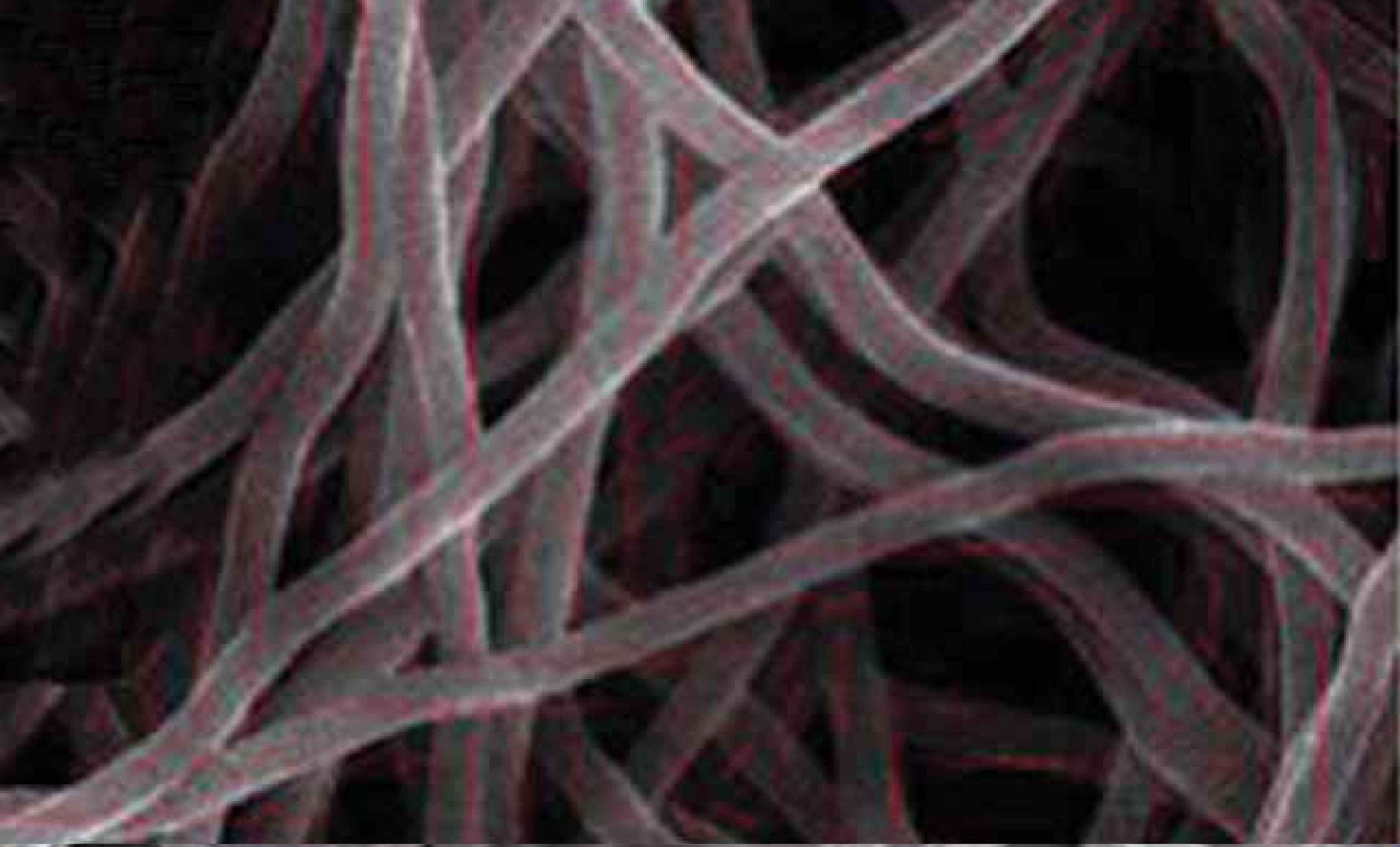
