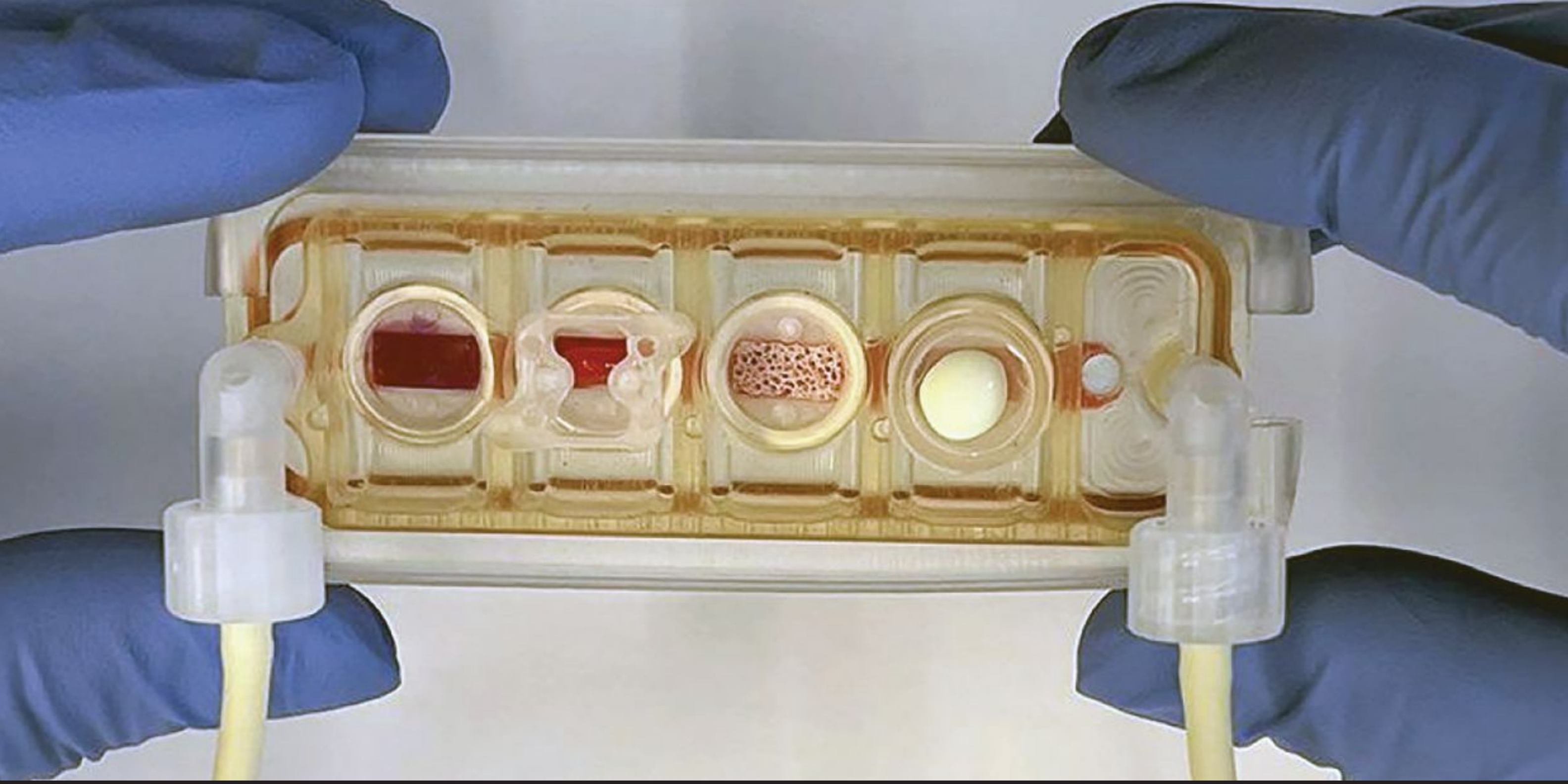


Biomedical Engineering: The Next Medical Revolution

BY ALAN S. BROWN

From artificial cartilage to new ways to revive muscle after a heart attack, engineers are creating new ways to diagnose and treat disease — if their funding holds.

THE BACKSTORY

One warm August night, David Murphy returned home with his family and was shot three times by a burglar. One bullet ripped through his thigh, slicing his sciatic nerve. Unable to control his leg and foot muscles, he fell to the ground and crawled under a car to escape the shooter until the police arrived.

