HOW TO USE COMPUTATIONAL FLUID DYNAMICS IN THE DEVELOPMENT OF CELL THERAPEUTICS

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Computational Fluid Dynamics (CFD) is an established method in fluid mechanics that allows fluidic problems to be solved through numerical methods. In recent years, CFD has established itself as a useful tool in biochemical engineering, where it is mainly used to characterise and optimize devices (e.g. bioreactors, pumps, etc.). By using CFD, fundamental bioengineering parameters (e.g. turbulent dissipation rates, shear gradients) can be predicted independently of time and location. This allows process related parameters to be defined in silico, which reduces the number of experiments and costs. This is particularly important for the development of cell therapeutics, where the starting cell material is restricted and the batch costs are high. Recent economic reports have predicted a significant increase in cell therapeutics over the next few years, especially for human mesenchymal stem cells (hMSCs). This situation can also be seen in the high number of clinical trials (269 trails, August 2016; clinicaltrails.gov) that are currently focusing on using hMSCs for the treatment of illnesses such as myocardial infarction, Crohn's disease and graft versus host disease. However, large amounts of hMSCs are required for one single therapeutic dose (35-350 million cells per dose), which explains the demand for efficient and scalable in vitro expansion procedures.

Following a brief introduction to CFD, we aim to highlight the capabilities of CFD for the development of bioprocesses and scale-up procedures. For this purpose, we will show how CFD data can be used to support the scale-up of a microcarrier-based hMSC expansion process in stirred and wave-mixed single-use bioreactors. Our presented investigations involve Computational Fluid Dynamics (CFD) simulations and data verification using 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). This combination of biochemical engineering and biological expertise enabled the establishment of a MC-based hMSC expansion process that resulted in up to 1.25 x 106 hMSCs/mL in stirred single-use bioreactors. Initial proof-of-concept expansions of hASCs in wave-mixed single-use bioreactors at a rocking angle/ -rate combination of 4° and 31 rpm resulted in the harvest of 2.85 x 108 hASCs after 9 days of cultivation without changes to the stem cell characteristics. All the investigations performed showed that the suspension criteria NS1U for stirred and NS1UW for wave-mixed bioreactors are beneficial for the cultivation of hMSCs.

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