COMPUTATIONAL FLUID DYNAMIC CHARACTERIZATION OF VERTICAL-WHEEL BIOREACTORS USED FOR EFFECTIVE SCALE-UP OF HUMAN INDUCED PLURIPOTENT STEM CELL AGGREGATE CULTURE

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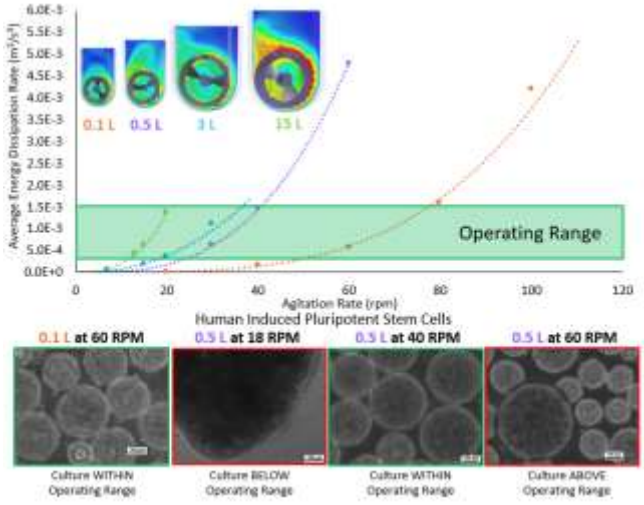
Innovations in engineering and bioprocess development have accelerated the transition of induced pluripotent stem cell (iPSC) cultivation and use from the bench-top to large-scale clinical manufacturing. Owing to their potency, proliferation capabilities, and ability to overcome the challenges associated with traditional sources of pluripotent stem cells (PSCs), iPSCs have generated significant interest in the field of regenerative medicine for more than a decade. However, traditional bench scale methods to expand iPSCs, including petri dishes and T-flasks, are insufficient to achieve clinically relevant numbers. For iPSC treatments, cell dosages will range from 10^9 – 10^{12} cells per patient depending on the therapeutic target. To achieve the required number of cells in an effective and scalable manner, bioreactors will need to be used. Induced pluripotent stem cells (iPSCs) have proven to be extremely sensitive to the bioreactor hydrodynamic environment, making the use of suspension bioreactors to produce quality-assured cells at clinical and commercial scales very challenging. The PBS vertical-wheel (VW) bioreactor combines radial and axial flow components to produce uniform hydrodynamic force distributions, making it a promising platform to overcome the scale-up challenges associated with iPSCs.



Trendline equations for the VW bioreactors (0.1L-15L) where generated using CFD modeling. A suitable operating range was defined for successful culture of hiPSC aggregates that would result in high cell expansion rates, and healthy aggregate formation, growth, and uniformity. Biological validation at an agitation rate below the suggested operating range showed aggregate conglomeration and settling, while testing above the suggested operating range resulted in reduced growth and increased aggregate size heterogeneity.

In this study, hydrodynamic characterization through computational fluid dynamics (CFD) modeling of VW bioreactors was performed to assist in the generation of effective scale-up equations. CFD models offer a cost-effective method of understanding the hydrodynamics of bioreactors in silico, reducing the number of biological experiments required to develop a scale-up process. It also enables characterization of bioreactors at any scale, giving detailed three-dimensional data as well as volume average (VA) values for parameters such as velocity, shear, and energy dissipation rate (EDR).

Analysis of the VW models proved that important volume average hydrodynamic variables could be maintained throughout scale-up from the 0.1L to the 15L VW bioreactor scale. Each bioreactor scale (0.1, 0.5, 3, and 15 L) was modelled at a minimum of three agitation rates to allow for the generation of scale-up correlation equations. These equations allow operators to define a working range of hydrodynamic variables at one scale and calculate the corresponding agitation rates at other modelled scales. A suggested operating range of agitation rates was determined for the successful culture of iPSCs in the VW bioreactor at each scale, corresponding to constant volume average energy dissipation rate. Agitation rates from the 0.1 L and 0.5 L VW bioreactor scale were experimentally tested with two PSC culture media to biologically validate the suggested range. High cell-fold expansion, healthy aggregate morphology, growth, and uniformity were demonstrated for all conditions tested within the suggested working range.