Emergency room surgeons quickly dealt with the wounds, but the severed nerve caused Murphy intense pain. It never went away and got worse at night when he tried to sleep. Three months later, physicians referred Murphy to Greg Kolovich, MD, a peripheral nerve surgeon based in nearby Savannah.

Dr. Kolovich was not surprised by the delay. "Nerves don't regenerate," he said. "So, there's a high proportion of surgeons, physicians, and providers who think that there is nothing you can do."

Kolovich's first goal was to treat Murphy's pain. The sciatic nerve is the body's largest nerve, about as thick as a thumb. When cut, the nerves at the ends knot themselves into a ball.

"Think of the nerves as a live wire," Kolovich said. "They were sending out signals into that ball of nerves, electrocuting and shocking him nonstop. It was unrelenting, unforgiving pain. When he came to see me, he couldn't sit down. He was sweating and pacing around the room in a brace."

Yet, Kolovich saw an opportunity to do more than unknot the neurons and relieve the pain; he thought he could rebuild the nerve.

This had been done before using an autograft. It involves removing a section of a patient's nerve (often the sural nerve alongside the Achilles tendon) and sewing it to bridge the gap between the two damaged nerve ends.

But this posed two problems: first, it would leave Murphy without sensation near his Achilles tendon. Second, the sural nerve is too thin to work well with the sciatic nerve.

Kolovich, however, had something else in mind — an experimental treatment based on the Avance allograft. It uses a nerve harvested from a cadaver and treated to remove all organic content — cells, fats, and blood vessels — so that the body's immune system does not attack it. The porous tubular extracellular matrix that remains is a perfect environment for nerve growth.

Allografts (**Figure 1**) are easier to use than autografts. They come in a variety of sizes and can be frozen until needed. Operations are much shorter since there is no need to first harvest nerves from another part of the body.

In surgery, Kolovich cut the sciatic allograft to the correct size (**Figure 2**). Using a microscope, he sewed bundles of sciatic nerves into the allograft using thread thinner than an eyelash. Then he wrapped everything to protect it.

"If you do everything right," Kolovich said, "the nerves will start growing about one millimeter per day."

Within weeks, Murphy was off pain meds. He returned to his job as a forklift operator, which involved constant use of his feet. One year later, he was walking; now he is running. "It's like it never happened," Kolovich said.

Since then, Kolovich has done thousands of allograft surgeries. Altogether, clinicians have performed more than 100,000 Avance procedures. This is likely to grow even faster since a report found that Avance allografts performed as well as autografts.

Allografts are just one of a new wave of startling advances emerging from biomedical engineering labs. They range from artificial cartilage and heart muscle — two tissues that do not regenerate in the body — to a technique to regrow bladder tissue on an artificial surface. They include new diagnostics, new medicines, and chip-grown kidneys, livers, and hearts that are changing the game in research and drug testing.

Engineers are still perfecting some breakthroughs in their labs but others have already moved into clinical trials and commercial use. They herald revolutionary changes in medicine. Yet many unanswered questions remain about the research — and the funding needed to move it forward.

Figure 1: The Avance allograft. Credit: Christine Schmidt Lab, Univ. of Florida.

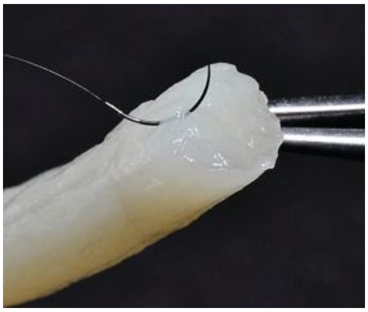
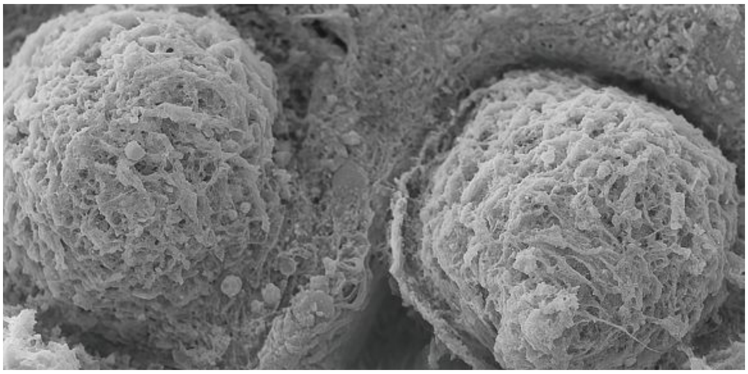


Figure 2: The Avance allograft. Credit: Axogen.



