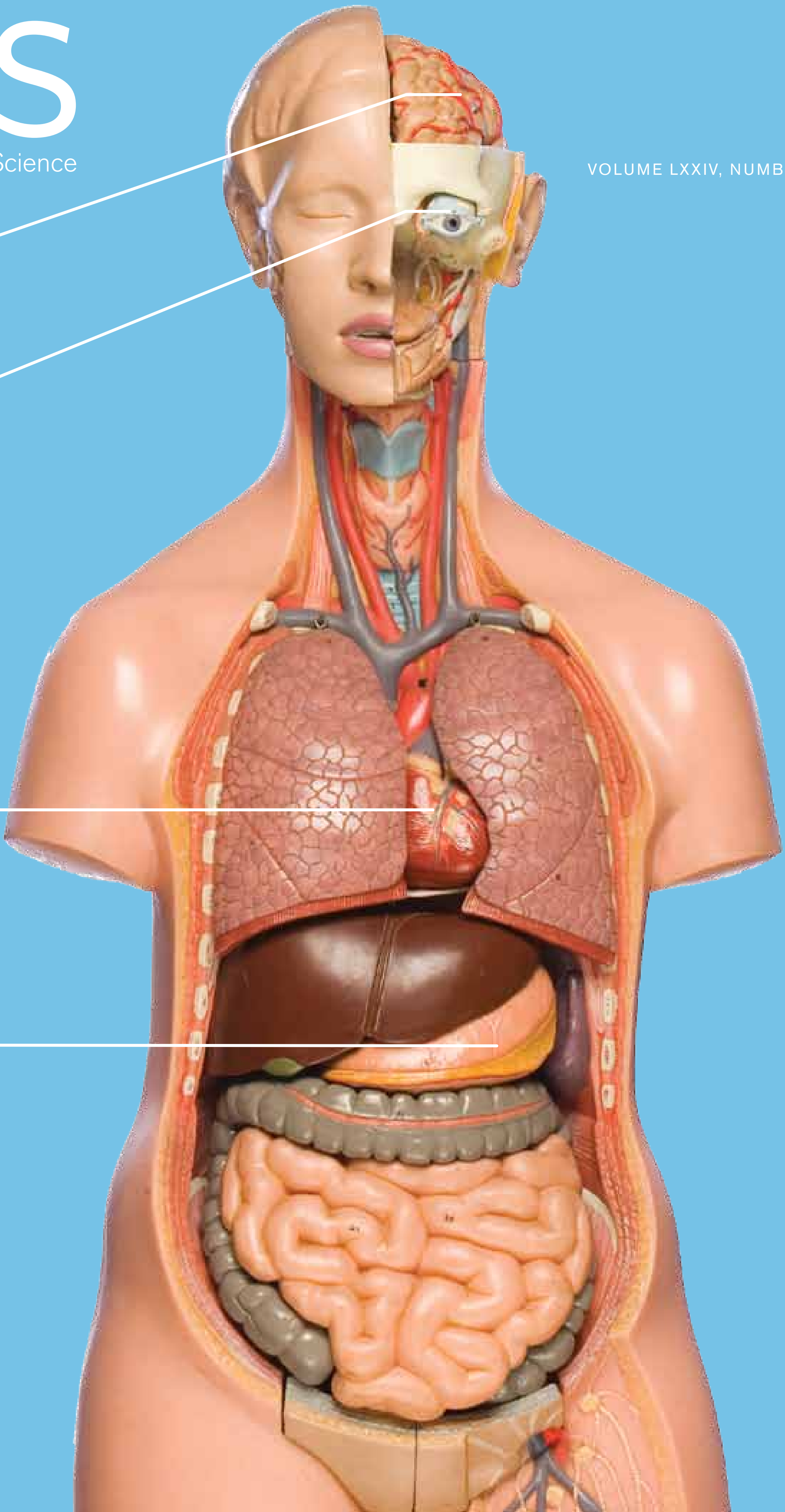
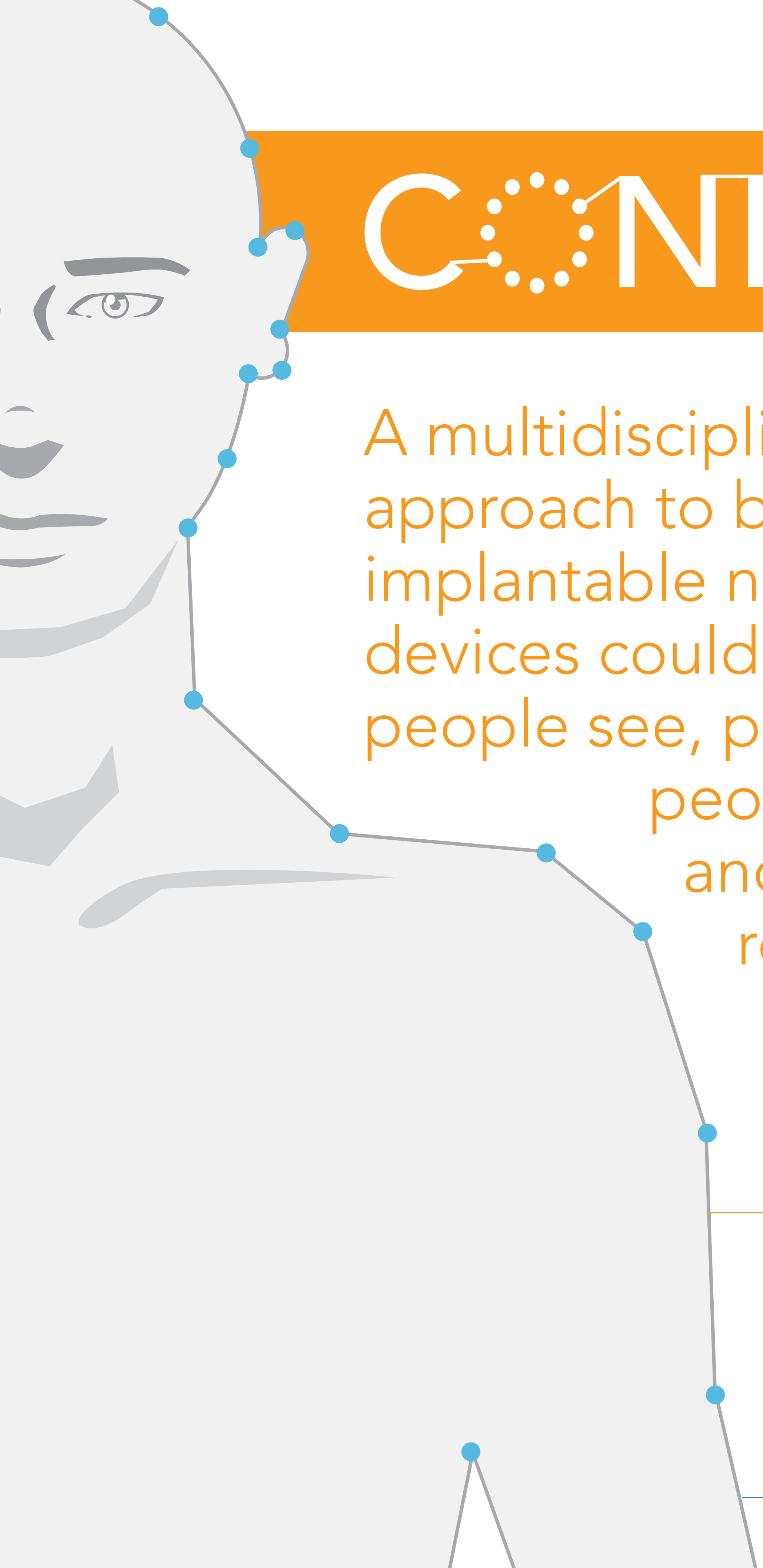
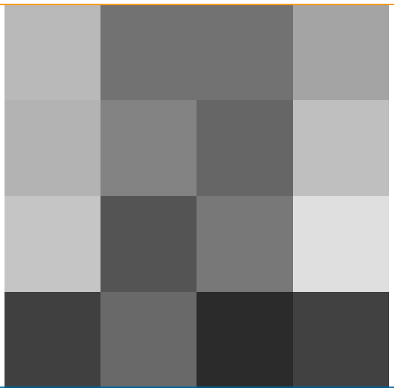