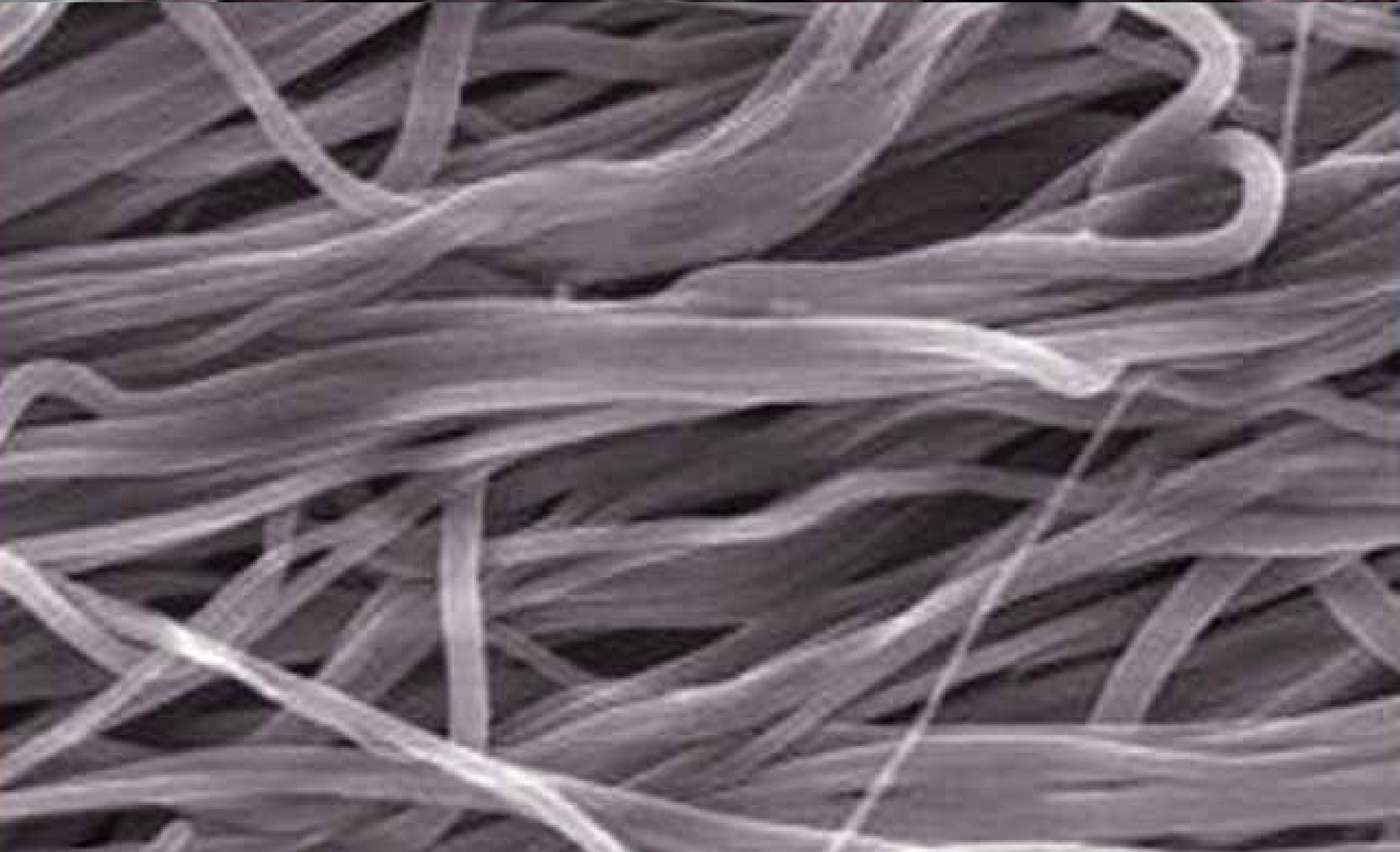




