Life Sciences and Facility Management

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Expansion of human mesenchymal stem cells

Summary

There is obvious growing interest in high amounts of human mesenchymal stem cells (hMSCs), such as those from adipose tissue and bone marrow, for the treatment of regenerative disorders. This concerns both research and clinical studies in which autologous and allogeneic therapies are performed. However, this presupposes alternatives to the static stacked plate systems which have, until now, represented the cultivation systems of choice. Controllable dynamic bioreactors and microcarrier-(MC)-medium combinations are stringently required which ensure desired stem cell quantity and quality, and are GMP compliant.

Biochemical engineering investigations

In addition to suspension studies in which the suspension criteria are determined, Computational Fluid Dynamics (CFD) is applied to calculate the fluid flow velocities, specific power inputs and local shear stress levels inside the cultivation system or bioreactor and to deduce the optimum main process parameters (see Fig. 1, and Schirmaier et al. 2014 and Jossen et al. 2014a). Our CFD-based approach reduces the number of cultivation studies and contributes to savings in process development time and costs. As described by Jossen et al. 2014b, CFD can also be applied to optimize the bioreactor design. In addition to Particle Image Velocimetry investigations, expansion studies are subsequently realized in order to verify the CFD results.

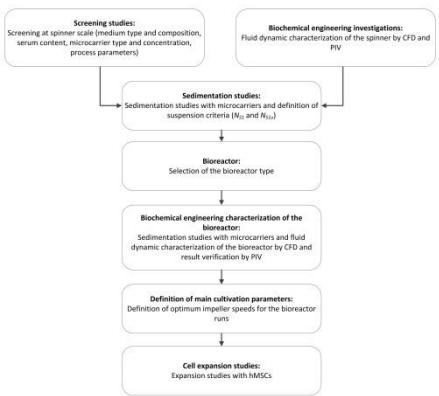

Fig. 1: Our scale-up approach for hMSCs.

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Vision

We want to better understand the dependence of the growth of hMSCs from biochemical and hydrodynamic conditions when expansions are carried out in serum-containing, serum-free and chemically defined culture media in stirred and wave-mixed bioreactors. A further aim is to combine our knowledge in biochemical engineering, cell biology and cell cultivation techniques to develop rapid process scale-up procedures from stirred to stirred and stirred to wave-mixed bioreactors. The basis for this work represent extensive screening studies executed on spinner scale and aimed at the selection of the optimum MC-medium combination and main process parameters (e.g., impeller speed, rocking rate, rocking angle).

Expansion studies

We realized hMSC expansion studies up to 50 L stirred single-use bioreactors, as shown in Figure 2. For adipose tissue-derived and bone marrow-derived hMSCs, expansion factors between 40 and 50 were reached within 7 days. Part of the expansion studies are also flow cytometric analyses and cell differentiations into adipocytes, chondrocytes and osteocytes in order to demonstrate that the expanded hMSCs maintain their stem cell properties.

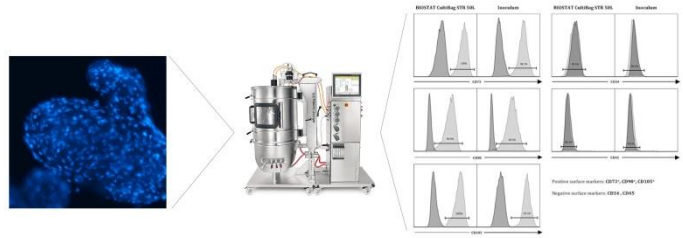

Fig. 2: Expansion studies of bone marrow-derived hMSCs performed in the BIOSTAT STR 50L (pilot scale) .

Selected publications

- Theoretical and practical issues that are relevant when scaling up hMSC microcarrier production processes. V. Jossen et al., *Stem Cell International*, 2016
- Mass production of mesenchymal stem cells – Impact of bioreactor design and flow conditions on proliferation and differentiation. V. Jossen et al., InTech, 2014a ISBN 978-953-51-4114-3
- Modification and qualification of a stirred single-use bioreactor for the improved expansion of human mesenchymal stem cells at benchtop scale. V. Jossen et al., *Pharmaceutical Bioprocessing,* 2014b
- Scale-up of adipose tissue-derived mesenchymal stem cell production in stirred single-use bioreactors under low-serum conditions. C. Schirmaier et al., *Engineering in Life Sciences*, 2014

Collaboration Opportunities

We collaborated successfully with Lonza and the Cardio Centro Ticino in this field.