ADVANCED MANUFACTURING PROCESS DESIGN FOR MESENCHYMAL STROMAL CELL THERAPIES

Bryan Wang, Georgia Institute of Technology, USA
bryanwang@gatech.edu
Annie Bowles-Welch Ph.D., Georgia Institute of Technology
Bharat Kanwar, Georgia Tech Research Institute, Georgia Institute of Technology, USA
Walker Byrnes, Georgia Tech Research Institute, Georgia Institute of Technology, USA
Zhaonan Liu, School of Industrial and Systems Engineering, Georgia Institute of Technology, USA
Chuck Zhang, Ph.D., School of Industrial and Systems Engineering, Georgia Institute of Technology, USA
Stephen Balakirsky Ph.D., Georgia Tech Research Institute, Georgia Institute of Technology, USA
Carolyn Yeago Ph.D., Georgia Institute of Technology , USA
Krishnendu Roy, Ph.D., Georgia Institute of Technology, USA

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For decades, the potential immunomodulatory effects of Mesenchymal Stromal Cells (MSCs) have prompted numerous cell-therapy clinical investigations targeting various diseases such as graft-versus-host disease and autoimmune diseases. Despite their ubiquitous usage in clinical trials, significant challenges related to their manufacturing and biological variabilities have led to poorly reproducible outcomes of therapeutic efficacy. Therefore, identification of validated critical quality attributes (CQAs) correlative to therapeutic function is of great interest to the MSC community. Such CQAs would also permit identification of critical process parameters (CPPs) to achieve and maintain MSC quality while producing a high yield. In this study, we designed and tested a “smart” feedback-controlled hollow fiber-based bioreactor for maintaining nutrient and waste levels for human umbilical cord tissue-derived MSC expansions. The bioreactor platform is a semi-autonomous system complete with in-line sensors, modeling, data-driven controllers, and an automated sampling platform. The small-scale system reduced costs, labor, time, and perturbations and improved yields of MSC products using a hollow fiber cartridge that closely models the basic design of the large-scale Quantum® Cell Expansion System. Our feedback-controlled bioreactor responded to in-line glucose and lactate levels while recorded pH and dissolved oxygen measurements. This information was fed into a controller, which auto-calculates cell growth rates based on our developed mathematical model, and subsequently regulated media feed rates to support cell growth and nutrient requirements. Compared to the manual expansion process, the automated expansion processes showed higher yields and comparative therapeutic potency of MSCs, indicated by indolamine 2,3-dioxygenase assay and T cell proliferation assay. Future directions of our study propose to correlate metabolites and secreted proteins in culture media as putative CQAs that can be used as in-line predictors of MSC yield and therapeutic potency. Moreover, we aim to maintain a metabolic and secretory profile throughout MSC expansions enabled by real-time modulation of CPPs and scale up of the “smart” bioreactor. The proposed bioprocess for MSC products can be adapted and applied to industrial cell therapy manufacturing and can enable high-yield and high-quality products while minimizing variabilities.

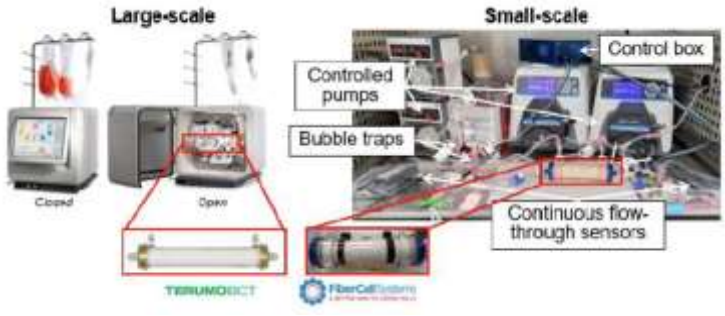

Figure 1. “Smart” hollow fiber bioreactor with in-line sensors informing feedback controls for autonomous feeding and regulation of culture environment.