ENGINEERING CARDIAC TISSUE

BY MELINDA WENNER

TELLTALE HEARTS, AND VEINS

COURTESY BIOMATERIALS, 27, COURTNEY T, SACKS MS, STANKUS J, GUAN J, WAGNER W, 3631-3638, © ELSEVIER 2006.

How do you mend a broken heart? Therapies involving synthetic cardiac tissue don't boast reliably good outcomes. But a new material designed by Pitt bioengineers looks promising. One key to its design, say William Wagner and Michael Sacks, is how you align the tissue fibers. TOP: Close-up of polyurethane fibers in a random alignment. BOTTOM: The fibers here mimic the smooth, coordinated alignment of cardiac tissue.

Patrick Fraizer's heart was the size of a football. He didn't know that, of course, or he wouldn't have driven all the way from his home in Fort Wayne, Ind., to Pittsburgh. He wasn't feeling as peppy as usual, but that's why he was making the trip in the first place. Fraizer, a kind man with a ruddy face and enormous grin, had suffered two heart attacks in the past nine years. He was planning to meet with Pittsburgh cardiologists about an experimental cardiac therapy. He didn't, however, know that things were as bad as they were.

When Fraizer arrived at the University of Pittsburgh Medical Center, doctors performed a routine catheterization to take a virtual snapshot of the condition of his heart. Then he and his wife, Mary Fraizer, waited around for the verdict. He was half-expecting to be sent back home.

"We don't think you can make it to the door," the doctors told him instead. They said it was a miracle that Fraizer was even alive—he had so much scar tissue on his heart from his previous heart attacks that his heart was barely functioning. Worse, two of his coronary arteries were fully blocked and another was disastrously close. The experimental therapy was a no-go. The doctors said instead they had to perform a much riskier open heart surgery—immediately.

That's when they discovered that his heart had swelled to the size of a football. Fraizer's previous heart attacks had, through the years, caused part of his heart muscle to balloon out. Often, the part of the heart that is starved of oxygen during an attack can become so damaged that it cannot do the work it used to do. The rest of the heart tries to make up for it, yet it can't always compensate. So the damaged part of the heart responds by thinning, ballooning, and stiffening. These reactions reduce the muscle's efficiency further and can lead to heart failure—something that Fraizer had been flirting with for years without even knowing it.

While Fraizer was having his heart resculpted in the operating room, William Wagner and colleagues were several blocks away exploring how to prevent the need for such operations in the first place. Wagner, the deputy director of the University of Pittsburgh–UPMC McGowan Institute for Regenerative Medicine, is a tissue engineer and Pitt professor of surgery, bioengineering, and chemical engineering. Along with Pitt colleague Michael Sacks, William Kepler Whiteford Professor of Bioengineering, Wagner oversees the development of a biodegradable heart patch that may one day prevent the long-term cardiac damage that Fraizer and others suffer after heart attacks. Wagner and Sacks' work was recognized by *Scientific American* as among the 50 most outstanding acts of leadership in science and technology in 2006.

Reportedly, heart tissue has been extremely difficult to engineer because of its mechanical properties. It is strong, yet flexible, and is more easily stretched in one direction than another, depending on the direction in which its fibers are aligned. In addition, the body is sensitive to the introduction of foreign materials that don't quite match heart tissue's natural properties.

In his office, Wagner is surrounded by old journal issues, images of blood vessels, a whiteboard on which someone has scribbled circuit diagrams and graphs, three cacti (remnants of a youth spent in Phoenix), and numerous photos of his two young boys. Someone wandering in might wonder whether he is a scientist or an engineer, a surgeon or a chemist. Wagner thinks of himself as a translator between the worlds of engineering and medicine. Through the years that has meant working closely with patients, doctors, and other types of scientists.

"The way I describe it is as engineering applied to address cardiovascular disease," Wagner says of his work.

Engineering cardiac tissue in the lab requires expertise in many areas—mechanical and materials engineering, chemistry, molecular biology, immunology, and surgery, to name a few. Pitt stands out, observers say, because it has established a cadre of experts who work cohesively together.

"That's really how high-impact science is being done nowadays," Wagner says. "It's being able to assemble teams of experts where you have world leaders in different areas coming together and hashing out ideas."