AI-generated image of a donor nerve before neurons and organic material are removed. Credit: Alan S. Brown.

AN EMERGING FIELD

Biomedical engineering is not new. The University of Pennsylvania launched the first academic program 100 years ago. By the 1970s, several universities had followed suit. Most early bioengineers, however, taught themselves and teamed with health professionals. Their collaborations ushered in devices ranging from lightweight prosthetics and hip and knee implants to heart pacemakers, hearing aids, and hospital monitoring equipment.

Many biomedical engineers continue to push boundaries in similar fields. Yet, an increasing number have shifted their focus to the human body, trying to repair or even create organs or influence biological processes with new materials or microscale and nanoscale devices.

New technologies make it possible to surmount barriers that once seemed impossible. Many grew out of biomedical research. Today, for example, researchers can map the surfaces of tumors and diseases. They can find proteins that grow only on specific cells and test thousands of drug variants for activity using high-throughput screening. And they can modify DNA and RNA to study or fight disease or improve a body's function.

In addition to medical research tools, biomedical engineers have developed their own unique toolkits. They can, for example, use 3D printing and advanced bioreactors to grow thin slivers of heart, kidney, liver, and other organ tissues. They are realistic enough to run experiments to nail down the molecular pathways that define a healthy organ or the progress of a disease.

And everywhere, advanced computation and artificial intelligence are helping to illuminate, model and envision molecules, and target incredibly complex living systems.

Biomedical engineers also use tools differently than biologists or medical researchers, said **Tejal A. Desai, Ph.D.,** *RI A '94*, dean of engineering and a noted biomedical engineer at Brown University.

"They approach biological problems with an engineering mindset," she said. "They are interested in running controlled experiments to see how things connect with each other and then putting those pieces together to come up with a solution."

They also learn and apply their craft differently, said **Guillermo A. Ameer, D.Sc.,** *TX A '93*, Director of the Center for Advanced Regenerative Engineering at Northwestern University. Today's learning emphasizes convergence research, the deep integration of knowledge and methodology from fields that are not usually related.

"This is different than interdisciplinary research, which is more of a conveyor belt approach, where you work on your part of a problem and your collaborators work on their part," he explained.

"In convergence research, that knowledge is intertwined. It enables us to work on challenges that seem too big to solve by understanding their pain points from different points of view. You embed yourself in two fields that appear to be separate but are not as long as you bring them together yourself. For example, you might study the structure of butterfly or cicada wings to see how their surface prevents bacterial infections. This creates entirely new areas of study."

Over the past decade, these changes have created a young and highly diverse discipline, one in which women account for slightly more than half of all undergraduates and master's candidates. It is a field that has begun to make a difference in how medicine gets done.

BUILDING CARTILAGE

From the start, researchers interested in regenerating body parts targeted cartilage. Strong, flexible, and incredibly durable, this connective tissue acts as a shock absorber in joints. As any athlete will tell you, damaged cartilage does not heal, so synthetic cartilage would be valuable.

Cartilage seemed like an easy lift. It absorbs oxygen and nutrients from surrounding tissues without hard-to-make blood vessels. Also, the immune system does not usually recognize and attack cartilage implants as a foreign object. This is why an early 1990s paper on tissue engineering in the prestigious journal, *Science*, tagged cartilage as low-hanging fruit for tissue synthesis.

"Twenty years later, we wrote a paper and in the second sentence we said, 'Cartilage ain't low-hanging,'" said Kyriacos Athanasiou, a well-known biomedical entrepreneur and distinguished professor at the University of California, Irvine. Originally a mechanical engineering student, he shifted to biomedical engineering in college and focused on the musculoskeletal system because of its mechanical nature.

Now, 20 years after his paper on cartilage, his group "can fabricate cartilage in a lab that is almost indistinguishable from native tissue," Athanasiou said. He has spun out a company, Cartilage, Inc., to grow massive amounts of cartilage cells. It is testing the cartilage on animals and plans to begin human testing in 2026.