CONNECTI

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."

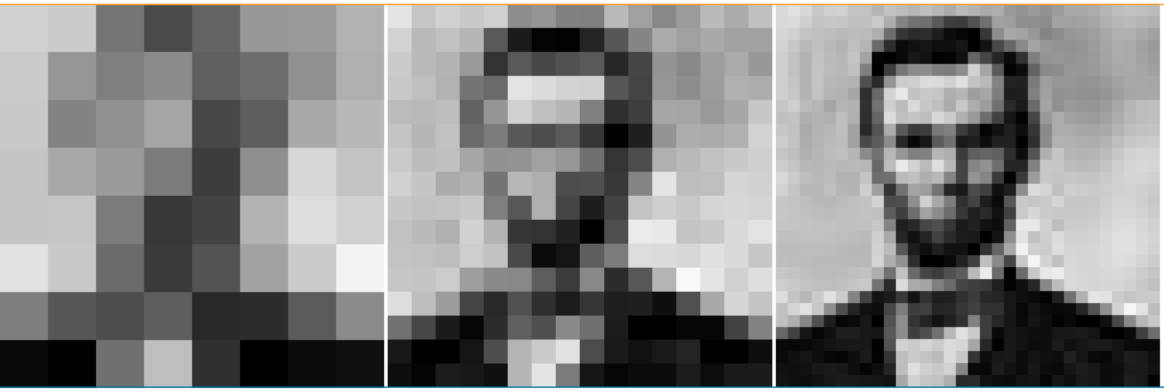
THE BODY ELECTRIC

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.

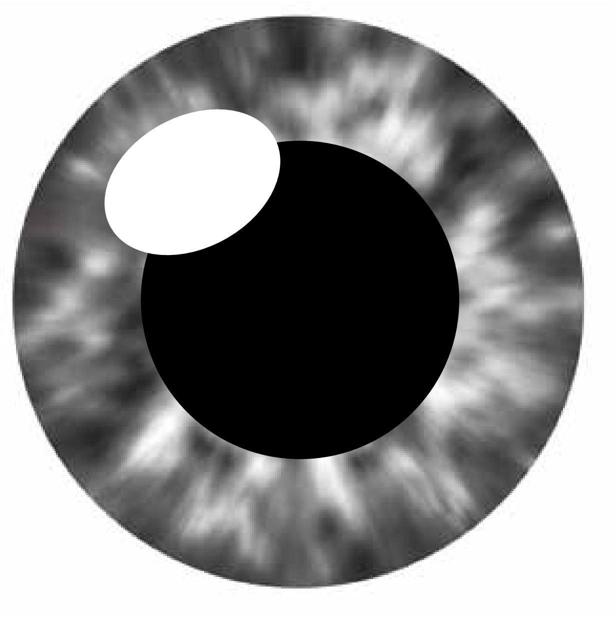
"I'm a small-device person, so when we started to brainstorm, you can imagine that we came up with many ideas," says Tai of the beginning of his partnership with Mark Humayun. "Since then, we've been working on retinal implants nonstop."

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.

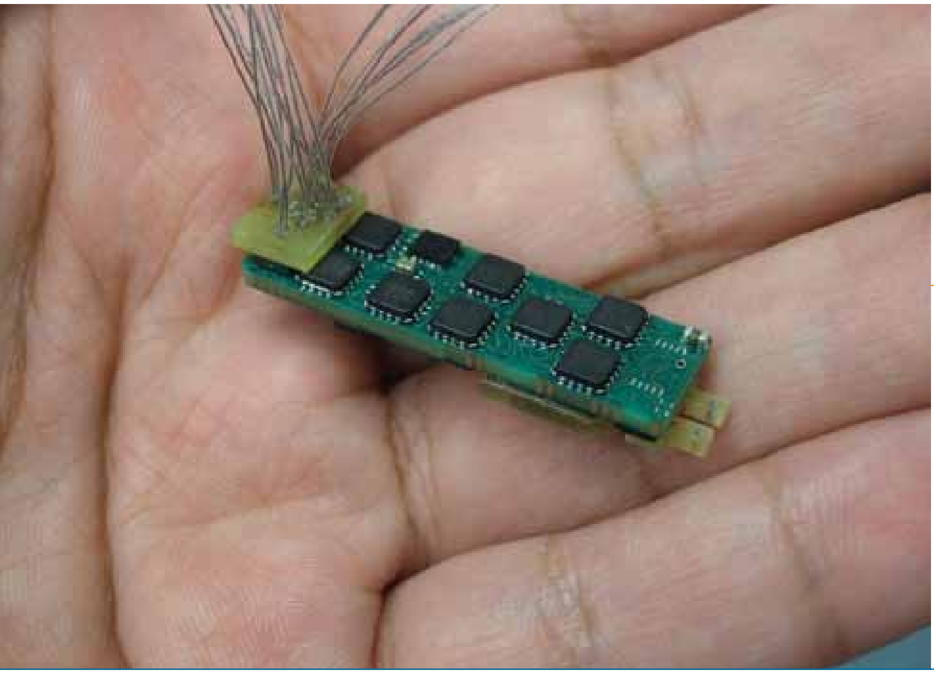
Beyond biocompatibility, the components need to be flexible, so that they can bend and stretch with the body. In addition, the implants need to be engineered to fit within tiny spaces: behind the eye, perhaps, or between vertebrae—without moving the body's own parts out of position. Andersen is also 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*