"They have really made things happen," says Kim Woodhouse about Pitt's cardiac bioengineers. Woodhouse is a professor of engineering and applied chemistry at the University of Toronto. The Pitt team is pragmatic, synergistic, and creative, she says, and this combination puts them right "at the leading edge."

Wagner first became interested in applying engineering to medicine when he was in graduate school for chemical engineering at the University of Texas at Austin. One day, when listening to an engineering professor talk about his work on blood clots, Wagner suddenly saw how the engineering science that he'd learned as an undergraduate could be applied to the human body.

"I immediately knew that's what I wanted to do," he says.

He graduated with a PhD in chemical engineering, after having spent many a Saturday at the Texas Medical Association Library, slouched over medical journal articles. Then Wagner got an unexpected call from a surgeon at the University of Pittsburgh looking to hire a postdoctoral fellow to study blood clots and artificial hearts.

"And I'm thinking, *Pittsburgh? I'm from Arizona*," says Wagner with a laugh. Nevertheless, he visited.

"Within a couple of meetings with people, I realized that it was kind of like Mecca," he recalls. The problems he had only seen on microscope stages or in library cubicles in Texas were right in front of him at Pitt, having a "very real impact on patients every day," he says. He accepted the position.

At that point, Wagner wasn't quite ready to step up to the role of translator—he was, literally, still learning the language of medicine. "I knew a lot of the terms, and I'd read them dozens of times," he says, "but I'd never actually heard them pronounced!" As he immersed himself, he started noticing an interesting trend: Some medical terms were oddly vague, and the reason for this, he realized, was that no one really understood the processes they were trying to describe. That, he thought, was a hole that engineering could help fill.

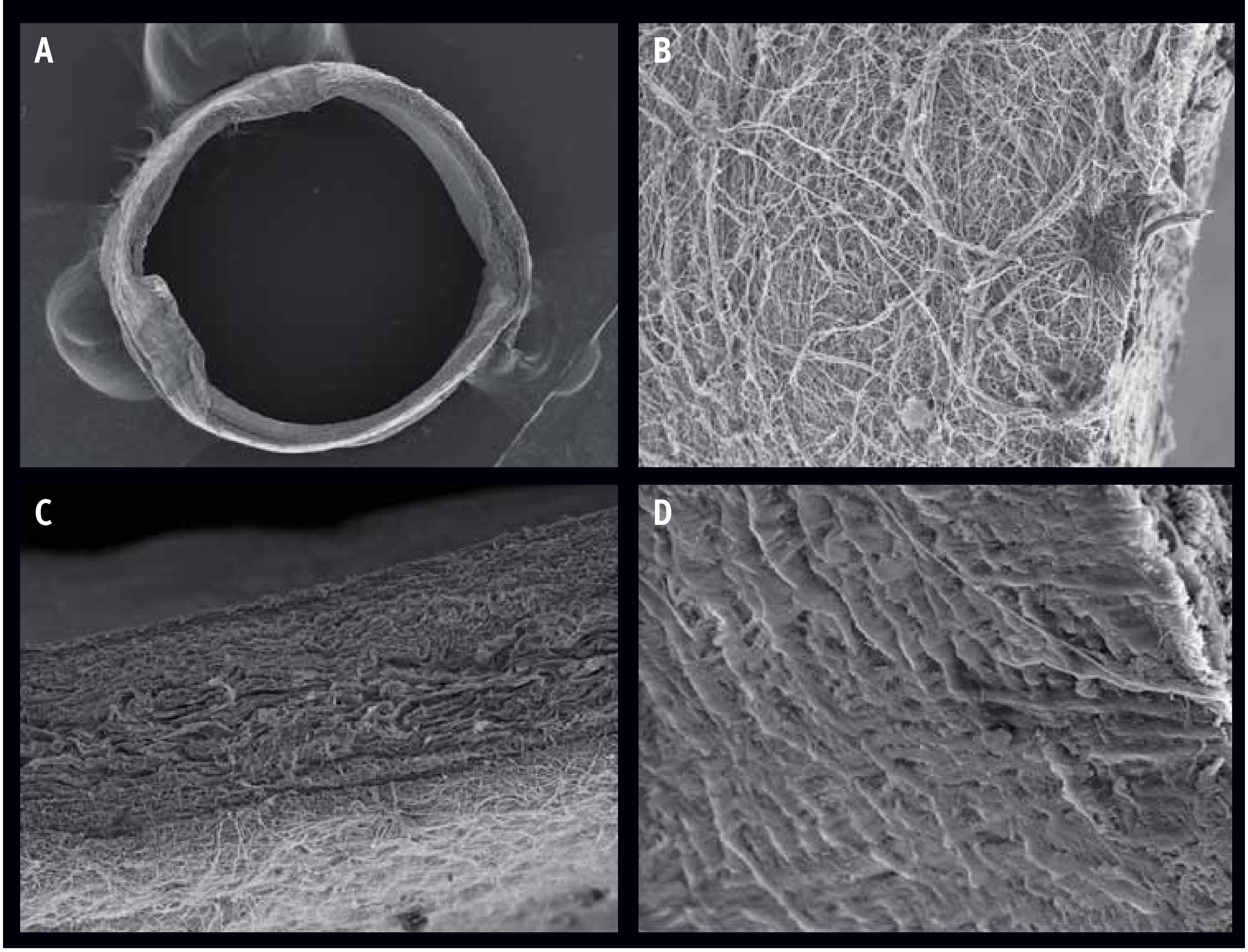
Wagner, along with Michael Sacks, a PhD biomechanical engineer with a dry sense of humor and an astute eye for detail, began closely studying the mechanics of cardiac processes, an area Sacks first started researching in graduate school at the University of Texas Southwestern Medical Center at Dallas. The heart can be thought of as a machine, and Wagner and Sacks wanted to understand it inside and out so that they could, in a sense, reverse-engineer parts of it. Wagner and Sacks realized there was a huge medical need for engineered cardiac tissue. Other bioengineers have typically used materials that poorly mimic the properties of cardiac tissue—so Wagner decided it was up to his team to develop something better.

