Explorations and revelations taking place in the medical school

It comes too late for Steve Austin, but the bionic knee brace could be part of the next generation of neuroprosthetics.

YOUR BODY, YOUR JUICE

HUMANS AS A POWER SOURCE

BY REID R. FRAZIER

Douglas Weber, a PhD assistant professor in the University of Pittsburgh's Department of Physical Medicine and Rehabilitation, is a biomedical engineer interested in neuroprosthetics, which may explain why he has a squeeze toy shaped like a human brain lying on his desk.

Weber, a self-described "gadgets guy," looks for something to show how his bionic knee brace, known as a biomechanical energy harvester, generates electricity based on the same principles as a Toyota Prius. Lacking anything that looks like a car, Weber grabs the squishy brain instead.

"That linear motion of a car carries a bunch of energy with it," says Weber, "driving" the squeeze toy down a straightaway on his bookshelf. "To slow that vehicle down, you have to get rid of that kinetic energy," he adds, then parks the little gray brain near the end of the shelf.

In a normal car, the kinetic energy of a car's motion dissipates into the brake pads, in the form of heat created by friction. Hybrid cars use that energy to spin a turbine, generating electricity.

Weber, who holds a secondary appointment in Pitt's Department of Bioengineering, helped create a device that does essentially the same thing with the human leg. After a 10-minute walk, the device generates enough juice to power a cell phone for a half-hour.

"All we're doing is we're taking energy from one form, and we're converting it to another," says Weber.

Instead of brake pads, the harvester uses the hamstrings as its unwitting power source. The hammies, it turns out, act a lot like brake pads when we walk. They slow the leg down, just as it straightens out at heel strike. (Otherwise, the knee would hyperextend with every step.)

The device Weber and his collaborators created offers resistance on the knee when it "brakes." The resistance turns gears and a motor, which, in turn, generate electricity. The brace provides resistance only at the moment when the leg is trying to slow itself down. If "turned on" during the entire step, the harvester would feel like a shackle.

"The elegance of the design is being able to harvest energy without the metabolic cost, so the person doesn't feel it," says Yad Garcha, the CEO of Bionic Power of Vancouver, British Columbia, which is marketing the brace. (The company's motto: "You're the Juice.")

"A lot of the device was built over beers at Doug's kitchen table," says Max Donelan, a collaborator of Weber's who is now an assistant professor of kinesiology at Simon Fraser University in Burnaby, British Columbia.

Weber and Donelan were both postdoctoral fellows at Edmonton's University of Alberta in 2002. Weber worked in the Centre for Neuroscience, studying ways to record brain signals for use in neuroprosthetics. Donelan, a physiologist, approached Weber about a question he had been kicking around: Could a knee brace generate electricity?

Weber headed to a local hobby shop to pick up gear sets and electric motors normally used in remote-control cars. The harvester was later born in his Edmonton home.

Weber and Donelan affixed the gears and motor to an orthopaedic knee brace with screws, tape, anything they could find. The result was more *MacGyver* than *The Six Million Dollar Man*, Weber says. (For the record, Weber was "absolutely" a fan of Lee Majors' character Steve Austin when he was growing up in the '70s.)

"It wasn't chewing gum and duct tape, but it really wasn't far from it," he notes.

The pair took the clunky brace and tested it in Donelan's lab. When they registered 1 watt of electricity pulsing out of the brace with every stride, "We knew we had something," says Weber. A few years later, they had a prototype, and in February, they published test results in *Science*.

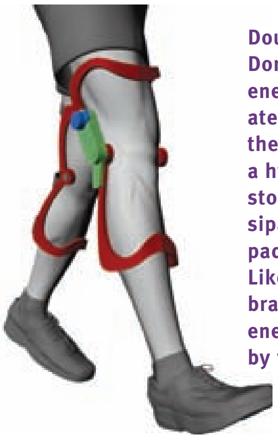
The first market for the device will be the military, whose forward-most personnel lug upwards of 30 pounds of batteries for various navigation, night vision, and communications equipment. Bionic Power will ship a batch of energy harvesters to the Canadian military next year.

Hikers and first responders are other potential users.

Weber hopes the device will dovetail with his research into the next generation of neuroprosthetics. Bionic sensors and motors currently in development require power.

His lab is researching ways to "tell" the brain about a limb's position, speed, and contact with objects.

