Proceedings of ICMMGH 2026 Symposium: Biomedical Imaging and AI Applications in Neurorehabilitation
DOI: 10.54254/2753-8818/2026.AU29757

Microcarrier-Based Bioprocess Engineering for Scalable Stem Cell Expansion: From Material Design to Clinical Translation

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Abstract. Regenerative medicine relies on the efficiency of large-scale expansion of stem cells and, even though conventional 2D systems cannot scale or provide quality control. Microcarrier-based bioprocessing provides scalable, controlled scaffold on the growth of adherent stem cells. This review presents the developments on the microcarrier materials and surface modification and structural design on MSCs, hESCs and iPSCs. Microfluidics and biodegradable hydrogels are some of the important methods of fabrications that enhance regulation of sizes, porosity, and biodegradation. The parameters of bioprocesses such as agitation, bead-to-bead transfer, and the design of the reactor are optimized, which allow expansion in a reproducible, GMP-compatible format. Lastly, the new smart microcarriers and data-driven control systems unveil the directions of standardized and cost-effective production of stem cells in the future.

Keywords: microcarriers, stem cell expansion, bioprocess engineering, scalable manufacturing, regenerative medicine

1. Introduction

Stem cells, including MSCs, hESCs, and iPSCs, are widely used inregenerative medicine due to their self-renewal and multi-lineage differentiation capacities [1, 2]. MSCs show strong immunomodulatory functions, while hESCs and iPSCs offer virtually unlimited expansion.

To translate these cells to clinical use, large volumes are necessary and, in most cases, hundreds of millions per dose, but quality and function [3]. Conventional 2D cultures are both inefficient and manpower intensive and open to variation [4].

Scalable and controlled systems of stem cell expansion through microcarrier- based culture systems may be coupled with bioreactors. The systems provide large surface-to-volume ratio and have the ability to achieve GMP standards [5]. Recent sources reveal their applicability in various stem cells. GelMA microcarriers are helpful in the growth of iPSC-derived MSCs [6], whereas HA-derived carriers are useful in the growth of ESC-derived MSCs without the use of serum [7].

This review examines achievements in microcarriers material, surface design, and structural optimization, fabrication and bioprocess methods of stem cell fabrication. It further indicates future trends in clinical translation.

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2. Microcarrier design for stem cell expansion

The performance of microcarrier systems depends on an integrated design that combines material choice, surface chemistry, and structural properties. These features influence cell adhesion, proliferation, differentiation, and harvestability.

2.1. Materials

Natural polymers such as gelatin and hyaluronic acid (HA) are widely used due to their biocompatibility and ECM-like properties. GelMA carriers have enabled scalable expansion of iPSC-derived MSCs, while HA-based systems support serum-free culture of hESC-derived MSCs [6, 7].

Synthetic polymers like polystyrene, PEG, and PLGA offer precise control over stiffness and degradation. Cytodex, a polystyrene-based microcarrier, remains a standard for MSC expansion [5]. Smart polymers such as PNIPAAm allow enzyme-free harvesting through temperature-sensitive hydrophilicity changes. Hybrid materials combining synthetic and natural components—for example, collagen–PEG composites—are also under investigation to balance structural support with biological signaling.

2.2. Surface functionalization

The microcarrier surface governs direct interactions with stem cells. Functionalization strategies, especially for synthetic carriers, are essential to enhance cell adhesion and preserve stemness. Coating with ECM proteins or RGD peptides improves integrin binding and supports proliferation. Surface charge also affects adhesion, with positively charged coatings like poly-D-lysine enhancing MSC spreading [5].

Stimuli-responsive surfaces are gaining attention. PNIPAAm-based coatings enable enzyme-free harvesting by shifting hydrophilicity with temperature. Other approaches include grafting growth factor–binding motifs or nanostructures to mimic native niches.

