STANDARDIZED EXPANSION OF HUMAN ADIPOSE TISSUE-DERIVED STROMAL/STEM CELLS (hASCs) IN WAVE-MIXED SINGLE-USE BIOREACTORS WITH ONE-DIMENSIONAL MOTION

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The large number of realized and ongoing clinical trials with human mesenchymal stem cells (200 by end of June 2016; www.clinicaltrial.gov) demonstrate their great potential in the field of regenerative medicine. However, new and standardized production technology is necessary to generate the number of cells required at the cell quality desired. The previously used parallelized plastic shells that consist of multiple layers (e.g. stacked plate systems) need to be replaced by instrumented, dynamically-mixed and scalable single-use bioreactors. In these systems the growth surface for the adherent growing cells is provided by microcarriers. While the first users have already worked with stirred single-use bioreactors (e.g. Lonza in Walkersville), there have only been two approaches described in the specialist literature for one-dimensional wave-mixed bioreactors, both of which were not completely successful. This is surprising, since these single-use bioreactors have dominated seed inoculum production for some time due to their uncomplicated operation. Furthermore, wave-mixed single-use bioreactors have proven to be successful in microcarrier-based vaccine production.

The investigations we present consist of Computational Fluid Dynamics (CFD) simulations and data verification by Particle Image Velocimetry (PIV) measurements, suspension studies in a serum-reduced culture medium with a suitable polystyrene microcarrier, and expansion studies with human adipose tissue-derived stromal/stem cells (hASCs) based on biochemical engineering investigations. They provide an important contribution to the development and production of stem cell-based cell therapeutics in single-use bioreactors with one-dimensional motion, and for the first time demonstrate the suitability of this type of reactor for the expansion of hASCs when working with culture specific suspension criteria (N_{S1UW} and N_{S1W}). The first proof-of-concept expansions of hASCs at a rocking angle/rocking rate combination of 4° and 31 rpm allowed 2.85 x 10^8 hASCs to be harvested after 9 days of cultivation without a change in the stem cell characteristics. Moreover, the results generated contribute to a better understanding of the parameter-dependent, hydrodynamic cell stress caused by mechanical stress in hASC expansions with microcarriers in wave-mixed bioreactors with one-dimensional motion, and allow for direct comparison with stirred single-use bioreactors, which was previously not possible. Finally, the results obtained are also beneficial for other microcarrier-based production processes, such as those for vaccines (e.g. shortening of process development time).