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With New Patent, Cesca Eyes Faster, Less Costly CAR-T Cell Production

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Chimeric antigen receptor T-cell receptor (CAR-T) and CAR-modified natural killer (CAR-NK) therapeutics can be produced faster and at less cost, Cesca Therapeutics says, through the cellular processing technology covered by a recently awarded patent.

Cesca Therapeutics' new cellular processing technology uses microbubbles to separate cells. Mutlu Kurtbas/Getty Images

Cesca said Friday, July 28, 2017 that U.S. Patent No. 9,695,394, titled "Cell Separation Devices, Systems, and Methods," has been awarded to SynGen—whose cell processing assets were acquired earlier this month by Cesca's 80%-owned device subsidiary ThermoGenesis. The patented technology relates to automated isolation of rare stem, progenitor, or immune cell populations from blood, bone marrow, leukapheresis product, and other sources, while maintaining the viability of the cells under aseptic conditions.

The patented technology has been incorporated into Cesca's proprietary CAR-TXpress™ platform, designed to integrate multi-component automation steps that include T-cell isolation, purification, culture expansion, and washing, as well as single cassette-based automated -196°C cryopreservation and retrieval.

Cesca says its automated cell-processing system provides greater cell yields and higher consistency in a fraction of the time compared with traditional manual cell-processing methods. Processing time is reduced, the company says, since the technology works in bulk volumes of cells, unlike conventional cell-isolation technologies that work on narrow streams of slowly moving suspended cells.

"The benefits in total CAR-T and CAR-NK manufacturing time are gained through higher yield of cells during separation, thus reducing the time required to expand cells to the target cell dose," Jon Ellis, senior director of technical services with ThermoGenesis, told GEN. "This reduces time from collection of starting material to administration of therapy, expansion medium, and cytokine costs."

Additionally, Ellis said, fewer expansions during manufacturing may improve the therapeutic effect due to higher proliferative capacity at the time of administration to the patient.

"There are also time savings throughout the process due to introduction of more efficient and automated processes," Ellis added. "For example, the total time to isolate specific cell populations from blood products is approximately 2 hours, which is between 4 and 8 hours faster than FACS/MACS platforms."

Integrating Cell Separation and BACS

The patent covers a device and methodology for integrating automated cellular separation and buoyancy-activated cell sorting (BACS) processes.

BACS uses microscopic bubbles to isolate a specific cell type from a complex mixture of cells, such as blood. The microbubbles bear antibodies on their surface, enabling them to bind specifically to a single desired target cell type.

When coated with microbubbles, the target cells float to the top of the

host liquid, while non-target cells sink to the bottom—a process that can be accelerated by centrifugation.

The floating target cell layer can subsequently be collected, and the cells released from their microbubbles, offering a highly-purified preparation of the target cells with high efficiency of cell recovery while retaining cell viability.

The patent also allows for the automated isolation of cells with low density surface antigens, a long-time challenge in cellular manufacturing.

Cesca won't discuss composition specifics of the microbubbles. The patent says the "gas-filled bubbles" are one of numerous "embodiments" or implementations of the methods of the invention, along with hollow polymers, glass beads, microporous beads with entrained gas, droplets of an immiscible liquid, gold nanoparticles, and silver nanoparticles.

Addressing Cell-Processing Problems

Cesca says its cell separation addresses problems that have arisen with density-gradient methods and fluorescence- and magnetic-activated cell sorting (FACS/MACS), such as lack of specificity, high cell loss, use of labels, and high capital/operating cost.

These problems were spotlighted in May by Michael P. Hughes, Ph.D., of University of Surrey, and colleagues, in a paper presenting a different cell-separation method, which uses dielectrophoresis (DEP) to sort cells electrostatically, using 3D electrodes on a low-cost disposable chip. The method offers orders of magnitude of improvement compared to FACS/MACS in throughput, efficiency, purity, recovery, cell losses, and cost, the researchers concluded in PNAS.

Ellis said the technology incorporated into CAR-TXpress does not suffer the throughput, cell loss or specificity issues as FACS/MACS platforms when isolating specific cell populations, as buoyancy is a much more constant force that can be applied over a much larger surface area.

"State-of-the-art IR optical sensing coupled with an innovative polycarbonate processing cartridge enables bulk depletion of unwanted red blood cell, platelet and granulocyte populations for the isolation of mononuclear cells," Ellis said.

As a result, according to Cesca, the technology is poised to revolutionize CAR-T cell manufacturing. Ellis says the company is in discussions with several CAR-T therapy developers, though to date no collaborations have been announced.

The technology has applications beyond CAR-T cell production, however. According to the patent, any of numerous cells can be separated via CAR-TXpress—including CD3+ cells, CD4+ cells, CD235a, CD14+, CD19+, CD56+, CD34+, CD117+, KDR+, SIRPA+, ASGR1+, OCLN+, GLUT2+, SLC6A1+, TRA-1-60–, SSEA4–, AP– (alkaline phosphatase), SSEA3–, TDGF1–, or CD349– cells.

"CAR-TXpress can be used to isolate a range of cell targets through positive and/or negative selection. The focus to date has been on cell populations used in immunotherapy, but it is likely the platform could be optimized for other applications," Ellis said. GEN