Human induced pluripotent stem cells (hiPSCs) harboring cardiomyopathy-associated mutations are increasingly used to generate models of heart disease for study and therapeutic discovery. However, cardiomyocytes differentiated from these hiPSCs often fail to reliably reproduce clinical phenotypes when cultured in 2D, thereby reducing the translatability of readouts from these assays. Developments in engineered heart tissue (EHT) technologies have improved the potential of hiPSC models of cardiomyopathy, leveraging significantly improved maturation in cardiomyocytes through the presentation of microenvironmental cues akin to those seen in vivo. Success of these approaches would enable the ability to validate and prototype therapeutic approaches in humanized models, thereby improving the probability of novel treatments reaching the clinic. Additionally, these models can greatly assist with the study of disease pathologies and mechanisms of action, leading to new discoveries of potential drug targets.

**MYBPC3 Mutations: Leading Cause of Genetic HCM and Tenaya’s Gene Therapy Approach**

**Disease Symptoms and Severity**
- Loss of MYBPC3 protein disrupts contraction, leading to remodeling of cardiac tissue.
- Cardiomyocyte hyper trophy, disarray and fibrosis contribute to diastolic dysfunction and abnormal heart rhythms.
- Sudden cardiac death is possible in adults and children.

**Epidemiology**
- MYBPC3 mutations account for ~19% of all HCM.
- Estimated >115k patients in U.S. alone.

**Generating MYBPC3<sup>−/−</sup> Human EHTs**

**MYBPC3<sup>−/−</sup> EHTs Exhibited HCM-Associated Contractile Dysfunction**

**Summary of Results**
- MYBPC3<sup>−/−</sup> EHTs exhibited impaired relaxation and diastolic contractile function relative to WT.
- Knockout EHTs also displayed increased contraction velocities in conjunction with deficits in systolic force-frequency.
- Treatment of MYBPC3<sup>−/−</sup> EHTs with AAV-MYBPC3 reversed these contractile dysfunctions.

**Correspondence:** jsui@tenayathera.com