"We're trying to send signals to the brain to create sensations of touch and limb position for artificial limbs, enabling amputees to literally feel the prosthesis as if it were their native limb," Weber says.



Douglas Weber and Max Donelan's biomechanical energy harvester generates electricity using the same principles as a hybrid car. A hybrid stores rather than dissipates energy into brake pads when it slows down. Likewise, this bionic knee brace harvests the kinetic energy normally absorbed by the hamstrings.

COURTESY BIONIC POWER

His research group is one of the first to test this somasensory technology. (*Soma* is Greek for "body.")

Donelan says of his friend and collaborator, "The way Doug thinks, the place where the person ends and the machine begins becomes kind of a gray area." ■

SHOCK TREATMENT

A NEW USE FOR OLD PROTEINS

BY CAROLE BASS

JOSHUA FRANZOS

Robert Binder is exploring the use of proteins known to protect cells from heat to instead protect us from cancer.

If Robert Binder were in advertising, his first assignment would be a new branding campaign for his pet subject: heat-shock proteins.

But Binder, a PhD assistant professor of immunology at the University of Pittsburgh, spends his days in the lab, not on Madison Avenue. So he is spared the task of devising slogans like, "Heat-Shock Proteins: They're not just for heat shock anymore." Instead, Binder can devote himself to understanding what these ubiquitous proteins do and how they do it.

Sure, HSPs protect cells against damage from heat and other stresses. But they appear to do even more—like fight cancer.

Binder is one of a growing number of researchers attempting to develop cancer vaccines.

Conventional cancer therapies typically poison healthy dividing cells along with cancerous ones. Binder and his colleagues envision using patients' immune systems to shrink tumors while sparing healthy cells. The trick is getting the immune system to recognize a cancer as an undesirable.

Like conventional vaccines, cancer vaccines use a tiny bit of the target for an antigen, which stimulates an immune response to the tumor. Binder's lab—and recent clinical trials building on his work—creates personalized vaccines by using antigens derived from heat-shock proteins in individual tumors.

Russia has approved selected use of such a therapy for kidney cancer—the first such sanction anywhere for a therapeutic cancer vaccine.

"These proteins are very abundant, and they're present in all cells," Binder says. And though HSPs are named for their first-discovered ability, protecting against heat damage, "there's no reason they should be limited to one function," he adds.

In fact, in 1986, a team led by the University of Connecticut's Pramod Srivastava discovered that heat-shock proteins can trigger a powerful immune response. Binder did his graduate work with Srivastava at Connecticut, delving into the question of how HSPs work.

Srivastava, an immunologist, calls his former student "a superb experimentalist."

Binder discovered that a protein known as CD91 is a receptor for heat-shock proteins. He now routinely creates cancer vaccines by purifying HSPs from a mouse tumor that binds to CD91 on the surface of specialized immune cells. The HSP is able then to get inside the cell and kick the immune system into gear.

"In mice, it works across the board," Binder says. "We've used over 15 different kinds of tumors."

When he vaccinates a healthy mouse, then injects tumor cells, the mouse stays cancer free. When he vaccinates a mouse that already has cancer, "the tumors shrink but they don't go away. But when we surgically remove the primary tumor, we're able to treat the metastatic disease," Binder reports.

But does the therapy work in people?

Binder experimented with the vaccine in mice for 10 years. Then Srivastava and colleagues—including John Kirkwood, director of the melanoma program in Pitt's Division of Hematology/Oncology—began clinical trials in human cancer patients. One study, a phase III trial involving 322 people with advanced melanoma, was published in February in the *Journal of Clinical Oncology*. (The vaccine goes by the trade name Oncophage. Antigenics, a company that Srivastava cofounded and of which he owns a small share, makes Oncophage and funded the clinical trials.)

"When you look at patients who actually got the vaccine, then you see that patients who had diseases of the lymph nodes, skin, or lungs did much better," Srivastava says.

Specifically, the median survival—the point at which half the patients had died—was about 900 days for the vaccinated group, compared to less than 400 days for the control patients, who received chemotherapy.

Another recent phase III trial involved 728 people with kidney cancer. In the July 5 issue of *The Lancet*, Srivastava and his coauthors reported no overall difference between patients who received Oncophage and those who didn't. But they are further exploring "possible improvements in recurrence-free survival in patients with early-stage disease."

