ACCURACY - Human cardiac microtissues for studying lamin cardiomyopathy

Lamin A/C cardiomyopathy (LMNA-CM) is a rare genetic disorder caused by mutations in the nuclear lamin gene LMNA. Affected patients typically exhibit dilated cardiomyopathy and reduced life expectancy, due to sudden cardiac death or accelerated functional decay requiring the heart transplant. Intriguingly, carriers of the same LMNA mutation show a wide spectrum of genotype-phenotype discrepancy, however a clear mechanistical understanding remains elusive. Recently, the host laboratory has developed an innovative multicellular three-dimensional (3D) human induced pluripotent stem cells (hiPSC)-cardiac microtissue (MT) model where hiPSCderived cardiomyocytes display post-natal maturation allowing more faithful investigation of normal and pathological cardiac physiology. I will leverage this model and combine it with my strong background in molecular and cellular cardiology to advance the understanding of LMNA-related pathologies. Specifically, I will use patient-derived hiPSC from two family members with a severe and less severe form of LMNA-CM and their isogenic controls to generate 3D MT models. Next, I plan to 1) characterize structural and functional properties and the transcriptome profile of multicellular LMNA MT models and their controls, 2) investigate cell-cell (cardiomyocytes, endothelial cells, cardiac fibroblasts and macrophages) interactions relevant to the disease development and progression, and 3) correct the identified molecular targets by pharmacological treatment or by CRISPR-mediated gene editing. The scientific, industrial and economic community will profit from this project twofold. First, I will establish a cost-effective model that provides better understanding of LMNA-CM pathogenesis, avoids cross-species variability and reduces the need for animal research and second, I will test the implementation of potential treatment options with the ambition to achieve a step forward in developing personalized therapeutic approach for the end users.

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