RANS and Large Eddy Simulation of the hydrodynamics inside mini-bioreactors designed for stem cell culture

M.-L. Collignon [(1,2,3)], C. Martin [(3)], F. Blanchard [(3)],
D. Toye [(1,2)], A. Marc [(3)], E. Olmos [(3)]*

[(1)] Laboratoire de Génie Chimique, Université de Liège, 3, allée de la chimie, batB6C B-4000 Liège, Belgique.
[(2)] F.R.S-FNRS, 5, rue d'Egmont, B-1000 Bruxelles, Belgique
[(3)] Laboratoire Réactions et Génie des Procédés, UMR 7274, CNRS-Université de Lorraine, 2 av. forêt de Haye, TSA 40602, F-54518 Vandœuvre-lès-Nancy, France

*Corresponding author: eric.olmos@univ-lorraine.fr

Human mesenchymal stem cells (hMSC) offer very promising therapeutic perspectives in tissue engineering (ligament and cartilage repair) and cellular therapy [1]. The development of an efficient expansion process of hMSC, both quantitatively (cell density and growth rate) and qualitatively (preservation of cell stemness), appears essential to ensure hMCS amounts required for clinical applications. However, due to low *in-vivo* availability of cells, limited accepted number of passages before culture seeding and low cell growth rate, smaller bioreactor working volumes seem required. For this purpose, a platform of six 200 mL mini-bioreactors, geometrically similar to usual lab-scale bioreactors, was previously designed using a scale-down approach [2]. As adherent-dependent hMSC, cultivated on microcarriers, are reputed sensitive to hydromechanical stress, mixing of the culture medium may induce hMSC damage, differentiation, detachment, death and/or lysis [3]. Therefore, to propose adequate mixing conditions, the objective of this work was to characterize local hydrodynamics inside such culture bioreactors *via* CFD simulations (ANSYS Fluent 14.5). Three impeller designs were considered: Rushton turbine (RT), Elephant Ear (EE) and pitched-blade turbine (PBT). The latter two were simulated in up and down-pumping mode. Each of these three culture systems was meshed using 200k, 900k and 1.5M non-conformal tetrahedral calculation cells. As a first step, the flow was simulated by a steady-state RANS multiple-reference frame approach using a realizable k-ε turbulence model. Various levels of power dissipation (from P/V = 0.1 to 50 $W.m^{-3}$), representative of those typically encountered in animal cell culture, were considered. As a second step, Sliding-Mesh Large-Eddy Simulations (LES) were used for selected operating conditions in order to reach a more precise description of the instantaneous velocity field. The power curves of the three impellers, deduced from torque or turbulent dissipation rate calculations were obtained, compared and allowed the identification of the critical Reynolds number for fully-turbulent flow. Among others, mean flow velocity fields of the up-pumping and down-pumping EE were respectively composed of 4 and 2 recirculation loops suggesting that the former impeller design was more adapted to microcarrier suspension. Our study brings new information regarding literature data as LES has so far only been successfully used in bioreactors operating in microbial culture mixing conditions (RT, high P/V) [4]. Perspectives of this work are a lagrangian tracking of microcarriers inside the LES simulated flow field.

[1] Caplan et al., Trends in Molecular Medecine 7, 259-264, 2001; [2] Blanchard et al., Proceedings of 23rd ESACT meeting, June 2013, 23rd-26th, Lille (France) ; [3] Tseng et al., Biomaterials 33, 556-564, 2012, [4] Delafosse et al., Chemical Engineering Research and Design, 86, 1322-1330, 2008.

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