Title: Miniature Engineered Heart Tissues from Human IPSC-Cardiomyocytes on a Chip

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Ischemic heart disease (IHD) is the leading cause of death globally. In IHD, the blood flow to the myocardium is reduced, leading to oxygen deprivation and tissue damage. The primary treatment is reperfusion to restore blood flow, and antiarrhythmic medication to prevent arrhythmias. Reperfusion, however, can lead to worsening of the tissue injury. Previous animal experiments have provided promising results for medical interventions, but have failed in human clinical trials, indicating the need for human based models. Induced pluripotent stem cell derived cardiomyocytes (iPSC-CMs) allow patient based cardiac research *in vitro*. Understanding pathophysiology on a cellular level promotes the development of more effective treatments.

Here, we present a novel 3D hypoxia platform, combining engineered heart tissue (EHT) with a system enabling precise control over oxygen concentrations on the chip. The base of the platform is an OxyGenie mini-incubator (BioGenium Microsystems, Finland) combined with field stimulation electrodes and an EHT-insert. The hypoxia-on-a-chip platform allows electrical stimulation on the tissue, and a real time analysis of cardiac functionality during hypoxic periods, including assessment of the beating rate, emerging arrythmias and contractile force.

With our hypoxia-on-a-chip platform, iPSC-CMs and EHT technologies can be effectively combined to study cardiac tissue function under hypoxia. The miniature EHTs start beating spontaneously within the first week of culture and develop over the four-week culture period. The chip design enables advanced imaging and precise control over temperature and oxygen concentration for real-time monitoring of oxygen dynamics. Our preliminary results show strong potential for use in IHD modeling.