Title: **Investigation of Human Engineered Heart Tissues from Human iPSC-Cardiomyocytes on a Hypoxia On-a-Chip Platform**

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Abstract
Ischemic heart disease is a major cause of death worldwide, and the only available therapy to salvage the tissue is reperfusion, which can initially cause further damage. Many therapeutics that have been promising in animal models have failed in human trials. Thus, functional human based cardiac ischemia models are required. Human pluripotent stem cell (hiPSC) derived cardiomyocytes (CMs) are a promising human in vitro model for studying ischemia, but their utilization in cardiac research is limited by their immaturity relative to adult myocardium. To better mimic physiological environments, in-vitro disease modelling and preclinical drug testing are being shifted from 2D to more complex 3D systems. Here, we introduce our 3D hypoxia platform, through integrating engineered heart tissue (EHT) from hiPSC-CMs into a system enabling precise control over oxygen concentration for real-time monitoring of the oxygen dynamics as well as the measurement of force while under electrical stimulation. The base of the platform is an OxyGenie mini-incubator (BioGenium Microsystems, Finland) combined with field stimulation electrodes and EHT-insert, in which the hiPSC-CMs are embedded in fibrinogen between two polyamide pillars to create the EHTs. The system shows strong potential for use in cell models with hypoxic or variable oxygen conditions, such as in ischemic heart models and stroke models.