Multifaceted Biomaterials Extend to Multiple Uses

By Leslie Mertz

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New Developments in Biocompatibility

In research laboratories around the world, scientists and engineers are taking newly reported insights about how the human body works, contributing new insights themselves, and then combining that new knowledge with innovative approaches to materials development. The result is a collection of biomaterials that promise to make a vast range of medical devices biocompatible and to increase the level of biocompatibility of those devices that are already considered biocompatible.

One of these research groups is that of Buddy Ratner, Ph.D., a professor of bioengineering and chemical engineering, and the Michael L. and Myrna Darland Endowed Chair in Technology Commercialization at the University of Washington (UW), as well as director of University of Washington Engineered Biomaterials (UWEB), the university's engineered biomaterials program. Rather than developing a completely new material, he and his research group found a new way to make an old material more biocompatible. He explained, "By adding specially engineered pores to the material, we get a very different healing: an integration, a vascularity, and a recreation of new tissue around the material. Just by adding pores of a particular size and pattern, we don't get the classic foreign-body reaction, where the body essentially walls off the materials by generating a tough, avascular, collagen sheath that forms around it."

On the basis of various observations of differences in the body's reaction to porous versus nonporous materials, Ratner became interested in how the body would respond to a material that contained uniform, interconnected pores. He gave one of his doctoral students the task of generating such a material. The student, Andrew Marshall (now the chief scientist of a company making these materials for human use), began using a process called sphere templating (Figure 1). "He

Digital Object Identifier 10.1109/MPUL.2013.2262140
Date of publication: 26 July 2013

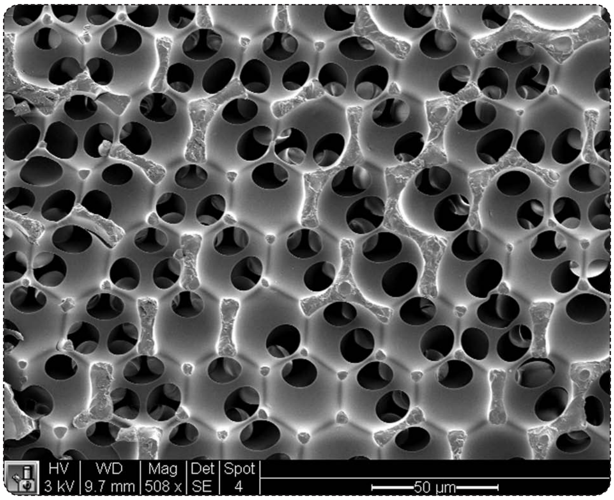

FIGURE 1 Ratner's research group at UW uses a process called sphere templating, which adds specially engineered pores to materials, making them biocompatible. Sphere templating begins with tightly packed, uniform microspheres. After surrounding the microspheres with a monomer solution, the microspheres are extracted to generate the material. (Image courtesy of UWEB21.)

used microspheres all of the same size, packed them down, surrounded them with monomer solution, and then extracted away the microspheres," Ratner said.

That project led to the discovery that uniform, interconnected pores 30–40 μm in diameter, or about half the diameter of a human hair, conferred superior healing [1]. Upon considerable testing and observation, Ratner's group learned why. Although the body still sends out its attack cells, the so-called M1 macrophages, which have the job of engulfing foreign materials, enter the pores and become mechanically constrained—they get stuck—so they cannot carry out their mission. According to Ratner, "These macrophages then transform into what are called M2 macrophages, and these M2 macrophages have a completely different role in that they are responsible for the healing, regeneration, and angiogenesis that produces new blood vessels."

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Ratner explained that his research group implanted the material with and without the engineered pores and then extracted and examined the samples a month later. "By one month, the material with the engineered pores was nicely healed in, and we had a heavy enrichment of M2 macrophages," he said.

In a separate collaborative project, Ratner reported a similar increase in M2 macrophages in a material developed by colleague Shaoyi Jiang, UW Boeing-Roundhill Professor of Chemical Engineering. "He has invented some materials that no proteins, no cells can stick to. Nothing sticks to it, even in full body fluids for long periods of time. These are extremely nonfouling materials," Ratner said. Like implantations with the engineered-pore material, implantations with Jiang's material also healed without a collagen scar forming around them. "Again, it was just an integrated, vascularized healing rather than this collagen encapsulation." Both of these projects lead Ratner and others to believe that the collagen-associated reaction might be driven by proteins that adsorb or stick to the surface of everything implanted into the body. He commented, "If you could get rid of those proteins, that could be one pathway to get the material to heal in."

