

Title: Generation of Cardiac Organoids for Hypertrophic Cardiomyopathy (HCM) Modeling

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Abstract

Hypertrophic cardiomyopathy (HCM) is a hereditary cardiac disease characterized by abnormal thickening of the heart, particularly left-ventricular myocardium, primarily due to cardiomyocyte hypertrophy and myocardial fibrosis, which leads to altered cardiac function and an increased risk of arrhythmias and sudden cardiac death. HCM is estimated to occur in one in 500 people and is a leading cause of sudden cardiac death (SCD) in young people, particularly athletes. Despite its clinical importance, understanding the molecular and cellular mechanisms of HCM remains limited, due to the lack of physiologically relevant human models. Current *in vitro* models, mainly 2D cultures of human pluripotent stem cell (hPSC)-derived cardiomyocytes fail to replicate the multicellular interactions that contribute to disease progression.

The aim of this project is to establish and optimize a 3D cardiac organoid platform to model HCM *in vitro* more accurately than existing models. Using patient-derived induced pluripotent stem cells (hiPSCs) harboring junctophilin-2 (JPH2) mutation, cardiomyocytes (CM) and epicardial cells (EPI) are first differentiated and then combined to generate organoids. Within these organoids, epicardial cells further differentiate into cardiac fibroblasts and smooth muscle cells. The main advantage of this model is its ability to better recapitulate disease mechanisms, particularly its capacity to model cardiac fibrosis.

Phenotypic characterization will include immunostaining, functional assays and gene expression analysis. We aim to establish a cardiac organoid model that provides a physiologically relevant platform that more accurately mimics *in vivo* cardiac function found in human hearts to model HCM.