Like many innovations, Athanasiou's journey began with a failed experiment. Twenty-five years ago, engineers were trying to grow cartilage on scaffolds, artificial versions of the body's extracellular matrix (ECM). The scaffolds provide support, mechanical prompts, and growth chemicals that help cartilage cells thrive and form tissue.

Unfortunately, ECM did not work well with cartilage cells. The cells sought to minimize their free energy by attaching themselves to scaffolds or other surfaces. As soon as their free energy dropped, they transformed into other types of cells.

One day, a graduate student asked Athanasiou to look at a scaffold that had failed to produce cartilage. Under a microscope, there was a small line of tissue outside the scaffold. When asked, the student said it was cartilage. Athanasiou realized immediately that there must be a way to grow cartilage without a scaffold.

It took 25 years. Athanasiou's first step was to build a bioreactor that could suspend the cells, so they expended their free energy by interacting with one another to form tissue rather than clinging to a surface.

"We put them in molds and exercise them by controlling pressure and nutrient media flow so that they produce the right combination of proteins and sugars," Athanasiou said.

The self-assembly process, he said, creates an environment similar to the one that forms cartilage in embryos. It enables Athanasiou to start with one cubed centimeter of cartilage cells and make enough 10 mm x 1 mm thick patches for 35 million patients. That will create new ways to treat injuries of the knee, hip, spine, nose, and jaw, he says.

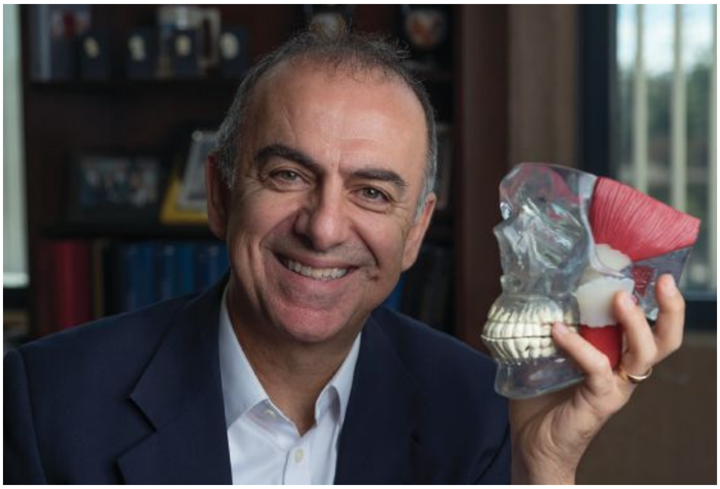
HARNESSING MECHANICAL FORCES

Biologists never suspected mechanical forces shaped cell and tissue development until researchers like Athanasiou began running controlled tests on artificial tissues. Today, many biomedical engineers believe manipulating those forces could open new doors in medicine.

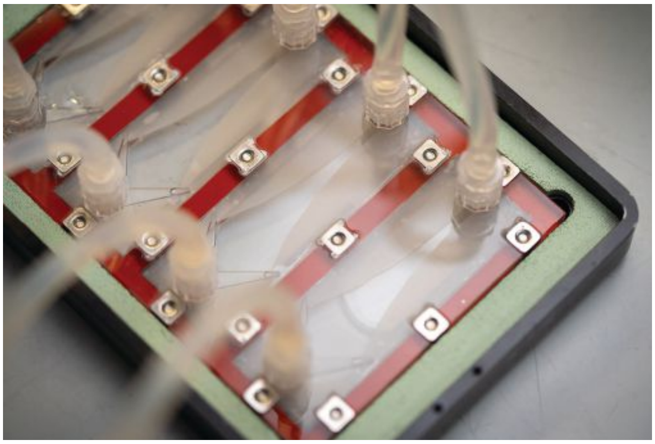
One of them is Adam Engler, Chair of the University of California San Diego's Department of Bioengineering. He had planned to become a pediatrician until he was "bitten by the lab bug" as an undergraduate. As a doctoral student, he learned to build ECM environments to study how muscle cells behaved in muscular dystrophy.

When he applied what he'd learned to stem cells, he found they responded to mechanical prompts. "If you put these cells in a soft microenvironment, they grow fat and turn into neurons," Engler explained. "Make it stiff and they form muscle. Make it even stiffer and they become bone. The stem cells don't have a preference. They just react to the environment and differentiate without any biochemical growth factors around."

Engler continued to probe how tissues' mechanical properties interacted with other biochemicals in the body to influence cell behavior. In 2010, his work pulled him into a government-supported cancer research program.