After that trial, which was funded by Antigenics, the treatment got the okay from the Russian government for use in the treatment of kidney cancer patients at intermediate risk for disease recurrence.

Binder now plans to investigate how heat-shock proteins might fuel vaccines for infectious diseases as well as for autoimmune disorders. ■

Construction of the Biomedical Research and Biotechnology Center of Sicily is slated to begin next year.

COURTESY RIMED

DON'T KNOW MUCH ABOUT SICILY

A PARTNERSHIP WILL PUT REGION ON SCIENTIFIC MAP | BY ELAINE VITONE

Admit to Sicilian Filippo Pullara that you don't know much about his native Palermo, Italy, and he'll sigh with pity. It's a blue-skied paradise, he'll tell you—a place where anything below 50 degrees Fahrenheit is considered a cold day.

"Palermo is perfect," he says.

The catch, however, is that for almost anyone outside of the tourism and hospitality industries—and especially for a young physicist like Pullara—jobs are hard to come by.

Fortunately, that's about to change.

Pullara is one of six young Italian scientists who arrived at the University of Pittsburgh this summer as the first recipients of a new annually awarded postdoctoral fellowship. (Three more fellows will arrive by year's end, and 12 per year are expected thereafter.) The scientists' living stipends and research are funded by RiMED, a foundation created in 2006 to receive government and other funds to build the Biomedical Research and Biotechnology Center of Sicily.

Construction of the $398 million center, which will be located in Carini, a quick drive from Palermo, is slated to begin next year. Planners expect it to be completed in 2011. The center will be managed by UPMC. Arthur S. Levine, Pitt's senior vice chancellor for the health sciences and dean of the School of Medicine, serves as RiMED's scientific director.

While the design plans are in the works, the office of Academic Career Development for the Health Sciences is grooming the RiMED fellows to staff it, supplementing their research efforts here at Pitt with training in ethics as well as communication, presentation, and management skills.

Instead of applying for positions in specific laboratories, as postdocs generally do, RiMED fellows spend the first month at Pitt rotating through several labs that match their interests, looking for the best fit. When Pullara completed his rotations, he chose to work in the lab of Guillermo Calero, PhD assistant professor of structural biology. Pullara is putting his physics background to use studying protein interaction in DNA and RNA repair—and loving every moment of it.

"It's more than just a job—it's a passion," says Pullara.

"In the evenings we often stop working just for a quick dinner. Then we come back to the lab, saying, 'Ah, I have an idea!'"

RiMED's momentum comes on the heels of the 10th birthday of ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione), a hospital in Palermo that provides transplants and other specialized services. ISMETT was founded by UPMC and the Italian government in 1997. The hospital is now at full capacity—70 beds—and performs 150 transplants per year, with some of the highest transplant survival rates in all of Europe.

ISMETT filled a dire need for Sicilian patients. Prior to its opening, the region had no transplant facility of its own and was forced to pay high costs to send patients abroad for such surgery.

"Our public-private partnership model was so successful that the government wanted to use it to start a research center, as well," says Bruno Gridelli, medical and scientific director of ISMETT and UPMC International. Gridelli also is a professor of surgery at Pitt.

In its short history, ISMETT has amassed an abundance of gadgetry that makes this small hospital seem anything but. Case in point: its telepathology lab.

"We're a small hospital, so we don't have a full staff of pathologists covering 24-7. In fact, we only have *one*!" Gridelli says. "But through this connection, we can count on the competence of pathologists in Pittsburgh and their round-the-clock availability."

ISMETT's 255-square-meter regenerative-medicine lab, dubbed the Cell Factory, was funded by a €5.3 million grant from Italy's Ministry of Technological Innovation in 2005. Last year, ISMETT added Web cameras and specialized microscopes, turning the site into a rare breed of laboratory known as a *collaboratory*.

"Many of the instruments can be connected to other labs around the world," says Gridelli.

"It's a great tool for training and for quality control. … We also have microscopes that can be controlled from any place that has a Web connection."

If the runaway success of ISMETT is any indication, Pullara and the other RiMED fellows can look forward to one day working in a researcher's paradise. In the meantime, they are ever eager to hear the latest on the planning stages of the building.

"This is a great opportunity for me, for Sicily, and for the region," Pullara says. "Building this center is a huge opportunity for research in general." ■