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# Mass Production of Stem Cell-Derived Progeny in Bioreactors

**Editorial**

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Stem cells, including mesenchymal stem cells (MSCs) and pluripotent stem cells (PSCs), have shown great potential for various biomedical applications including drug discovery, disease modeling, and tissue engineering [1-4]. Especially, the discovery of induced pluripotent stem cells (iPSCs) with similar characteristics to embryonic stem cells (ESCs) opens a new era for stem cell research and transplantations [5]. Bioprocess engineering provides a platform to generate a controlled microenvironment that could potentially recreate a stem cell niche in view of promoting stem cell proliferation or the lineage-specific differentiation.

A bioprocess engineering strategy, through the use of well-controlled bioreactors, aims at achieving the large scale production of stem cells, improving their biological properties, and ensuring the safety in clinical use following the guidelines of current Good Manufacturing Practices (cGMP) [6, 7]. For instance, microcarrier-based bioreactors enable easy scale up for anchorage-dependent stem cells, demonstrating high reproducibility on regulation of cellular behaviors with the compliance under cGMP. Microcarriers have been investigated for stem cell expansion and differentiation in stirred tank bioreactors and rotating wall bioreactors, including MSCs and PSCs as well as the differentiated tissue-specific cells (e.g. osteoblasts, neurons, cardiomyocytes etc.) [8-13]. As for custom-made biomaterials, the accurate biochemical and biomechanical characterization of the microcarriers (i.e. surface composition and modulus) will help to fully exploit their potential in regulating the stem cell fate decision. For instance, it has been shown that microcarrier surface properties modulated MSC adhesion and cytoskeleton, which in turn regulated chondrogenic differentiation [14]. Another suspension culture organization in bioreactors is the self-assembled aggregates, which has been shown recently for both PSCs and MSCs [6, 15]. This 3-D organization promotes cell-cell adhesion and the secreted factors, allowing the large scale expansion as well as the enhanced therapeutic potential. Most importantly, suspension culture in bioreactors with either microcarriers or aggregates enables the process integration of iPSC reprogramming, stem cell self-renew-

al, and the lineage-specific differentiation [16, 17].

Bioreactors promote efficient mass transfer and enable the control of nutrient feeding mode to regulate cell metabolism [18]. For instance, glucose and oxygen metabolisms play a key role in MSC and PSC expansion and differentiation [19]. The efficient expansion of stem cells relies on glycolysis, while during differentiation stem cells generally switch the metabolism to oxidative phosphorylation (e.g. cardiomyocytes derived from PSCs) [20-22]. As a consequence, the requirements for glucose and oxygen vary upon different phases of stem cell production. Accurate understanding of stem cell metabolism is critical for the rational design of culture parameters such as feeding regime in bioreactors for efficient integrated expansion and differentiation at large scale. In the same vein, the generation of gradient of cytokines and growth factors in the bioreactors enables the design of *ad-equate* niches to promote efficient stem cell differentiation, as shown in mesodermal lineage commitment and the regulation of ESC self-renewal [23, 24].

Besides the improved mass transfer and diffusion, bioreactors also enable the control of stem cell's exposure to mechanical force, providing additional signaling for differentiation or sustainment of the stem cell properties [25]. For instance, the activation of Wnt signaling for MSC osteogenic differentiation or the sustained self-renewal of ESCs and alternatively their commitment is regulated by mechanical force [26-28]. The mechanical stress has also been shown to induce autocrine/paracrine signaling of transforming growth factor (TGF)-β superfamily and activate Smad2/3 pathway to suppress spontaneous differentiation of human PSCs [29, 30]. These findings underscore the importance of reciprocal interactions of autocrine/paracrine signals and mechanical force in 3-D cellular organizations during stem cell self-renewal and lineage commitment.

Together, this editorial indicates that rational bioprocess engineering strategies applied to stem cell cultivation in bioreactors constitutes the ideal way to monitor the microenvironment of stem cells. Accurate microcarrier characterization, the controlled feeding mode, and the magnitude of applied mechanical force should lead to the improvement in stem cell expansion and differentiation *ex vivo* that ultimately meet the clinical demand with the large number of cells as well as the safety considerations.

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