Scalable Manufacturing of Human Pluripotent Stem Cell-Derived Cardiac Microtissues

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Abstract

In recent years, tremendous advances have been made in differentiating human pluripotent stem cells (hPSCs) to cardiomyocytes and evaluating these cells in preclinical models of heart disease. While hPSC-derived cardiomyocytes have improved cardiac function in animals after myocardial infarction, cell viability and immature phenotypes limit efficacy. Also, a lack of robust and scalable manufacturing platforms plagues efforts to advance these cells into human clinical trials. In an effort to improve cell quality and increase manufacturability, we have developed aggregates consisting of iPSC-derived cardiomyocytes, cardiac fibroblasts, and endothelial cells that can be maintained in suspension culture. We found that endothelial cells and cardiac fibroblasts enhance distinct maturation phenotypes of cardiomyocytes including marker expression, morphology, contractility, and electrophysiology in 2D and 3D models. These effects on maturation are most pronounced if endothelial cells and fibroblasts are in direct contact with cardiomyocyte progenitors during manufacturing. Finally, we have developed methods for scalable production of therapeutically relevant numbers of cardiomyocytes (~10^9 cells) in 3D aggregates and found that suspension manufacturing reduces costs by ~80% as compared to 2D manufacturing, largely due to reductions in media costs. These 3D manufacturing platforms have the potential to advance manufacturing of human cardiomyocytes for therapeutics and in vitro testing applications.

Biography

Sean Palecek is the Milton J. and Maude Shoemaker Professor and Vilas Distinguished Achievement Professor in the Department of Chemical & Biological Engineering at the University of Wisconsin – Madison. Sean is the Bioengineering Thrust Leader for the UW Stem Cell and Regenerative Medicine Center, the Director for Research for the National Science Foundation Center for Cell Manufacturing Technologies (CMaT), and the Director for Research Innovation for the Forward BIO Institute. Sean is also a Fellow at the Allen Institute for Cell Science. Sean's research lab studies how human pluripotent stem cells (hPSCs) sense and respond to microenvironmental cues in making fate choices, with a focus on differentiation to cardiovascular lineages. Sean's lab has generated novel mechanistic insight and developed protocols for differentiation of hPSCs to cardiovascular and neurovascular cell types. They strive to engineer fully-defined, animal component-free differentiation platforms, compatible with biomanufacturing of cells and tissues for *in vitro* and *in vivo* diagnostic and regenerative medicine applications.