The engineered-pore material already has a track record in human patients. Ratner mentioned, "Our materials have been used in patients for about a year now, and currently I'm working with a number of clinicians to explore medical applications." He said that these could include urethra replacement, heart muscle wall to address heart failure, and blood access for hemodialysis. "There are so many places where the collagen scar is the issue, so this improved healing will be much better."

Shaking It Up

A research group at Michigan Technological University (MTU) in Houghton is developing materials that can be produced as coatings or other structures and could also be used to confer biocompatible properties to a wide assortment of devices.

These new materials have the capacity to change shape when subjected to a magnetic field, and the magnetic field vibrates the material's way to biocompatibility [2], according to Rupak Rajachar, Ph.D., who is collaborating with fellow MTU biomedical engineer Keat Ghee Ong, Ph.D. on the project.

To explain the concept, Rajachar used the example of a rock climber scrambling up either a hard rock wall or a wall of Jell-O. "When you're climbing on rock, you're putting your fingers into little holes and using your fingers to create leverage, so you're essentially generating tension at your fingers. If you're climbing a wall made of Jell-O or something elastic, the material gives, so that you are pulling the wall toward you." Cells usually exist in a relatively soft environment, but most implanted devices and materials are harder and stiffer by comparison. When a cell encounters a hard implant, he said, it not only switches from its normal round morphology to one that is more spread out, but its behavior also changes, making scar tissue formation more likely. Since the lifespans of devices are often shortened by the formation of scar tissue, finding a way to curtail that formation made sense.

To do that, the MTU engineers employed magnetoelastic materials that physically deform when exposed to a magnetic field and simulate the pliability of the internal body. "Basically, if you have a strip of material and add cells to it, they would weigh down its surface," Rajachar explained. "By adding an applied magnetic field, you can generate oscillations in the material—it stretches and contracts, stretches and contracts." Depending on how many cells are added to the surface, the oscillations change. "This allows us to 'soften' the material mechanically, so that the cells remain rounded and hopefully reduce their scar-forming nature, and preliminary experiments in vitro show that's what might be happening," he said (Figure 2).

The MTU engineers now hope to expand their work to test magnetoelastic coatings on various devices, such as implanted prosthetics and transcutaneous catheters, and to use the material to manufacture nanoparticles and nanoscale rodlike shapes. “With the nanoshapes, the idea is to place them in drug-releasing polymer spheres and by mechanically activating those rods or particles, we could provide an extra level of control over when and how much drug is delivered.”

Rajachar stated that they are also pursuing the development of a new composition of magnetoelastic material rather than the off-the-shelf variety they are currently using. Unlike the current material, the new composition can degrade and is extremely biocompatible. Tests in Rajachar’s laboratory show that the new material works just as well, if not better, than the current material. “We’ve exposed cells to this material, and they behave as if it’s not even there,” he said.

Rajachar remarked, “Now that we have a fully biocompatible material, this work is getting very exciting. It’s opening up so many avenues for potential applications.”

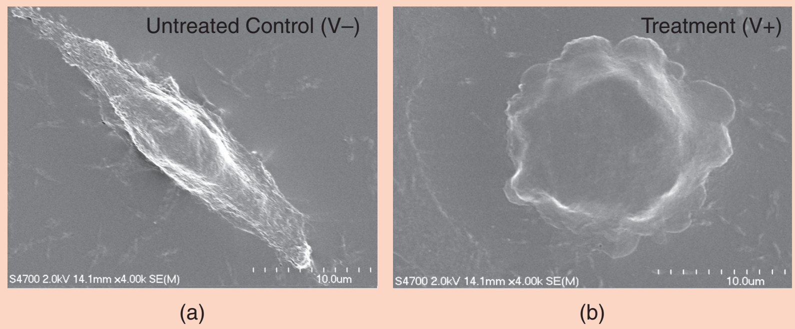

FIGURE 2 MTU biomedical engineers Rajachar and Ong are collaborating on a project to produce biocompatible materials. Their work focuses on the shape of cells and the fact that the lifespans of devices are often shortened by the formation of scar tissue. Normal cells are rounded, while cells in scar tissue are typically spread out, as shown in (a) the scanning electron microscope (SEM) image. With vibration loading, they found that the spread-out cells transform back into a round shape indicative of a normal cell, shown in (b). The rounded cells are also less adherent. (Images courtesy of Rupak Rajachar.)

