# Researcher pursues synthetic scaffolds for muscle regeneration

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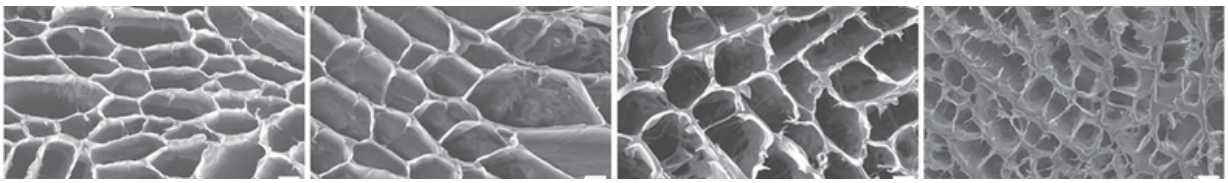

A microscopic view of porous chitosan scaffolds, visualized using a scanning electron microscope. From left to right, each scaffold was constructed with an increasing density of chitosan. Credit: Miqin Zhang

The word "engineering" can bring to mind images of bridges, spacecraft and even particle colliders. But the human body could use assistance from engineers as well, especially when the natural processes that shape and govern our cells, tissues or organs need a helping hand.

Miqin Zhang, a professor of materials science and engineering at the University of Washington, is looking for ways to help the body heal itself when injury, disease or surgery cause large-scale damage to one type of tissue in particular: skeletal muscle. Muscles have a limited ability to regenerate, repair and realign themselves properly after certain types of damage.

Zhang and her team are taking a synthetic approach to muscle regeneration. Their goal is to create a synthetic, porous, biologically

compatible "scaffold" that mimics the normal extracellular environment of skeletal muscle—onto which human cells could migrate and grow new replacement fibers.

As she recently showed in a review article published online Nov. 16 in *Advanced Materials*, this endeavor builds on decades of work into the growth, repair and behavior of normal skeletal muscle, but also relies on keen knowledge of engineering and materials science. Zhang sat down with UW Today to explain the project's goals and progress to date.

## What drew you to work on tissue engineering?

I suppose it's easier to say first where I didn't come from in choosing to work on this problem: I'm not a biologist. I'm an engineer. That is my training and that is how I like to work—building things up one at a time to solve problems.

And a lot of the problems I like to work on are in biology or medicine, but I come at them from an engineering standpoint. So engineering solutions for these biological "problems"—like finding effective treatments for cancer or creating scaffolds for cell growth—means assembling components that are compatible with our bodies, which our cells can respond to.

For tissue engineering and repair, we've been focusing lately on skeletal muscle. There's really a medical need for platforms or scaffolds for muscle fiber regeneration, since after injury the body's abilities to repair skeletal muscle are really quite limited.

## How so?

Skeletal muscle makes up a large part of the human body—40 to 50

percent by weight. And when damage occurs to skeletal muscle on a small scale, we've seen that skeletal muscle possesses innate repair mechanisms. Through these mechanisms, a new fiber can grow, for example, essentially repairing or replacing the damaged one.

But above a critical threshold of damage to skeletal muscle, our bodies no longer employ those effective repair mechanisms. Instead, the body forms scar tissue at the wound site—and then you've essentially lost control of that muscle function. You can't get it back. Surgically, you could graft in skeletal muscle. But that depends on the availability of donor tissue.

So we know that the body can repair skeletal muscle. It just doesn't do so beyond a certain threshold of damage.

## What do you envision as a solution to the problem of scar tissue formation?

Natural skeletal muscle is surrounded by a complex extracellular matrix that supports muscle fibers as they form and grow in the body. What we would like to do in this field, which many researchers are working on, is to create an artificial extracellular matrix into which we could introduce a progenitor type of cell—like stem cells or muscle progenitor cells—and then provide them with the proper signals to differentiate into muscle fibers. We believe that scaffold and signals are what is needed to grow new muscle fibers, which you could then transplant to the site of damage.

## What types of materials are these scaffolds made of?

In general, with designing scaffolds for cell growth, the material we work with really depends on the type of cell we'd like to introduce into

the scaffold to proliferate. For bone tissue regeneration, which we've worked on in the past, we created a scaffold made of chitosan—a complex polysaccharide, essentially long chains of sugar-like molecules—combined with other materials to create a calcified scaffold.

For skeletal muscle, we and other researchers work with a variety of anisotropic materials.

## What are anisotropic materials?

These are materials with physical properties that differ based on direction or orientation. They form the basis of the scaffolds and are usually complex polymer materials. The innate "directionality" of anisotropic materials helps the progenitor cells grow into three-dimensional forms like a myotube, which is a precursor to a muscle fiber.

But there are structural challenges to overcome. The scaffold must be micropatterned to promote cell migration, growth and proliferation in the right direction. This involves nanoscale design details, and some polymers are better for this than others. The production of highly aligned nanofibers in a large area remains a great challenge.

We have developed several methods to produce nanofibers made of natural polymers with a high degree of alignment and uniformity over large areas. In addition, we often coat the scaffold with biomolecules that help the cells stick to the scaffold and provide them with the right signals to grow and differentiate.

## What types of biomolecules provide these signals?

There are adhesion proteins, growth factors and transcription factors that

deliver specific messages to cells depending on their structure and location in the scaffold. We have used growth factors in combination of anisotropic materials to successfully induce high-level and rapid differentiation of human embryonic cells into muscle cells. As I said before, I approach this project from an engineering perspective. But the knowledge basis we use comes from cell biology and physiology—because in the end, we're trying to get cells to grow, differentiate and form tissues on a large scale.

## Are there other uses for these scaffolds beyond tissue regeneration?

Of course! In my lab, we have also used them to study certain cancer cells, such as stem cell-like cells in glioblastoma. By changing what we make the scaffolds out of, the protein messages we coat them with or the nanopore structures within the scaffolds, we can reveal many different properties of cells. We can also test the types of external signals, be it a structural feature of the scaffold or a protein message, that can promote or inhibit cell growth. And those are just the sorts of information we need to understand to create effective cancer cell treatments.

It uses the same principle—using nanoscale scaffolding polymers—but to find better ways of doing the opposite: inhibit cell growth rather than promote it. That really demonstrates the utility of these technologies. And we're at the right time to combine biological and engineering approaches to make it happen.

**More information:** Soumen Jana et al. Anisotropic Materials for Skeletal-Muscle-Tissue Engineering, *Advanced Materials* (2016). DOI: 10.1002/adma.201600240