A remarkable substance extracted from pigs enables the body to regenerate lost tissue, including fingertips and big chunks of muscle. And that may not be all it can do...

by Adam Piore

The strange sensation in his right thigh muscle began as a faint pulse. Slowly, surely, it was becoming more pronounced. Some people would have thought it impossible. But Corporal Isaias Hernandez could feel his quadriceps getting stronger. The muscle was growing back.

When he first arrived in the trauma unit of San Antonio's Brooke Army Medical Center in December 2004, Hernandez's leg looked to him like something from KFC. "You know, like when you take a bite out of the drumstick down to the bone?" Hernandez recalls. The 19-year-old Marine, deployed in Iraq, had been trying to outfit his convoy truck with a makeshift entertainment system for a long road trip when the bomb exploded. The 12-inch TV he was clutching to his chest shielded his vital organs. The doctors kept telling Hernandez he would be better off with an amputation. He would have more mobility with a prosthetic, less pain. When he refused, they took a piece of muscle from his back and sewed it into the hole in his thigh. He did all he could to make it work. He grunted and sweated his way through the agony of physical therapy with the same red-faced determination that got him through boot camp.

Generally people never recovered from wounds like his. Flying debris had ripped off nearly 70 percent of Hernandez's right thigh muscle, and he had lost half his leg strength. Remove enough of any muscle and you might as well lose the whole limb, the chances of regeneration are so remote. For Hernandez, it had been three years and there was no mistaking it: He had hit a plateau. Lately the talk of amputation had cropped up again. The pain was constant, and he was losing hope. Then his life took another radical turn. He saw a science documentary that told the story of a war veteran in Cincinnati named Lee Spievack whose fingertip had been severed by the propeller of a model airplane. Spievack's brother, a surgeon in Boston, had sent him a vial of magic powder—the narrator called it "pixie dust"—and told him to sprinkle it onto the wound. Lee was to cover his hand with a plastic bag and reapply the powder every other day until his supply ran out. After four months, Lee's fingertip had regenerated itself, nail, bone, and all.

Hernandez recalled that one of his own doctors—Steven Wolf, had once mentioned some kind of experimental treatment that could "fertilize" a wound and help it heal. At the time, Hernandez had dismissed the therapy as too extreme. The muscle transplant sounded safer, easier. Now he changed his mind. He wanted his leg back; even if it meant signing himself up as a guinea pig for the U.S. Army. So Hernandez tracked down Wolf, and in February 2008 the two got started. First, Wolf put Hernandez through another grueling course of physical therapy to make sure he had indeed pushed any new muscle growth to the limit. Then he cut open Hernandez's thigh and inserted a paper-thin slice of the same material used to make the pixie dust: part of a pig's bladder known as the extracellular matrix, or ECM, a fibrous substance that occupies the spaces between cells. Once thought to be a simple cellular shock absorber, ECM is now understood to contain powerful proteins that can reawaken the body's latent ability to regenerate tissue.

A few months after the surgery healed, Wolf assigned the young soldier another course of punishing physical therapy. Soon something remarkable began to happen. Muscle that most scientists would describe as gone forever began to grow back. Hernandez's muscle strength increased by 30 percent from what it was before the surgery, and then by 40 percent. It hit 80 percent after six months. Today it is at 103 percent—as strong as his other leg. Hernandez can do things that were impossible before, like ease gently into a chair instead of dropping into it, or kneel down, ride a bike, and climb stairs without collapsing, all without pain.

The challenge now is replicating Hernandez's success in other patients. The U.S. Department of Defense is funding a team of scientists who will attempt to use the material to regenerate the muscle of patients who have lost at least 40 percent of a particular muscle group, an amount so devastating to limb function that it often leads doctors to perform an amputation. If the trials are successful, they could fundamentally change the way we treat patients with catastrophic limb injuries. Indeed, the treatment might someday allow patients to regrow missing or mangled body parts. With an estimated 1.7 million people in the United States alone missing limbs, promoters of regenerative medicine eagerly await the day when therapies like ECM work well enough to put the prosthetics industry out of business.

To many medical practitioners, the idea of using pig parts to regenerate human tissue sounds outlandish—so outlandish that the doctor who discovered the technique in the mid-1980s was reluctant to talk to clinicians about it for years. "They didn't believe my results," says Stephen Badylak, a researcher who is deputy director of the McGowan Institute and head of the 80-patient muscle study. "Most people didn't believe it." Badylak seemed to be saying that he could replace human tissue with tissue from another species without triggering a virulent immune response—something that medical scientists considered impossible. Even harder to swallow was the claim that the material could transform, in a matter of months, into whatever type of body tissue had been damaged—muscle, skin, or blood vessel.
When Badylak first published his findings, in 1989, the field of regenerative medicine was nonexistent. Badylak's debut paper on ECM went to press right around the time scientists first coined the term "tissue engineering" to describe what was then considered a small but burgeoning growing field—the far-out-there efforts to coax cells into tissue to restore, maintain, or improve tissue function or whole organs. Today, the most widely publicized efforts in the field concentrate on growing tissue outside the body in specially designed, easily controllable "bioreactors." Badylak's ECM techniques, however, stimulate the body's own army of stem cells to do the healing, no external equipment needed.

Badylak is still testing the clinical limits of ECM. Last February he and collaborators announced that they had regenerated one of the body's most scar-prone tissues, the inner lining of the esophagus, in five cancer patients. Esophagus tissue is so sensitive that even minor surgical manipulations often result in a thick buildup of strictures that make it impossible to swallow. As a result, most surgeons wait as long as possible to operate on an esophageal tumor, then remove the entire organ using a procedure that has an extremely high complication rate. Badylak was able both to suppress all scarring in his patients and to prompt the fragile lining of the esophagus to regenerate completely. He is now awaiting FDA clearance to begin a large-scale clinical trial.