Based on cartilage implants in large animal models, Kyriacos Athanasiou has shown he can heal certain types of jaw diseases that cause pain and difficulties in talking and eating.
Credit: Steven Zylius, University of California, Irvine.



A close-up of the tools used to measure cancer cells' stickiness in the Engler Lab at UCSD. Credit: David Baillot/UC San Diego Jacobs School of Engineering.

"We postulated that there should be physical markers when cancer spreads," Engler said. "In solid tumors, a cell has to detach. It must migrate through a stiff tumor and punch through a soft blood vessel to access the bloodstream. Then, it must do the opposite when it reaches its destination so it can begin to proliferate. That process is extremely physical."

Almost all body cells prefer to migrate from soft to stiff tissue. Through a series of controlled experiments, Engler showed that cancer cells are the exception; they move from stiff to soft. While this made sense, no one had ever run the experiments to prove it before.

Quantifying this movement enabled him to show that some drugs influence cell migration. But which ones worked best?

To find out, Engler tested migration growing cancer cells on artificial scaffolds the size of a quarter. He could test six at once, far too few to query the millions of molecules pharmaceutical companies kept in their libraries. To speed this search, he invented a way to make pencil head-sized scaffolds so he could screen 96 of them at a time. The technique makes high-throughput drug screening possible for other types of human organoids as well. He plans to commercialize the technology through a spinoff company later this year.

At the same time, Engler continued to search for biomarkers that could warn physicians that a tumor was likely to enter the bloodstream and metastasize. Most researchers were looking for clues among biochemicals associated with cancer, but each cancer had its own unique set of molecules.

Engler wanted a more general marker. So, he studied how cancer cells break away from the tumor. Eventually, he hit on a physical property that defined this behavior — stickiness.

"If cancer cells are too sticky, they attach to the matrix and don't move," he explained. "If they are not sticky enough, they cannot pull themselves through the ropelike ECM. But if they are optimally adhesive, then we should worry."

Engler carefully measured cancer cell stickiness to predict their behavior. His predictions matched with clinical measurements and may one day provide physicians with a new tool to diagnose the danger of metastasis.

"Today, medicine will tell you to treat similar tumors the same way," he said. "This extra data point gives physicians more confidence in treating you aggressively if cells are in that optimal range or less aggressively if they are not."

UNLOCKING MICRO/NANO RESPONSES

Brown's Desai also embraces mechanical forces, but in a very different way. Her goal is to use material microstructures and nanostructures to manipulate cells and tissues.

"These are not like the passive systems used to get direct medicine somewhere," she explained. "Instead, they are designed to interact with tissues in order to cause their cells to remodel or regenerate or heal."

One example involves cardiomyocytes, the cells that power heart contractions. Heart attacks may scar those muscles and keep them from contracting. Scaring keeps cardiomyocytes from regenerating. But applying physical forces may prompt those cells to heal.

"We're giving them a workout," she said. "We squeeze and stretch them and do things that prevent them from scaring and becoming useless. We don't need a medicine if we can create a material with the right properties."

She often screens materials to see how they interact with tissues and the immune system. "Some architectures can prevent the body from generating excess scar tissue, while others can call in immune cells to clear systems or deposit things," she said. "We think this is an interesting way of changing the behavior of cells implicated in diseases."

"We can also mimic how nature accomplishes certain tasks. We could, for example, use gecko-like nanostructures to get drugs to stick in certain parts of the body. Or, we can copy the spiky structures that viruses use to cross certain types of barriers and use them to cross into the intestinal system."

Desai's work led her to study the properties of long, high-aspect-ratio particles roughly 200 nanometers in diameter and 1,000 to 10,000 nanometers long.

These polymers have a surprising property – they moderate immune response. Most foreign particles in the body trigger an immune response. High-aspect-ratio molecules, on the other hand, signal hormones to slow it down. The effect is powerful but very local since their log-like shape locks them into place. Desai believes that physicians could one day use these physical prompts to counter autoimmune diseases, injecting them into the pancreas to fight diabetes, under the skin to treat psoriasis, or into joints to reduce rheumatoid arthritis.

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She has also developed a soft gel that slowly releases insulin to diabetic patients. Others have tried to infiltrate insulin through porous materials but failed. The problem, Desai said, is that gels could not maintain the pore sizes needed to screen out immune cells while harder materials were quickly attacked and blocked by immune cells.