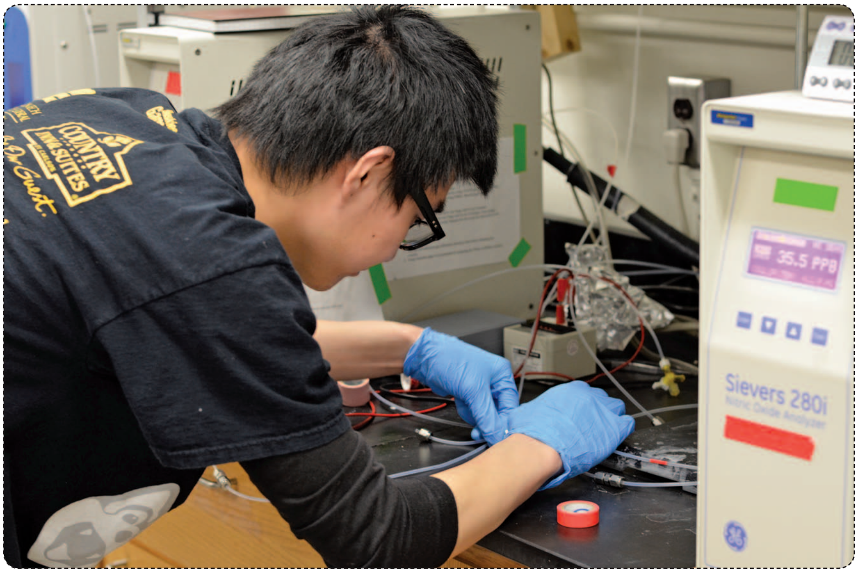

FIGURE 3 Ph.D. student Weilue He sets up an experiment in Frost’s laboratory at MTU. Frost’s group is exploring NO as a key to biocompatible materials because NO mediates many of the initial steps for the body’s response to foreign materials. (Photo courtesy of Megan Frost.)

Say NO to Biocompatibility

Another research group at MTU is developing biocompatible materials, but it is focusing on nitric oxide (NO).

“Prior to the mid-1980s, NO was known to be highly toxic, but it wasn’t until 1987 that it was identified as something that was produced in the body,” said Megan Frost, Ph.D., assistant professor of biomedical engineering at MTU. “It turns out your body makes it all over the place.” NO also happens to be a free-radical gas that mediates many of the initial steps for the biological response, including inflammation and thrombus formation, which occurs when materials come into contact with blood and tissue.

With that in mind, Frost and her research group are working on a method (Figure 3) to deliver NO at an appropriate dose and time to control the biological response and not only eliminate associated health risks to the patient but also prolong the functional lifespan of implanted devices.

One of the most important parts of their work involved learning new details about the amount of NO that cells actually produce in various physiological conditions (Figure 4), and they developed a unique method to do it. “Because NO is a free-radical gas, it’s very challenging to actually measure its production in an oxygenated solution like the human body,” Frost said. Their answer was to grow the cells on a gas-permeable membrane, and “rather than sampling NO *above* the

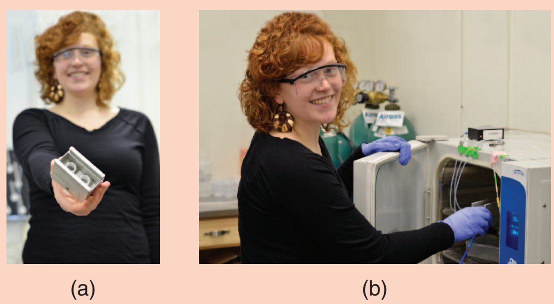

FIGURE 4 Frost and her research group developed a device, shown in (a), to deliver NO to in vitro cell cultures. (b) Here, undergraduate research assistant Genevieve Romanowicz sets up the device in an incubator. Through this work, they are gaining an understanding of how cells respond to different doses of NO. Romanowicz will begin studies toward dual Ph.D. and D.D.S. degrees at the University of Michigan in the fall. (Photos courtesy of Megan Frost.)