The discovery that led to this radical approach in wound healing happened quite by accident. It all started with what Badylak's associates called a "harebrained" idea and a mutt named Rocky.

After college Badylak had attended veterinary school at Purdue and practiced animal medicine until he realized that most pet owners could not afford the tests necessary to diagnose the conditions that interested him. He decided to go to medical school and set up a lab in his home to diagnose ferret lymphoma and dog breast cancer for former veterinary classmates who mailed him samples. At Purdue, Badylak became fascinated by an experimental technique called cardiomyoplasty, in which a flap of a patient's back muscle is removed and wrapped around the patient's ailing heart. A pacemaker shocks the muscle into contractions and helps the heart squeeze blood through the body. When Badylak decided to investigate the technique on his own, it was only natural that he would gravitate back toward animal patients, this time as test subjects.

He quickly discovered a downside to cardiomyoplasty. It used synthetic tubing to replace the aortic artery, and this often triggered aggressive inflammation and blood clots. Badylak became convinced that if he could find a blood vessel substitute within a patient's own body, he could stop the inflammation. So one afternoon he sedated an affable dog named Rocky, removed part of the animal's aorta, and replaced it with a piece of its small intestine, the part of the body that most resembled the tubular structure of Rocky's blood vessels. When Badylak arrived for work the morning after Rocky's surgery, he found the mutt wagging his tail and ready for breakfast. Every day he would find Rocky healthier and more energetic than the last. Days turned to weeks and Rocky continued to thrive. Hoping to make sense of his unexpected result, Badylak repeated the procedure on 14 other dogs. They, too, thrived. Six months later he finally operated on one of the dogs to understand why. That, he recalls, is when "things got really weird." Badylak could not find the transplanted intestine.

After checking and double-checking to make sure he had the right animal, he placed a piece of tissue called selected from the transplant target area under a microscope. What he saw floored him. "I was looking at something that wasn't supposed to happen," Badylak says. "It went against everything I had been taught in medical school." Under the glass he could still see traces of the sutures, but the intestinal tissue was gone. The aorta had grown back in its place. “Nobody would confuse an intestine and an aorta,” Badylak says. “The microscopic picture is entirely different. Badylak examined several other dogs in the weeks that followed and watched the intestinal tissue transform again and again. He began to suspect that something in the intestine was suppressing inflammation and simultaneously promoting regeneration. Thinking back, he recalled a bizarre finding on liver regeneration he had heard about in a veterinary school pathology lecture: If you eat poison and it destroys all the cells in your liver, the organ can still regenerate, but only if its structural scaffolding remains intact. Destroy the scaffolding and the body responds by producing massive scar tissue and no regeneration. Perhaps the scaffolding was the key.

The next step, then, was to strip away the layers of the intestine, until he was finally left with a paper-thin sheet of connective tissue called the extracellular matrix—the magical ECM. When he replaced the dog intestine with just this tissue, the transplant still worked. Badylak repeated the experiment, this time using ECM derived from cat intestine. He was sure the dog's immune system would reject the cat gut, but once again the transplant was successful. At this point Badylak realized he would be working with small intestines for a long time, and he was going to need lots of them. So for his next experiment, he used intestine obtained from one of the many pig slaughterhouses dotting the Indiana countryside surrounding Purdue. There would be no shortage of material if it worked. He tried it and, sure enough, his test dog was up and waiting for breakfast the day after it received the first of Badylak's pig intestine transplants.

In 1999 the FDA approved the material for clinical use, and soon surgeons across the nation began using it on patients to repair rotator cuffs, abdominal hernias, and esophageal reflux damage, and even to induce the regrowth of the outer lining of the brain. Badylak's published results caused a stir in the fast-growing field of regenerative medicine, and his professional reputation flourished. To the outside world, however, the researcher remained largely
unknown until 2007, when an odd confluence of events involving his old friend and collaborator, Alan Spievack, and Spievack’s injured brother catapulted him into the public eye. Spievack, who had coauthored several papers with Badylak, eventually went on to found a company called ACell to market his own special formula of the powder.

That is how Spievack, by then 73, was in a position to heal his younger brother, Lee. When news got out that Lee had regenerated his fingertip with a mysterious powder he called pixie dust—and graphic pictures displaying the regenerative process landed on editors’ desks—a media frenzy erupted. The stories and the photos sparked the imagination of amputation victims around the world, including Corporal Isaias Hernandez.

Four years later, Badylak still gets several emails a day asking about his miraculous pixie dust. Spievack did not get to share in much of the glory; he died of cancer in May 2008. Now that Badylak’s regenerative work has finally gone thoroughly mainstream, he is once again seeking to push the outer limits of healing—and is back to square one seeking grants for his far-out research. Badylak, along with Tufts University biomedical researcher David Kaplan and Susan Braunhut of the University of Massachusetts Lowell, is using a device called a bio-dome, a sleeve with a liquid reservoir that envelops an amputated mouse digit and allows researchers to control the healing environment. By adding growth factors, liquids such as water and amniotic fluid, and varying electric currents, he and his colleagues are replicating the conditions that exist in a human embryo—an environment that is perfectly conducive to the transformation of stem cells into the complex tissues that make up a body.

The idea of replicating an embryo on the end of a mammal limb to regrow it is considered too unconventional by most peer reviewers. The project is still without funding. But Badylak is undeterred. After all, he never let skepticism stop him before.

As for Rocky? He lived another eight years.