# Researchers develop a gel for growing large quantities of neural stem cells

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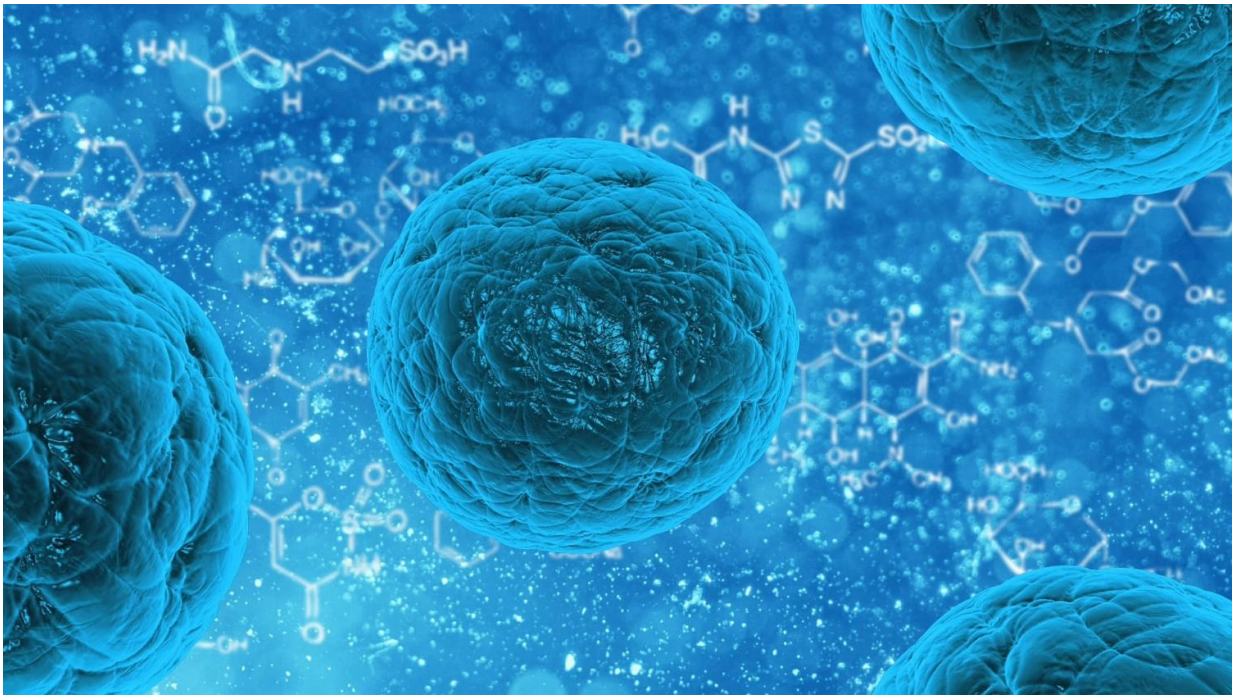

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In many ways, stem cells are the divas of the biological world. On the one hand, these natural shapeshifters can transform themselves into virtually any type of cell in the body. In that regard, they hold the promise of being able to cure ills ranging from spinal cord injuries to cancers.

On the other hand, said associate professor of materials science and engineering Sarah Heilshorn, stem cells, like divas, are also mercurial and difficult to work with.

"We just don't know how to efficiently and effectively grow massive numbers of stem cells and keep them in their regenerative state," Heilshorn said. "This has prevented us from making more progress in creating therapies."

Until now, that is. In a recent paper in *Nature Materials*, Heilshorn described a solution to the dual challenges of growing and preserving neural stem cells in a state where they are still able to mature into many different cell types. The first challenge is that growing stem cells in quantity requires space. Like traditional farming, it is a two-dimensional affair. If you want more wheat, corn or stem cells, you need more surface area. Culturing stem cells, therefore, requires a lot of relatively expensive laboratory real estate, not to mention the energy and nutrients necessary to pull it all off.

The second challenge is that once they've divided many times in a lab dish, stem cells do not easily remain in the ideal state of readiness to become other types of cells. Researchers refer to this quality as "stemness." Heilshorn found that for the neural stem cells she was working with, maintaining the cells' stemness requires the cells to be touching.

Heilshorn's team was working with a particular type of stem cell that matures into neurons and other cells of the nervous system. These types of cells, if produced in sufficient quantities, could generate therapies to repair spinal cord injuries, counteract traumatic brain injury or cure some of the most severe degenerative disorders of the nervous system, like Parkinson's and Huntington's diseases.

## Seeking stemness

Heilshorn's solution involves the use of better materials in which to grow stem cells. Her lab has developed new polymer-based gels that allow the cells to be grown in three dimensions instead of two. This new 3-D process takes up less than 1 percent of the lab space required by current stem cell culturing techniques. And because cells are so tiny, the 3-D gel stack is just a single millimeter tall, roughly the thickness of a dime.

"For a 3-D culture, we need only a 4-inch-by-4-inch plot of lab space, or about 16 square inches. A 2-D culture requires a plot four feet by four feet, or about 16 square feet," more than 100-times the space, according to first author Chris Madl, a recent doctoral graduate in bioengineering from Heilshorn's lab

In addition to the dramatic savings of lab space, the new process demands fewer nutrients and less energy, as well.

The gels the team developed allow the stem cells to remodel the long molecules and maintain physical contact with one another to preserve critical communication channels between cells.

"The simple act of touching is key to communication between stem cells and to maintaining stemness. If stem cells can't remodel the gels, they can't touch one another," Madl explained.

"The stem cells don't exactly die if they can't touch, but they lose that ability to regenerate that we really need for therapeutic success," Heilshorn added.

## Striking results

This need for neural stem cell to remodel their environment differs from what Heilshorn has found in working with other types of stem cells. For those cells, it is the stiffness of the gels – not the ability to remodel – that is the key factor in maintaining stemness. It is as if for these other types of stem cells, gels must mimic the rigidity of the tissue in which the cells will eventually be transplanted. Not so with neural progenitors, said Heilshorn.

"Neural cell stemness is not sensitive to stiffness and that was a big surprise to us," she said.

The result was so striking and unexpected that Heilshorn, at first, didn't believe her own results. The lab ended up testing three entirely different gels to see if their conclusion held, an unusual supplementary step in this kind of research. With each new material, they saw that those that could be remodeled produced quality stem cells; those that could not be remodeled had a negative effect on stemness.

Next up on Heilshorn's research agenda is to create gels that can be injected directly from the lab dish into the body. The possibilities have her feeling optimistic about stem cell therapies again. For a time, she said, it felt as if the field had hit a wall, as initial excitement for regeneration gave way to uninspiring results in the clinic. With her new finding, she said, it feels like new things may be just around the corner.

"There's this convergence of biological knowledge and engineering principles in stem cell research that has me hopeful we might finally actually solve some big problems," she said.

**More information:** Christopher M. Madl et al. Maintenance of neural progenitor cell stemness in 3D hydrogels requires matrix remodelling, *Nature Materials* (2017). DOI: 10.1038/nmat5020

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