2.3. Structural optimization

Carrier architecture influences diffusion of surfaces and nutrients. Porous microcarriers have better surface-volume ratio and allow cell-cell interactions to advance MSC yield and differentiation [7]. Focal adhesion and mechanotransduction signaling is also enhanced by roughness of the micro or nanoscale. Harvesting of enzyme-free cells can be performed with degradable carriers like hydrogel-based systems and maintaining cell activity [7]. All of these characteristics aid in the formation of favorable microenvironments of stem cell growth and maintenance of therapeutic quality.

3. Fabrication methods

Microcarriers can be fabricated through methods such as solvent evaporation, emulsion, or microfluidics, allowing control over size, porosity, and surface features—key factors for stem cell adhesion and growth. Traditional approaches produce uniform particles from polystyrene or gelatin, while microfluidic technologies offer precise control and enable integration of bioactive agents.

For example, VEGF-loaded microcarriers with BMP-2-functionalized polydopamine coatings have been developed using microfluidics to enhance stem cell behavior. (Fig. 1) [4].

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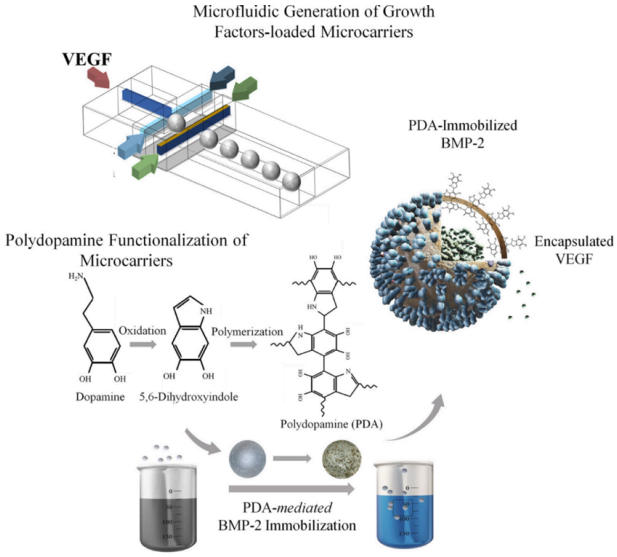


Figure 1. Microfluidic fabrication of growth factor–loaded microcarriers with polydopamine (PDA) surface functionalization [4]

Agitation rate in bioreactors is also critical: optimized stirring maintains suspension and minimizes shear damage, while improper rates lead to aggregation or detachment [8].

4. Bioprocess engineering and parameters

Scalable stem cell expansion requires optimizing agitation, bead-to-bead transfer, and bioreactor configuration. Stirring must maintain microcarrier suspension and minimize shear—too much causes detachment, while too little leads to aggregation and uneven growth. Dynamic control of stirring stages improves expansion efficiency and phenotype retention [8].

Bead-to-bead transfer enables cells to migrate to fresh carriers without enzymes, increasing yield and maintaining homogeneity [5].

Stirred-tank bioreactors are commonly used, while perfusion or wave systems offer low-shear alternatives for sensitive cell types. Monitoring oxygen, pH, and metabolites ensures stable expansion.

Figure 2 illustrates a representative workflow integrating seed train development, inoculation, and quality monitoring [1].

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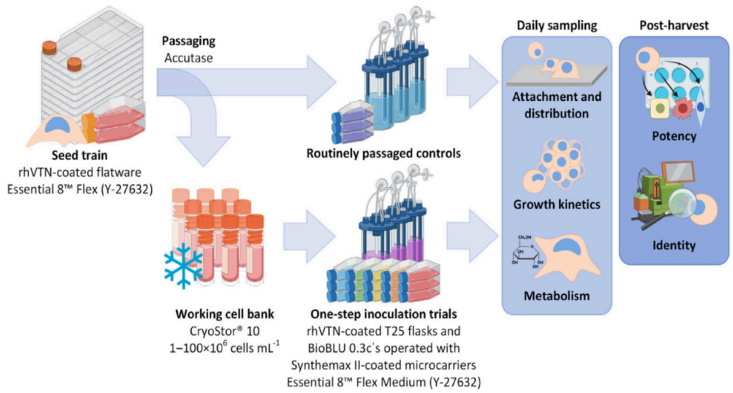


