COMPUTATIONAL FLUID DYNAMICS (CFD) MODELING OF SINGLE-USE, VERTICAL-WHEEL BIOREACTORS AS A PREDICTIVE SCALE-UP TOOL FOR LARGE SCALE STEM CELL CULTURE

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Hydrodynamic variables in bioreactors such as velocity, shear rate, and energy dissipation rate have been shown to affect stem cell properties including: aggregate size, growth, plenotype, and differentiation potential. Unlike traditional bioreactor scale-up equations, CFD modeling allows the user to customize geometry so that scale-up equations can be derived between reactors of any given shape and size. We have recently published data that suggests maintaining the volume average energy dissipation rate, derived from CFD simulations, provides a robust method for scale-up of aggregate culture in stirred suspension bioreactors. Turbulent flow consists of eddies formed when kinetic energy is transferred. Energy dissipation rate is the parameter that determines the amount of energy lost by viscous forces in the flow, and interactions with turbulent eddies influence aggregate size. Aggregates in the culture that are smaller than eddies are engulfed and aggregates that are larger are sheared apart.

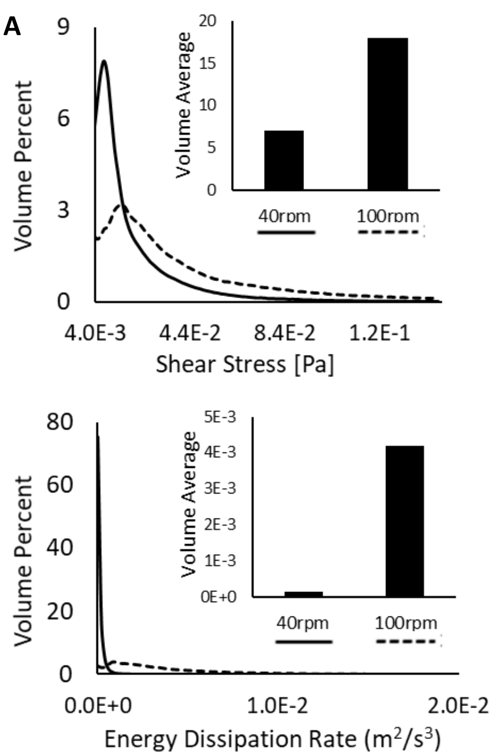

Figure 1: Shear stress [A] and energy dissipation rate [B] distributions and volume average values in a 100mL vertical-wheel reactor

In this study, PBS Biotech's 100mL Vertical-Wheel bioreactor was modeled at various agitation rates using CFD software, Fluent. Results were compared to models generated for traditional horizontal impeller 100mL NDS and 500mL DasGip bioreactors (modeled with the addition of control probes). It was discovered that volume average hydrodynamic values between the vertical-wheel and horizontal blade 100mL reactors were nearly identical, with velocity and shear stress scaling linearly, and energy dissipation rate scaling exponentially relative to agitation rate. While volume average shear rates between the 100mL and the 500mL reactors remained similar at set agitation rates, the average energy dissipation rates varied greatly. At 100rpm, the volume average energy dissipation rate in the 500mL DasGip was nearly 10 times higher than in the 100mL vertical-wheel reactor. This increase can likely be attributed to the addition of control probes that occupy a large portion of the liquid headspace in the DasGip. These results suggest that a drastic decrease in agitation rate the between the 100mL and 500mL reactors would be required for aggregate size to be maintained through scale-up.

Another important finding comes from evaluating the 100mL vertical-wheel hydrodynamic variable distributions graphs. Typical distribution graphs highlight the variance in hydrodynamic variables throughout the bioreactor, resulting in small volume percentages occupying a single value, as was the case for the shear stress distributions, Figure 1A. Unlike traditional horizontal impeller bioreactors, the energy dissipation rate proved relatively constant throughout the volume of the vertical-wheel reactor, Figure 1B. This was particularly evident at a lower agitation rate (40rpm), where nearly 80% of the bioreactor volume was at a single energy dissipation rate. Given the relationship between energy dissipation and aggregate size, this should result in increased aggregate size control and a decrease in size distribution. Data generated from the CFD models was used to test the predicted theories outlined and further optimize bioreactor operating conditions to culture human induced pluripotent stem cells as aggregates in the vertical-wheel reactor. Future experiments will use CFD modeling for larger sized vertical-wheel bioreactors to evaluate the consistency of the hydrodynamic characteristics during scale-up of cell culture processes.