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Automated Closed-Cell Production Platform for Mesenchymal Stromal Cells (MSC)-Based Therapy

Yirui Feng[1,2], Bin Wang[1]*

[1]Clinical Stem Cell Centre, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

[2]Department of Life Science, Nanjing University, Nanjing, China

Commentary

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***For Correspondence:**

Bin Wang, Clinical Stem Cell Center, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210000, China

E-mail: wangbin022800@126.com

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DESCRIPTION

Mesenchymal Stromal Cells (MSCs), which are proven for their therapeutic biological activity, are widely applied as a cellular drug to treat various illnesses. Before broad clinical application, MSCs derived from patients or donors need to be extensively expanded on a large scale. However, conventional planar cell culture systems require multiple manual processes, which impede large-scale industrial production and batch-to-batch quality stability.

Mesenchymal Stem/Stromal Cell (MSC) proliferation on a big scale and efficiently has long been a difficult problem for researchers in cell-based therapeutics and regenerative medicine. We creatively created an Automated Closed Industrial Scale Cell Production (ACISCP) platform based on GMP-grade microcarrier for the culture of Umbilical Cord-Mesenchymal Stem/Stromal Cells (UCMSCs), in accordance with the criteria of stem cell banks, to address the major shortcomings of the 2D planar culturing system. The ACISCP system is a completely closed system that uses various vivaSPIN bioreactor models from CytoNiche Biotech in China for scaling up cell culture as well as vivaPREP from the same company for automating cell harvesting and cell dose preparation.

A team led by Yanan Du has developed an automated closed industrial-scale cell production (ACISCP) platform with GMP-grade 3D TableTrix® microcarriers, which allows the suspension culture of industrial-scale clinical-grade MSCs [1]. The 3D TableTrix® is a dissolvable porous microcarrier, approved as a pharmaceutical excipient by the Centre for Drug Evaluation (CDE, China) and the Food and Drug Administration (FDA, USA), that permits cells to attach to the inner wall of its open pores,

mimicking the microenvironment *in vivo*. This technology avoids the use of trypsin or TrypLE to digest MSCs from the culture substrates, which can damage cell viability and quality [2,3].

The microcarrier can rapidly dissolve within 1 hour using a special reagent, 3D FloTrix Digest, thereby facilitating the harvesting of MSCs. MSCs were expanded in a three-stage process using 1, 5 and 15 L vivaSPIN bioreactors, respectively. After inoculating 1.5 × 10^7 MSCs and 0.6 g 3D TableTrix into a 1 L vivaSPIN bioreactor, the cells expanded in the 5 L and 15 L bioreactors, yielding 2.09 × 10^{10} cells in two 15 L bioreactors with a cumulative 1975-fold expansion achieved within 13 days. Notably, the ACISCP platform enabled the automatic harvesting of MSCs by enzymatic digestion of 3D TableTrix, avoiding the manual digestion of MSCs.

The large-scale amplified MSCs maintained a high viability of 95%-100% and exhibited similar critical quality attributes in safety, purity, identity, chromosome stability, and immunoregulatory potency, as compared to the MSCs cultured under conventional two-dimensional conditions. The MSCs produced using the ACISCP platform are capable of meeting current quality standards of therapeutic cell products, while possessing numerous benefits over conventional two-dimensional culture models.

The ACISCP cell manufacturing system is a fully enclosed automated industrial scale cell production platform with great potential to enhance process efficacy, reduce associated costs and ensure reproducibility and product uniformity. This system is a promising tool to minimize the limitations of monolayer culture and can enable the automated industrial-scale production of clinical-grade MSCs in one batch to meet the needs of a large number of patients. The system could also provide large-scale industrial solutions for other types of adherent cells and/or their derivatives, such as vesicles or exosomes.

To comply with drug manufacturing regulations, the ACISCP system should also be compliant with Good Manufacturing Practice (GMP), despite the 3D TableTrix micro carriers being GMP-grade. Thus, further efforts are needed to ensure the device manufacturing compliance of the ACISCP system and transition from academic research to commercialized products. This way, large-scale industrial production of clinical-grade MSCs can facilitate the steady development of stem cell-based therapies in the clinic.

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