Figure 2. Stem cell expansion workflow using microcarrier-based bioreactor systems, including seed train, inoculation, sampling, and quality assessment [1]

5. Applications

Microcarrier systems enable large-scale expansion of stem cells, especially MSCs, due to their therapeutic relevance and scalability. Polystyrene-based carriers like Cytodex support robust MSC proliferation with preserved phenotype and osteogenic potential [9].

Pluripotent stem cells also benefit: iPSCs retain pluripotency in suspension bioreactors [8] while HA- and GelMA-based biodegradable carriers enable xeno-free MSC derivation [6, 7]. These systems support GMP-compatible workflows for clinical manufacturing [3].

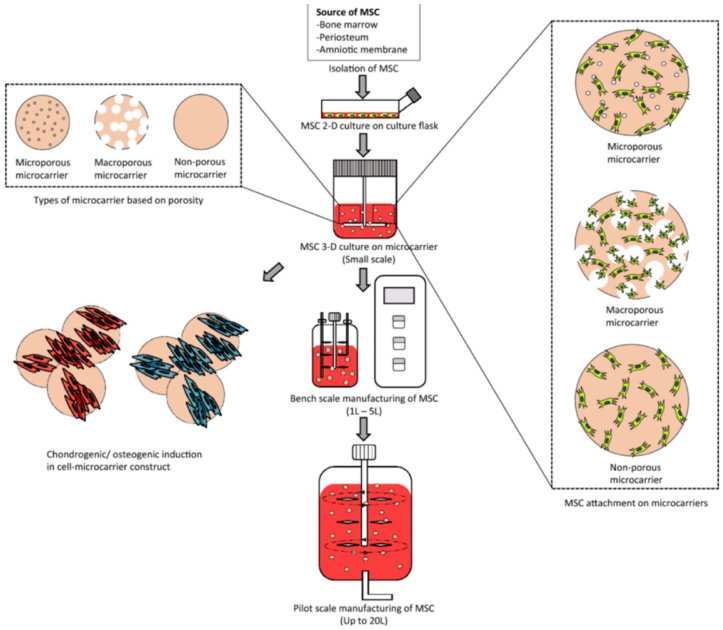


Figure 3. Scalable MSC manufacturing using microcarriers with different porosities, showing 2D to 3D culture transition and cell expansion outcomes [5]

Figure 3 illustrates how carrier porosity affects MSC expansion from 2D to 3D scales [5].

Applications include cell therapy, tissue repair using injectable carriers, disease modeling, and drug screening. Emerging directions—such as co-culture, organoid generation, and extracellular vesicle production—further demonstrate their potential in next-generation regenerative medicine.

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6. Conclusion

An efficient platform to achieve scalable stem cell expansion is provided by microcarrier systems, which is effective in managing issues of yield, quality, and standardisation. They support the growth of MSCs, hESCs, and iPSCs in suspension on a 3D growth surface with preservation of phenotype and functionality.Material selection, surface functionalization, and structure have been improved to increase the cell adhesion, proliferation, and recovery. New advancements that have been achieved in fabrication through Microfluidics and biodegradable hydrogel allow tight control of the characteristics of carriers.Microcarriers can enable reproducible and GMP compliant manufacturing when combined with optimized bioprocess engineering, such as agitation and bead-to-bead transfer.These can be applied in cell therapy, tissue engineering and disease modeling. There are future trends of smart carriers responding to environmental signals and automation by sensors and this leads that normalised, cost-effective and scalable in a clinical way production of stem cells in regenerative medicine.

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