The engineers imagined developing a cardiac patch that could help damaged hearts repair themselves. This patch would work best, they theorized, if it could mimic the types of temporary scaffolds the body makes on its own all the time.

"When you cut yourself, you make a clot, and then you put a temporary scaffold in there," Wagner explains. Then special immune cells arrive, release enzymes that help the tissue regenerate, and clear the temporary scaffold away.

But when the heart gets injured during a heart attack or because of other defects, it might not be able to repair itself. Instead, it might respond the way Fraizer's heart did—by ballooning out, which causes further problems and makes the heart even less efficient. Wagner and his team then wondered whether it would be possible to create a synthetic scaffold that, if applied to the heart within a few weeks of a heart attack, could allow the heart to repair itself.

They went to work. One of Wagner's postdoctoral fellows, Jianjun Guan, created a polyurethane material that was nontoxic, highly elastic, strong, and biodegradable. Polyurethane is the stuff of seat cushions, and Wagner explains that, like a good cushion, the material is strong yet flexible, able to bounce back after being compressed or stretched. His team found ways to manipulate the material so that it stretches more in one direction than the



COURTESY D. VORP AND M. EL-KURDI

David Vorp uses material developed in Wagner's lab to keep veins from hardening when used as arterial grafts: A) Vein with girdle. B & C) Polymer attaches to vein. D) Interior of vein remains intact.

other—just like real cardiac tissue—and so that it can degrade at different rates after coming into contact with particular bodily enzymes. The team found ways to make the material release growth factors to promote cell growth and differentiation. All the better, the material is easy to make.

"An undergraduate chemistry major could be taught to do it," Wagner says.