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."

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.

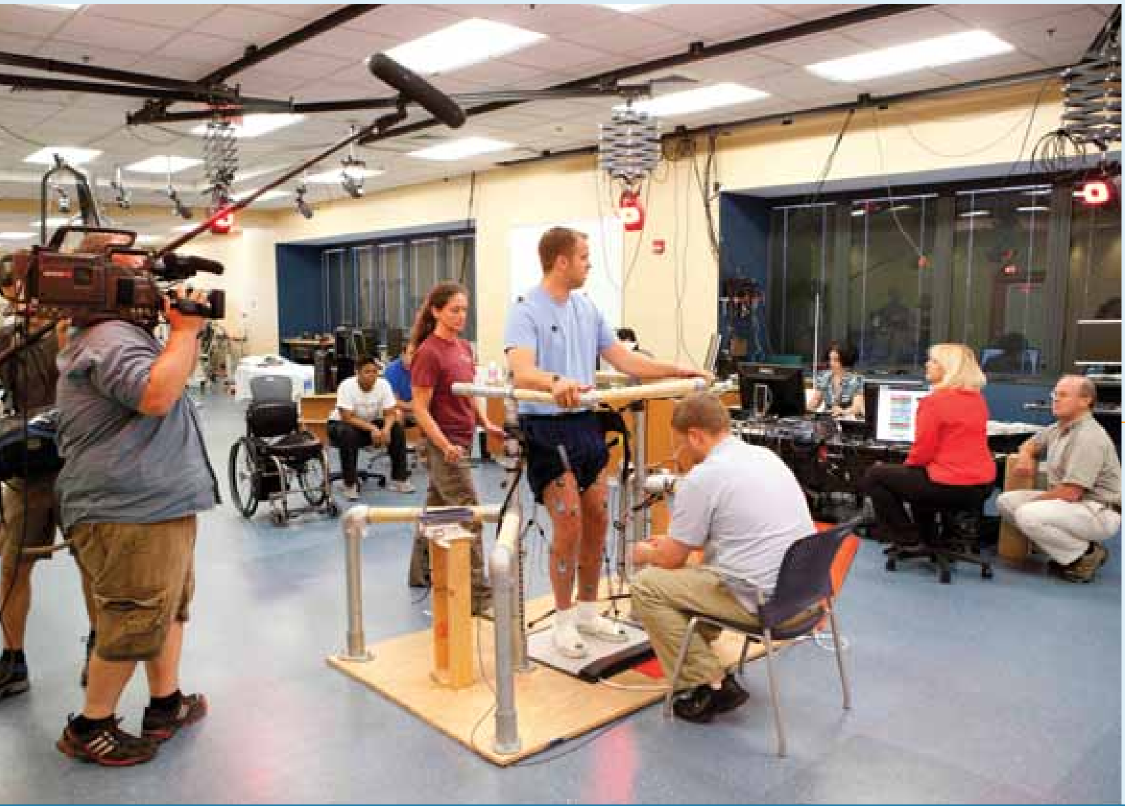
“I’m building Rob a series of increasingly sophisticated devices that he can use in his apartment,” says Burdick. “It’s a prototype phase, so that if our therapy continues to be successful in more patients, we’ll have them available.”

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*



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.