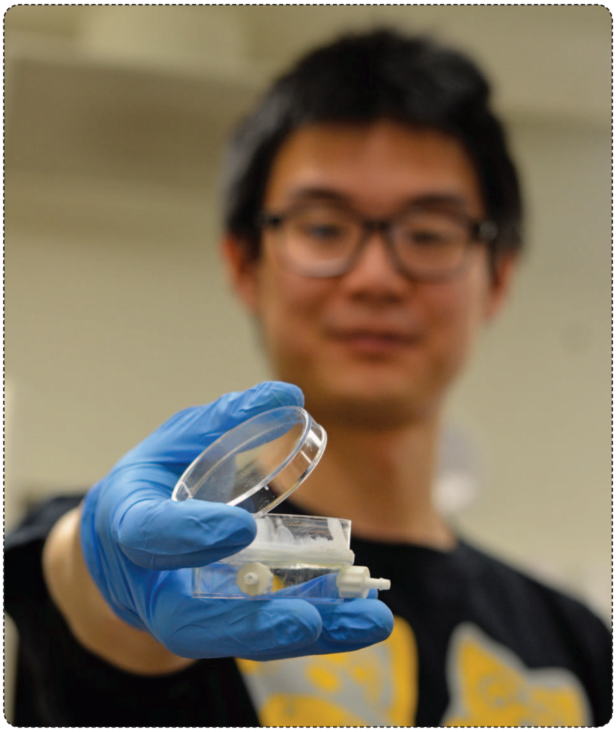

FIGURE 5 Frost's research group uses a unique method to gauge the amount of NO that cells produce in various physiological conditions. To do it, they grow the cells on a gas-permeable membrane and use a device (shown here) that they developed to measure NO below the cell culture. (Photo courtesy of Megan Frost.)

cells in the culture medium and in the solution phase, we send them to a chemiluminescence detector that samples *below* the cells in the gas phase where we can measure NO directly and in real time," she said (Figure 5). "Once we determine how much NO we want to release, we can design materials to release those precise amounts passively and without the need for a light source, such as through transmission of metal ions present in the body or through pH-mediated, proton-driven decomposition."

Frost's group has also developed a photosensitive polymer that can mimic the patterns of NO release that occur in a cell. "Our polymer contains an S-nitrosothiol, which is an NO donor, covalently linked to the backbone of a polydimethylsiloxane" [3], Frost said. "The more light we shine on the polymer, the more NO is released, so it provides a trigger to release an exact amount of NO."

They are testing the polymer with a device they designed to mediate biological response toward intravascular and subcutaneous biosensors. "Our goal is controlled release of NO, so that our device will still function once it's implanted in the body," she said. "The most common question we get is, 'How do you get light inside the body for an implanted device?'" One way is to coat optical fibers. They have shown that they can use a light-emitting diode to shine a light via a wireless circuit down the coated optical fiber and, thus, control the NO release very precisely. "For things like intravascular sensors, many of which are already optical sensors, you would just dedicate one fiber in the bundle of sensors to the release of NO," Frost said. The same would work for subcutaneous sensors.

Although they still have a considerable amount of work ahead of them, she remarked, "I think this approach has a lot of potential. We're just getting to the point where we're really starting to probe a number of interesting biological questions. Now that we have the tools to do this, we want to make them useful."

It Is Biocompatible, Too!

While biocompatibility is the goal for most medical material- and device-development projects, it was somewhat of an afterthought for a research group at North Carolina State University (NCSU), Raleigh. "I could offer you a revisionist history where we were actually trying to make a biocompatible material, but the reality is that we made an interesting observation and just pursued it," said Michael Dickey, Ph.D., assistant professor of chemical and biomolecular engineering at NCSU.

"With our work, we were trying to accomplish an entirely new type of memory device that would work on different principles and be made out of materials that were soft and water-based, and had other properties. It just so happens that these properties also make them biocompatible," Dickey said [4].

What makes the research so intriguing is that it combines two different fields that have been evolving on their own, said coinvestigator Orlin Velev, Ph.D., INVISTA Professor of Chemical and Biomolecular Engineering at NCSU. "One of these areas is in materials that are biomimetic, or that take inspiration from live tissue; and the other area is in circuits, which have traditionally been based on metals and semiconductors," he said. "The major difference in what we have done is that we have accomplished conduction that is based not on electrons as traditional semiconductor circuits are, but is based on ions" [5]. He noted, "Because ionic conduction is the basis of operation of the brain and of live tissue-based circuitry signaling, such an ionic current device could potentially bridge artificial and biological circuit and sensing systems."

The project started with a "strange observation" by two graduate students: Ju-Hee So from Dickey's laboratory and Hyung-Jun Koo from Velev's group. The two students, who happen to be husband and wife, noticed an oxide produced at the interface between a liquid metal (an alloy of gallium and indium metals) and a water-based gel, or hydrogel (Figure 6). "The oxide is kind of like a layer of rust that forms," Dickey said. "When the oxide is there, it's resistive between the metal and the gel, and when we apply a voltage, we can actually make that oxide go away so it becomes conductive."

