New approach moves cell therapy closer to treating many disorders

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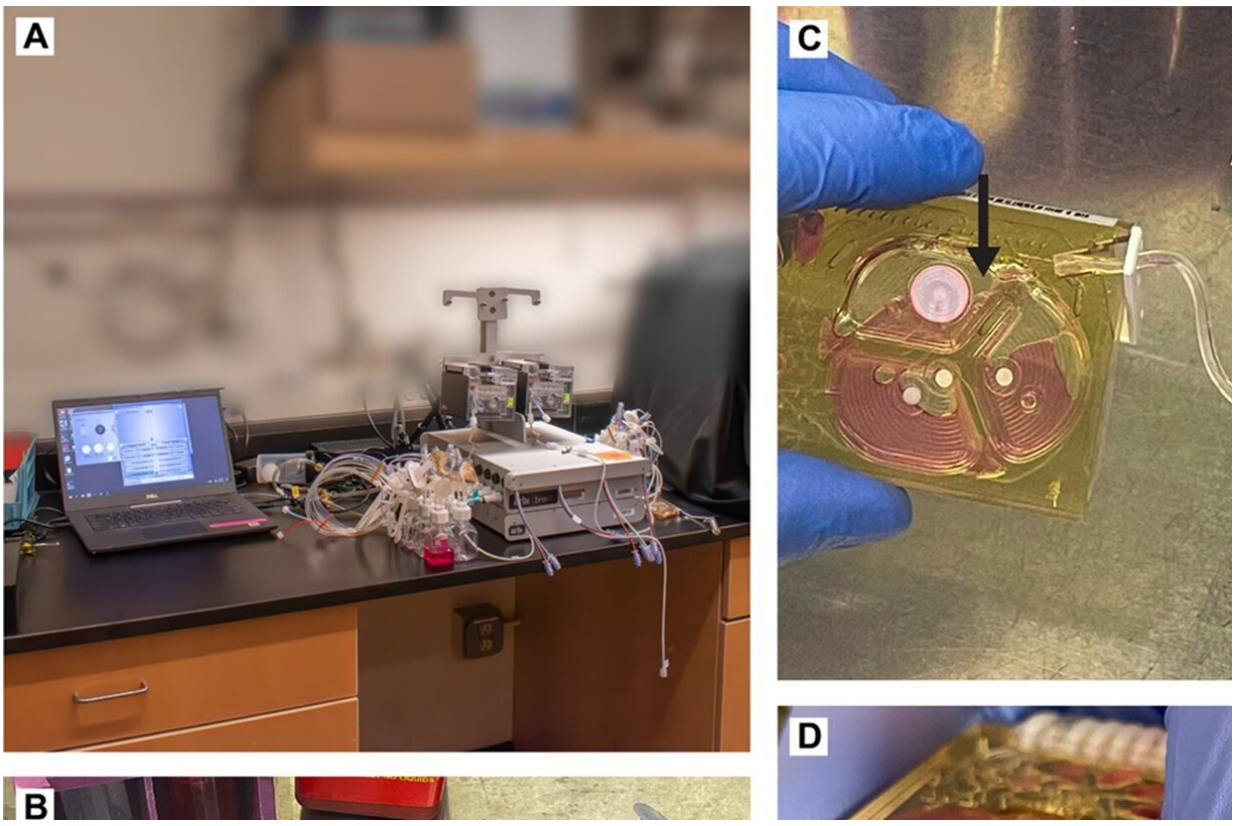

Microcarrier-microbioreactor setup and protocol. Credit: *Journal of Translational Medicine* (2024). DOI: 10.1186/s12967-024-05373-7

A new approach to manufacturing cells that secrete and deliver therapies to specific parts of the body has taken a big step toward one day

repairing joints and damage after heart attacks, countering transplant rejection and healing currently untreatable lung conditions.

The cells, called mesenchymal stromal cells, can differentiate, like stem cells, to become connective tissue cells of cartilage, bone, fat and many organs. They can also be made to secrete mRNA drugs naturally produced by cells to induce repair and then deliver that payload to needed areas using a honing mechanism similar to immune cells.

While such cell therapies hold the promise to revolutionize treatment for many disorders, the research faces technology bottlenecks. Scientists have not completely understood the cell properties that are required to safely and effectively treat a condition, and developing a method for reliably increasing cell numbers during manufacturing has been challenging.

Now, a study published in the *Journal of Translational Medicine* describes a system designed and tested at Cornell and the Massachusetts Institute of Technology that addresses these challenges.

"We haven't known how to increase cell numbers without changing the attributes of the cells unintentionally, and then, we need to understand what those attributes are supposed to be in the first place," said Krystyn Van Vliet, vice president for research and innovation and professor of materials science in the Meinig School of Biomedical Engineering in Cornell Engineering and the paper's senior author.

"Both of these problems are related; you need to measure what's important, and then you need to maintain that measurement while you're trying to increase the cells up to a good dosage," she said.

The researchers, including the paper's first author Brandon Krupczak, a doctoral student in Van Vliet's lab, designed a "microcarrier-

microbioreactor" platform that allowed them to control many variables—cell signaling characteristics, pH, temperature, gases—and create a consistent high quality environment for the cells. Early results suggest that this approach may prime those cells to make more of the therapeutic proteins for treating conditions.

"We think that this microcarrier-microbioreactor approach does a much better job than the conventional gold standard, maintaining very tight control and regulatory conditions during the manufacturing process," Krupczak said.

In the study, the researchers developed a microcarrier—a supportive structure constructed from a dissolvable gelatin that allows the mesenchymal stromal cells to anchor and grow. These were placed within a company-made microbioreactor that contains milliliter-sized containers for culture that the researchers had to modify for their purposes. The entire cell-growing apparatus is the size of a smartphone.

The study itself is a proof-of-principle for creating mesenchymal stromal cells that could potentially treat acute respiratory distress syndrome, a disorder that leads to runaway inflammation in the lungs and is the main cause of death from COVID.

Using the microcarrier-microbioreactor platform, the team grew stromal cells from three different donors, respectively, and then repeated the experiment three times for cells from the same donor. They took multiple steps to make sure their data was legitimate and repeatable from one donor to another and for a single donor. They compared their results against the currently used flask technique, using tissue culture polystyrene flasks with culture media to grow cells, which served as an experimental control.

For context, Kupczak said, when gene expression from cells in the

experimental condition is three to five times higher than the control, results are generally considered a success.

"In some cases for this paper, we had results that were up to 400-fold higher in our experimental condition as compared to the flask control, which would indicate that there's 400 times as much of our therapeutic particle floating around in our experimental condition as in the flask control," he said.

By making the environment more consistent through the microcarrier-microbioreactor process, and measuring those variables, they found the method provided high quality control and primed the cells to start making more of the proteins that correlated with treating acute respiratory distress syndrome, though they didn't test their effects in a mouse or human.

The study paves the way for using the novel manufacturing process and quality controls to move cell therapy production further along toward applying it in a clinic, the authors said.

Camille Farruggio, a materials scientist at MIT, is a co-author.

More information: Brandon Krupczak et al, Manufacturing mesenchymal stromal cells in a microcarrier-microbioreactor platform can enhance cell yield and quality attributes: case study for acute respiratory distress syndrome, *Journal of Translational Medicine* (2024). DOI: 10.1186/s12967-024-05373-7

Provided by Cornell University

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