Injectable 'bone spackling': A cell therapy approach to heal complex fractures

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Nick Schott, BME graduate student research assistant, develops injectable cell clusters that create microclimates accelerating bone regeneration. Credit: Robert Coelius/Michigan Engineering

Large, complex bone wounds are hard for doctors and patients alike to contend with. They often require grafts and multiple surgeries.

Jan Stegemann, a University of Michigan professor of biomedical engineering, is reprogramming adult cells from bone marrow so that they can be injected directly into a wound and grow into bone. The marrow-derived cells are known as progenitor cells, a type of adult stem cell that maintains the ability to differentiate into several different cell types.

Testing in mice has shown that a cell-based therapy created at U-M can drastically accelerate the bone regeneration process after injury.

His research team's latest work, "Injectable osteogenic microtissues containing mesenchymal stromal cells conformally fill and repair critical-size defects," is published in the journal *Biomaterials*.

For minor breaks and fractures, bones typically mend themselves over time. What kinds of bone problems are you targeting?

We're targeting large, complex defects—where a lot of bone has been lost and the tissue around the bone has been damaged. These wounds don't always heal, and they can be highly debilitating. Sometimes the muscle and surrounding blood vessels have been disturbed. There are treatments to stabilize the bone and even fillers you can put in to try to help the bone regenerate, but these options are not suitable in all cases and current treatments are not ideal—they don't work for some of the most serious cases.

For a larger defect, the only option right now is to take bone from another part of the patient's body—for example, a hip or part of another bone—crush it up and put it into the large defect to help that bone regenerate. But, of course, that is not a great option because you have to do a second surgery and take bone from one place and then put it back in to heal another place.

What's your approach?

The only thing that can create or regenerate living tissue, and therefore living bone, is a cell. So to heal a wound, you can try to recruit cells from elsewhere in the body to go to the damaged site and regenerate bone. That's one approach.

In our case, we're being much more direct. We are using progenitor cells that have been taken from the patient, grown outside the body, and stimulated to be very effective at creating bone tissue. We use these cells like a therapeutic drug and deliver them directly to where they need to be. Our approach is designed so that when we transplant the cells, they are more likely to survive and regenerate bone where it is needed.

How do you do it?

The cells that we use are a type of adult progenitor cells, meaning they can form a variety of tissue types. They can be derived from the bone marrow or other tissues. You can even get them from liposuctioned fat. You can isolate those cells and then expand their number until you have many multiples of the initial number of cells that you took from the body. You can also treat them so that they form the type of tissue you are interested in.

In our case, we treat them with specific biological factors in order to help them differentiate into bone cells. We also use carefully selected biomaterials, materials that cells recognize and can bind to. Through this binding, these materials also give the progenitor cells specific cues to form bone. Therefore, by combining the biological stimulation with the appropriate physical environment, we are able to get the cells to really potently regenerate new tissue.

Once you have the cells ready to go, how do you deliver them?

We inject the cells into the wound. But if you inject naked cells into that environment, they will not be able to survive. A large bone wound doesn't have much blood supply, there's a lot of inflammation, and there's really no healing going on. It is likely that the injected cells will die or migrate away before they have a chance to actually function and regenerate the tissue.

To solve this problem, we created what we call microtissues, which are designed to promote the survival and function of the cells when they're transplanted into the body. Essentially, these are small protein beads, with tens to hundreds of cells trapped inside each one. We can make millions of these microtissues in a single batch and design them to provide the physical and biochemical cues that allow the cells to survive and function after they are transplanted.

With the cells inside these microtissues, we can inject them into the body through a needle as a paste or a slurry, directly into the damaged bone. In some ways this is analogous to the spackling compound that can be used to repair damage to drywall in homes. This delivery method means that, in some instances, there's no need to do an invasive surgery and open the wound site in order to deliver the therapeutic cells.

At this stage, you're working with mice. What sort of results are you seeing?

The work that we've accomplished so far has shown very clearly that our biomaterials-based approach has a lot of merit. We are able to consistently control cell function and cell phenotype to regenerate tissue types that we're interested in—most specifically bone right now.

We've shown that the idea of creating these little microtissues, culturing them outside the body and priming them to regenerate bone before we transplant, has merit as well. And we've validated that the culturing process, and delivering them in conjunction with a biomaterial, very significantly increases the amount of bone that you can regenerate.

Do you see any other potential uses for this approach?

We consider the microtissues we have developed to be a platform technology that could also be applied to other types of tissue regeneration. An example is Type I diabetes because it's a disease where a certain cell type dies, and if you could just get that cell population back, you regain essentially all of the function needed to be healthy. We don't currently focus on diabetes, but a properly designed cell-based therapy has a lot of potential in this kind of situation.

So in any case where you want to deliver cells back to the body to recreate or regenerate a certain function, and it's a function that we know is performed by cells, we might be able to use this approach.

More information: Ramkumar T. Annamalai et al. Injectable osteogenic microtissues containing mesenchymal stromal cells conformally fill and repair critical-size defects, *Biomaterials* (2019). DOI: 10.1016/j.biomaterials.2019.04.001

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