From there, it was a natural progression. The students were able to figure out how to control the resistive and conductive conditions. These became the on and off states—the ones and zeros of binary language—for the memristor.

The resulting memristor is different from a typical computer memory device, Dickey said. "A computer memory device is rigid, brittle, two dimensional, and intolerant of moisture. Our device is soft and pliable and works extremely well in wet environments, like those found in the body. And since hydrogels are polymers that work almost like a sponge to absorb water, they're biocompatible because the body is also primarily made of water."

In addition, because the memristors are "soft and squishy," Dickey explained, they conform well to and make excellent contact with the surface of the skin, and he envisions them being used to pick up biomarkers in sweat or to measure pulse rate, blood pressure, or oxygen in the blood. "That information could then be transmitted wirelessly to your cell phone or computer, and by extension, potentially lower health-care costs," he said.

A new student working with Dickey and Velev within the framework of NCSU's National Science Foundation Nanosystems Engineering Research Center for Advanced Self-Powered Systems of Integrated Sensors and Technologies (ASSIST) is already using the technology to devise a replacement for standard electrocardiograph (EKG) probes. "The current EKG probes are based on conductive plastic, which is solid, irritates the skin, and requires technicians to rub the skin to remove the outer dry layer before placing the probes, so they can get a better contact," Velev said. Alternative probes made of conductive hydrogel would be hydrated and therefore much less foreign to the skin, and they would provide considerably better electrical contact with the skin, he said. Results have been successful so far.

While they readily describe their research as being at a beginning stage, both Dickey and Velev consider it as an early demonstration of principle and hope to inspire others to consider the possibilities it presents and perhaps help forge a new generation of biocompatible electronic devices. Velev remarked, "Ionic current devices show great potential as the next research frontier."

What's Next?

With the wide variety of research on materials, a new level of biocompatibility is emerging. Researchers, engineers, and medical professionals are beginning to push for materials that not only have no adverse effects on the patient but also are themselves nearly or completely unaffected by the body's response to foreign objects. Rather than implants that function only until the body walls them off with collagen or sufficiently degrades them, new materials and devices promise ever-increasing lifespans.

"We may not ever reach a point where the artificial materials that we put in the body perfectly integrate to become completely part of the natural tissue, but I think what we can do is bridge a gap," Frost said. "We need materials that can continue to function and that will allow the body to actually rebuild itself."

Ratner holds that complete integration of biomaterials and devices is indeed an attainable goal and thinks it will propel medical care forward. He remarked, "Think about all of the work that's being done on implanted electrodes alone. With current technology, the body deals with an electrode by putting a collagen scar around it, and that certainly impedes the electrical function of the electrode. If, on the other hand, you can get the electrode to heal into normal vascularized tissue without that wall, you would get far better electrical performance."

He added, "By using some of these new concepts, I think we will get longer-performing implants, whether they are electrodes, sensors, glaucoma drains, or breast implants. And I think these devices and materials, and many more, are going to have a huge impact on medicine."

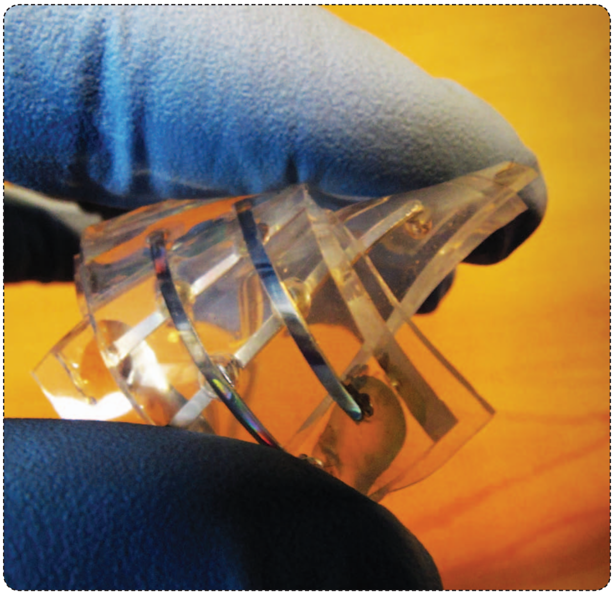

FIGURE 6 Building on an observation made by students in the laboratories of Dickey and Velev, the researchers at NCSU have developed a new type of biocompatible memory device—a memory resistor, or memristor. Composed of water-based gel, or hydrogel, and liquid metal, the soft and squishy device accomplishes conduction based not on electrons, as traditional semiconductor circuits, but on ions. (Image courtesy of NCSU.)

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