At the same time, Sacks studied the mechanical properties of heart tissue. *How would a synthetic patch need to behave in order to closely mimic real cardiac tissue?*, he wanted to know. Wagner collaborated with investigators working with stem cells—including Pitt's Johnny Huard, who is a PhD and the Henry J. Mankin Professor of Orthopaedic Surgery Research, and assistant professor of surgery Amit Patel, an MD—to eventually "seed" or embed the synthetic scaffold with patient cells that could later be coaxed into developing into functional heart cells. Wagner and Sacks imagined a seeded patch that could be sutured onto a person's heart—not a particularly invasive procedure, because the heart does not need to be cut—and restore working function to the muscle.

While developing their überpatch, Wagner's team made a serendipitous discovery. They were testing the effects of a patch on rats that had experienced recent heart attacks when the team found that even without stem cells, the patch improved heart performance.

"That's a lot more attractive and a lot closer to clinic than messing around with stem cells," Wagner says. A plain patch would not have to undergo as much testing for approval by the FDA, he says, and it could be implanted without first having to harvest cells from the patient.

That the patch worked well by itself was unexpected, but Wagner has some ideas as to why. First, the patch acts like a kind of girdle, he notes, preventing the injured heart from ballooning out as it tries to heal. This keeps heart cells healthier, so they are less likely to die. Second, as the body's immune cells come into contact with the patch, they might release enzymes that help the heart heal faster.

In the past, engineers have designed heart patches out of permanent materials like Gore-tex. If doctors use Gore-tex patches to treat children born with heart defects, "the kid's going to grow and [the patch is] not going to grow, so they're going to have to go in and keep changing it out in many instances," Wagner says.

In older patients, Gore-tex patches applied to help support the weakened heart wall after a heart attack present other problems. In these cases, surgeons must open the heart and place the Gore-tex patch on the inside surface. Wagner's patch does not require such risky surgery; it is fastened to the outside surface of the heart, a less invasive procedure.

Blood contact with foreign materials can trigger clot formation and these clots can break free and cause strokes. So patients with Gore-tex patches often have to take blood thinners. But the Pitt patch avoids blood contact and, by design, clotting and the need for blood thinners.

The Pitt team has also figured out a way to manufacture tissue scaffolds quickly, both with and without seeded cells. This breakthrough is important clinically and could have implications beyond a cardiac patch. The method could be useful for engineering other thin, elastic tissue in the body, such as bladders, as well as tube-like structures like the urethra and esophagus.

Although Fraizer's surgery went well—and his hospital recovery was sweetened upon learning that he would soon be a grandfather for the first time—his heart will forever be weak. "If I see 65, I'll be a blessed man," he says, now almost 61.

Perhaps 10 years from now, if all goes well in the laboratories at McGowan, a patient with Fraizer's heart condition will be able to live a lot longer than that. Wagner and Sacks will be testing the patch, with and without stem cells, in large animals and humans over the next few years.

After his second triple-coronary-bypass surgery in 2002, then-43-year-old Douglas Laney was told by his doctors that there was nothing more they could do. Even two triple bypasses hadn't fixed his problem permanently. The average lifespan of a vein graft is seven to 10 years—a lifespan that diminishes with every additional bypass surgery. So Laney was scared, especially when he began having chest pain again last year.

"I didn't know what to do," he says. But he did do something: He got a second opinion.

After performing a catheterization, the doctors treating Laney visited him in his recovery room. Laney was waiting anxiously, afraid of what they might tell him. But the doctors delivered good news: They were willing to take the chance that his previous doctors refused to take. They were willing, they said, to try to perform another bypass.

"I experienced probably every human emotion within five minutes," Laney says. "I was overwhelmed with joy."

In patients with clogged arteries, bypasses usually fail because the replacement veins, which are often nonessential veins taken from another part of the body, aren't up to the job.

Veins are used to living "a pretty cushy lifestyle," according to Pitt vascular engineer David Vorp, and are not prepared for the demanding arterial environment. Veins are used to low blood pressure and low flow, and they don't feel the pulsations of the heart. Arteries, on the other hand, have higher blood flow, higher shear stresses, and they pulsate because of their proximity to the heart. So when veins from the leg are plugged into the arterial environment, they tend to panic.