Desai’s group solved the problem by growing oxide nanostructures—they look like blades of grass—through a gel dome and then dissolving them chemically. This leaves behind a well-structured system of pores. Her group spun off a company, Encellin, to commercialize the technology.

BUTTRESSING BONES AND BLADDERS

Many of these advances are made possible by our improved ability to grow realistic organoids. They let researchers run controlled experiments, rather than try to focus on a particular biochemical pathway while screening out the noise of billions or even trillions of other biochemical interactions that are always going on in living animals.

As a result, they make it possible to study the precise mechanisms of biological pathways under controlled conditions. They enable drug companies to test medications on human tissue, improving the probability that it will work on people. One day, organoids grown from a patient’s own stem cells could help physicians determine the best cancer treatment for his or her specific genetic makeup.

Today, biomedical engineers build organoids on very thin scaffolds. This is because researchers have not yet discovered how to grow blood vessels that could deliver oxygen and nutrients to a thicker sample. This limits the type of cells they can grow and the realism of the response.

Yet, even this barrier is crumbling. Researchers have made significant progress growing blood vessels and may one day grow complete organs for replacement from a patient’s own stem cells.

Of course, organs interact with one another in healthy and diseased bodies. To understand how, researchers must work out how they communicate with one another by biochemicals moving through blood, lymph, the immune system, and more.

This is already leading to surprises. At Columbia University, Gordana Vunjak-Novakovic has engineered bone tissue that generates its own immune cells. This enables her to study interactions between bone and breast cancer. One startling result – breast cancer cells can suppress the immune response of bone marrow tissue.

Meanwhile, others, like Northwestern’s Ameer, are searching for ways to leave behind artificial scaffolds. As a graduate student at MIT, he began looking for synthetic materials that emulate the stretchiness of the lungs and skin but are easier and cheaper to make.

He found what he was looking for in polydiolcitrate, a material with three end groups that crosslinked easily with one another to form materials that could range from elastic to solid. Based on citric acid, which gives lemons and limes their bite, the polymer was biocompatible and biodegradable.

Polydiolcitrate also stabilizes hydroxyapatite, a mineral that gives bone its strength and stores most of the body’s citric acid. That got Ameer thinking about fixation screws and anchors used for reattaching ligaments or muscle to bone.

“The citric acid is like an energy bar for bone cells,” he says. “As the polymer degrades, it releases citric acid, which speeds up bone healing without any need for growth promoters.”

Polydiolcitrates worked fast and investigators soon discovered that they had antioxidant properties that suppressed inflammation and reduced complications after surgery.

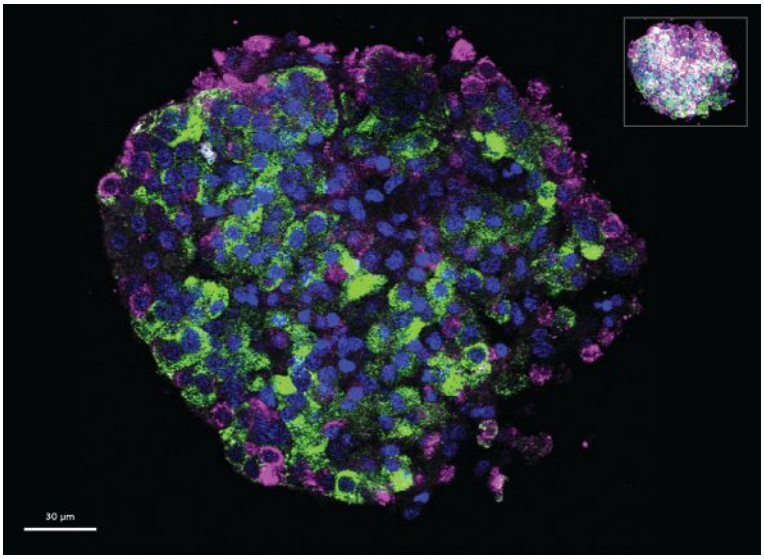
Now, Ameer’s team is using the same family of polymers to create grooved ECMs that can support bladder tissue growth. “The matrix is similar to what bladder tissue wants,” Ameer said. “This could lead to a new way to treat diabetes and pancreatitis. And they seem to last. We have implanted them in baboons two years ago, and they continue to do well.”

