A SCALABLE XENO-FREE MICROCARRIER SUSPENSION BIOREACTOR SYSTEM FOR REGENERATIVE MEDICINE BIOMANUFACTURING OF hMSCs

Josephine Lembong, RoosterBio, Inc.
josephine@roosterbio.com
David Wang, RoosterBio, Inc.
Robert Kirian, RoosterBio, Inc.
Ang-Chen Tsai, PBS Biotech, Inc.
Kenny Cruz, PBS Biotech, Inc.
Francisco Rosello, PBS Biotech, Inc.
Kayley Cox, PBS Biotech, Inc.
Yas Hashimura, PBS Biotech, Inc.
Taby Ahsan, RoosterBio, Inc.
Sunghoon Jung, PBS Biotech, Inc.
Jon Rowley, RoosterBio, Inc.

Key Words: bioreactor, hMSCs, scalable manufacturing

An economical biomanufacturing paradigm for human mesenchymal stem/stromal cells (hMSCs) is in critical need, as indicated by over 800 clinical trials investigating the use of hMSCs for regenerative medicine. To meet the demand for clinical manufacturing, a scalable process and production technology platform that can generate billions to trillions of cells per manufacturing lot is needed. Suspension bioreactors show great promise in reaching commercially-viable working volumes, however, scalability of cell production remains an issue. Overcoming this challenge is necessary to drive widespread adoption of this culture system for hMSCs. We have taken the Quality by Design (QbD) approach to develop a scalable xeno-free (XF) hMSC bioreactor process that maintains the final cell population doubling level (PDL) within the recommended range of 16-20 to ensure product quality. Our strategic XF bioprocess was designed using high volume XF cell banks, an optimized XF fed-batch media system, and XF microcarriers, all combined in a scalable bioreactor system to meet our design criteria and streamlined production at different culture scales.

In this study, we demonstrated the scalability of a XF hBM-MSC microcarrier suspension culture in a low shear, single-use, vertical-wheel suspension bioreactor (PBS Biotech) at small scale (0.1 L), development scale (3 L), and pilot scale (15 L). Cell yields of >0.5M cells/mL were achieved in all bioreactor scales within 5 days of culture with no media exchange. Comparable nutrient and waste metabolite levels, pH, and cell growth curves (Fig. 1) were observed at each scale. In addition, cells harvested from all bioreactor scales maintain the hMSC critical quality attributes of osteogenic, adipogenic, and chondrogenic differentiation potential, as well as functional attributes of angiogenic cytokine (FGF, HGF, IL-8, TIMP-1, TIMP-2, and VEGF) secretion and inducible immunomodulatory potential (as measured by functional IDO activity), which are comparable to 2D control of similar PDL. Our development data supports the expansion of XF hMSCs in a scalable bioreactor culture platform, providing significant time and cost savings as a standardized system for translational researchers and product developers in the regenerative medicine, tissue engineering, and cell therapy fields.

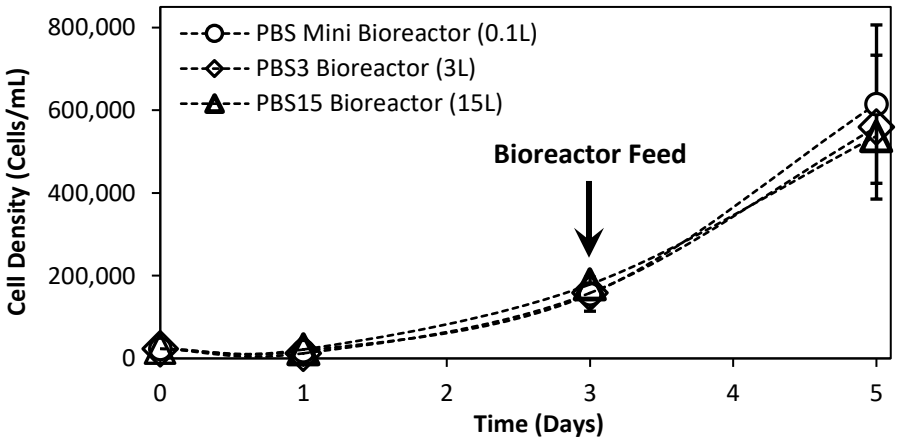

Figure 1 – Growth profiles of XF hBM-MSCs are comparable across various scales of microcarrier suspension culture: 0.1 L, 3L, and 15L. Cell yields of >0.5M cells/mL were achieved within 5 days.