NOVEL IMPELLER DESIGN FOR STEM CELL BIOPROCESSING AND ITS APPLICATION IN HMSC STIRRED-TANK BIOREACTOR CULTURES

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Cell-based therapies such as hMSCs have been shown to improve patient conditions across a wide range of complex diseases and are thus being increasingly investigated in late-stage clinical trials. The reproducible and scalable manufacturing of hMSCs is hence more and more important prior to the anticipated market approvals. hMSCs are being expanded in 2D culture vessels, though due to poor process control and numerous manual processing steps, the use of microcarriers to grow the cells in stirred-tank bioreactors has been explored extensively. However, the impeller technology has barely changed over the last decades, with impeller designs that originated from the chemical engineering industry still being used for biological cell production. Here, we present a novel and innovative impeller design (Cellmotions, Inc., Canada) that was purposefully developed for the expansion of biological materials. The engineering tools and methods to advance novel impeller designs for cell-specific growth to reduce the reliance of generic impeller solutions from other industries will be discussed in this presentation. The novel Bach impeller (Figure 1) has been shown to effectively suspend microcarriers at low power inputs due to a novel flow mechanism that induces a combined axial, radial, and tangential flow pattern. In addition, the fluid flow has been evaluated in detail to derive bioprocess-relevant parameters such as the energy dissipation rate and shear forces in proximity to the impeller blade. From an engineering/process parameter point of view, the impeller represents a novel and innovative alternative to conventional axial flow impellers utilized across the cell therapy bioprocessing industry (i.e. 3-blade segment impeller or Marine propellers) for low power-input bioprocessing applications. In addition, the results from the engineering characterization have been applied to process development and scale-up of hMSC expansion at the 1 L to the 5 L stirred-tank bioreactor scale. To assess the impeller during biological experiments, the growth performance of Wharton Jelly (WJ)-hMSCs in a 1 L STR equipped with the Bach impeller was evaluated at a variety of culture conditions. The cells attached to Cytodex 1 microcarriers at a concentration of 5.6 g/L and were cultured for 5-7 days. The (batch) growth phase was carried out at varying impeller speeds N=75, n=3; N=115 and 150 rpm, n=2, respectively. Aimed at reducing culture time and cost, the cell growth kinetics were additionally evaluated at even higher microcarrier concentrations, e.g. 11.2 g/L Cytodex 1. Here, a maximum cell density of up to $1.7x10^6$ cells/mL and cell viability >90% was achieved within 5 culture days, which is amongst the highest cell densities ever attained for a hMSC batch culture (to the best of our knowledge, following an extensive literature review from articles over the last 15 years). Critical cell quality attributes of the WJ-hMSCs were assessed upon completion of the growth phase, i.e. FACS to identify stem cell surface markers, tri-lineage differentiation, and capacity of the cells to form colonies (CFU-assay). In addition, informed by the previously described engineering characterization, the process at N=75 rpm was scaled-up to the 5 L scale, where the hMSCs were again confirmed to have retained the relevant cell quality attributes. The reported findings are important to determine the design space to which scale-ups to even larger tank sizes can adhere. We believe the presented research will further promote an interdisciplinary approach of engineering technologies, bioreactor fluid mechanics and cell culture to advance the field of stem cell bioprocessing.

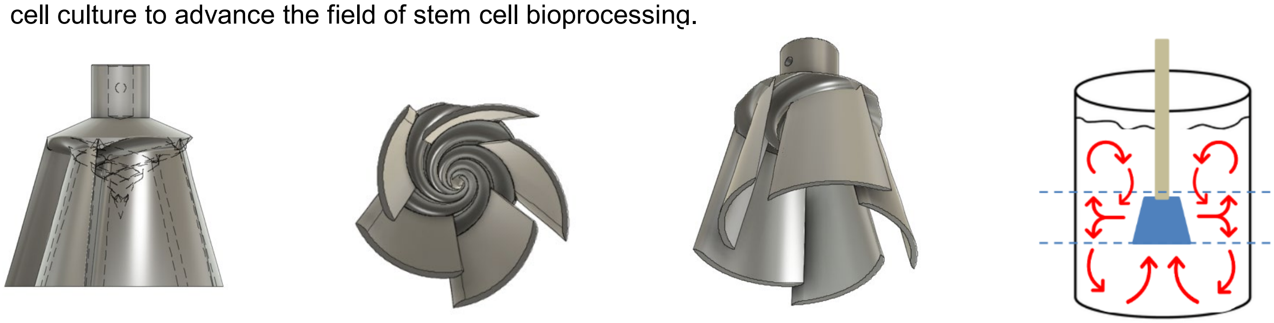

Figure 1 – Design of novel Bach impeller for cell culture requiring low power inputs in stirred-tank bioreactors, including a schematic of the novel flow mechanis

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