AN UNCERTAIN FUTURE

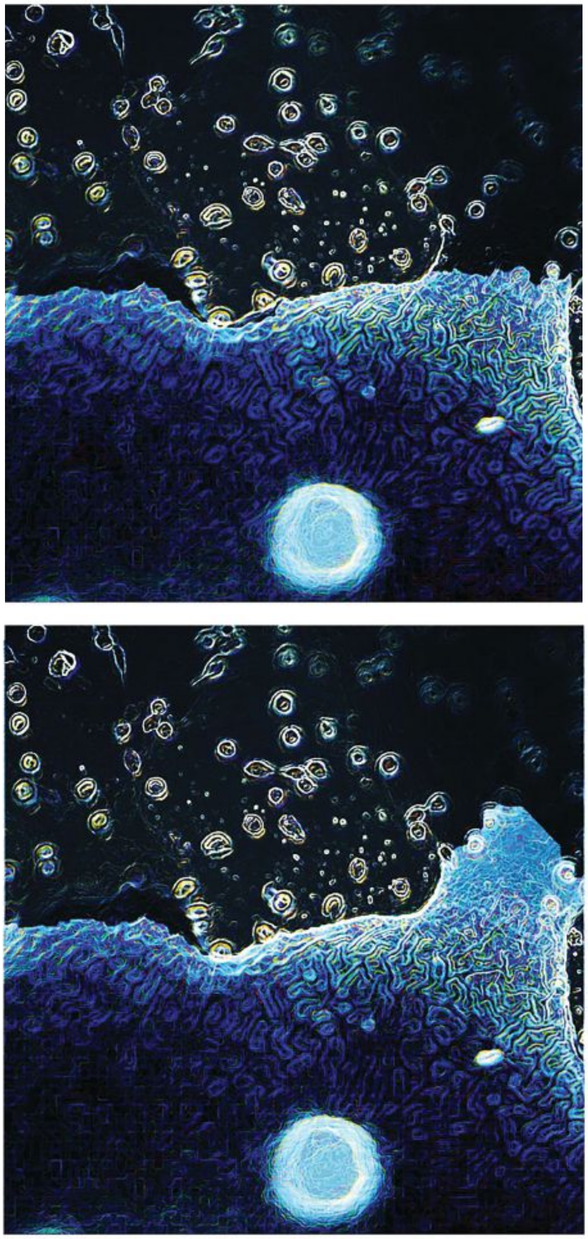
This is a tantalizing and hopeful picture. But progress is not assured. Reductions in government research funding have hit biomedical engineers hard.

“A lot depends on being funded in a way that we can make mistakes because there are always more mistakes than not,” Engler said.

Desai agrees, “There is a lot of uncertainty. It’s going to be hard to support our lab and people and to move things forward without federal funding. We’re not going to take the risks we want to take because we don’t know ahead of time what is going to work.”



Top Right: An image showing some of the chemistry that allows slow-release of insulin and other hormones (Desai). Credit: Excellin.



Middle and Bottom Right: Image of bladder growth in Ameer Desai's novel-scaffolding-biomaterial, which improves bladder regeneration and body function. Credit: Rebecca Keate.

Ameer's Center for Advanced Regenerative Engineering has 35 members, but his donors cannot fund all his research programs. The decline in funding will make a difference.

"My colleagues and I go to meetings around the world," he said. "The only reason U.S. researchers are different from those in other countries is that we have high levels of funding. If that funding goes away, we'll be like anybody else."

He hesitated for a moment, then added, "It's important to have those grants. I'm against waste, just like everyone else. But we don't want to cut the type of grants that are enabling us to create entirely new industries."

Athanasiou, an accomplished entrepreneur, remains optimistic. "I'm hoping it is a temporary situation," he said. "I don't think anybody in their right mind would support permanent cuts."

Hopefully, he is right. A future revolution in medical care might depend on it.

ALAN S. BROWN has written broadly about engineering, technology, and science for more than 30 years. He is a board member of Science Writers in New York, a writer for The Kavli Foundation, a former senior editor of ASME's *Mechanical Engineering* magazine, and contributes to a wide range of publications. He graduated *magna cum laude* in 1974 from Hofstra University and can be reached at: **insight01@verizon.net.**

Hero Image on page 6: Columbia University's Gordana Vunjak-Novakovic developed a chip that links multiple organoids via blood flow to study how the liver, heart, bone, and skin respond to one another and disease.
Photo credit: Kacey Ronaldson-Bouchard/Columbia Engineering.