"They say, 'Wait a minute, we're veins, we're not supposed to be experiencing this,'" says Vorp, an associate professor of surgery. He explains that a vein implanted into the arterial environment assumes that it is injured, so it immediately begins trying to counteract the problem. It does so by thickening. As it thickens, however, the canal also begins to narrow. Sound familiar?

"You end up having the exact same problem as you had before. You have narrowing and clotting off of the blood flow, and that's one of the primary failure mechanisms of vein grafts," Vorp says.

That's exactly what happened to Laney after his first two bypasses—his grafts failed. Although he was understandably nervous about going in for another triple bypass, he says that, psychologically, it was easier the third time around. "This time, I had reached a point of acceptance that what was going to happen was going to happen," he says. Luckily, the surgery was a success; even so, he can't be as active as he once was, though he likes to help out with his church and do other volunteering. And there is always the fear that the grafts could fail again.

Vorp, who is soft-spoken and sports a reddish-golden beard, hopes that his collaboration with Wagner will eliminate the need for repeat bypass surgeries by making implanted veins stronger. If the vein to be used in bypass surgery is first wrapped in a biodegradable polymer material like the one developed for Wagner and Sacks' cardiac patch, it may not thicken as much upon exposure to its new environment. Then, after a few days perhaps, the wrap degrades, allowing the vein to slowly adapt to its new harsh environment. The vein girdle has a patent pending.

Vorp describes himself as being "born, bred, raised, trained, and differentiated, if you will, in Pittsburgh." What actually "differentiated" him from a typical mechanical engineer into a bioengineer was a class he was required to take as a Pitt student. "This silly little course, that I tried to put off and tried to get out of taking, pretty much changed my life," he says. In it, he was required to write a report on how mechanical engineering impacts society. When he explained this to his girlfriend at the time, who was in dental school, she noted that mechanical engineering plays a big part in dentistry. That piqued his interest.

"I went to the library, and I stumbled across two journals. One was the *Journal of Biomechanics*, and the other was the *Journal of Biomechanical Engineering*. I just was devouring these, and I thought it was the coolest thing," he recalls.

At the time, Pitt didn't have a bioengineering department, but Vorp was able to get a research position after graduation working with bioengineer Harvey Borovetz, who was then in the Department of Surgery. That's where Vorp developed his expertise in vascular bioengineering. He also worked closely with patients and doctors in the artificial heart program.

The "bread and butter" of Vorp's work these days is studying the mechanics of the abdominal aortic aneurysm, a condition in which the large blood vessel supplying blood to the lower body becomes abnormally large. Vorp is developing noninvasive ways to predict which types of aneurysms are at risk of bursting.

He also is trying to develop fully synthetic arteries using tiny biodegradable polymer-based tubes that can be seeded with stem cells. He wants to coax the stem cells to develop into vascular cells. Then, as the polymer breaks down after implantation, the cells would take over and create a complete blood vessel. If his team can find a way to do this, it will have become the first to create a successful artificial artery.

Asked how long it will be before all of these procedures, including the vein girdle, are tested in humans, Vorp laughs, saying, "It's funny, it seems like every time someone asks me how far away we are from clinical translation, I say five years. I said that 10 years ago, and I said that five years ago." Then he smiles. "This is probably the first time that I can think about it and believe that it's going to be less than five years."

Wagner and Sacks are also pursuing other projects. For example, they are developing an engineered heart valve using the same polyurethane material as the patch. Although it will be a year or two before they begin testing it in small animals, the mechanical properties of their engineered valve seem to match natural valves.

The value of life has become even clearer for Fraizer since his surgery. Although his heart is no longer as big as a football, metaphorically, it still seems to be. He pours as much of it as he can into his 1-year-old granddaughter, BreAnna, whom he babysits every day. He admits that he spoils her a little, but, he says, that way she will always know she only deserves the best.

"Things really do blossom out of tragedy," he says. "I absolutely love being around this girl."

"What we are doing," says Vorp, reflecting on his work one day recently, "is really trying to make life happen." ■