

# Novel pharmacological strategies for the treatment of the Long QT Syndrome

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## Description:

Congenital long-QT syndrome (LQTS) is a rare inherited disorder (prevalence approximately 1:2500) associated with life-threatening arrhythmias and sudden cardiac death (SCD) in relatively young and otherwise healthy individuals. LQTS has a heterogeneous genetic basis, with various LQTS subtypes caused by mutations in distinct genes related to cardiac ion channels or cardiac proteins involved in the excitation-contraction coupling. Current symptom-directed therapies aimed at reducing arrhythmia triggering events, including lifestyle changes, beta blockade, and left cardiac sympathetic denervation, only partly prevent arrhythmic events, and SCD still occurs in a substantial number of LQTS patients. New therapies for LQTS are then required to reduce the burden of this disorder.

This project will investigate a novel, mechanism-targeted therapy, comprising pharmacological inhibition of the serum and glucocorticoid regulated kinase-1 (SGK1). In contrast to current symptom-directed therapies, this novel approach is designed to correct the pro-arrhythmic alterations in sodium homeostasis caused (in)directly by the underlying genetic defect. Our lab will functionally characterize the effects of SGK1 inhibition in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) obtained from LQTS patients. This will be performed through advanced electrophysiological techniques in isolated hiPSC-CMs and in 2D/3D engineered hiPSC-CM tissues. These pre-clinical studies will establish the anti-arrhythmic potential of SGK1 inhibition, paving the way for future clinical application aimed at preventing SCD in LQTS. In addition, other consortium partner aim to establish the therapeutic potential of pharmacological SGK1 inhibition to prevent ventricular arrhythmias and SCD *in vivo* and *ex vivo* (whole heart, isolated cardiomyocytes) in established animal models of different subtypes of congenital LQTS. The project also aims to demonstrate the therapeutic potential of SGK1 inhibition to restore intracellular ion homeostasis and correct pro-arrhythmic alterations in hiPSC-CMs generated from patients with different subtypes of congenital LQTS. The results from this project will define a genotype- and mutation-specific efficacy of SGK1 inhibition in LQTS at the cellular and 2D/3D engineered hiPSC-CM tissue levels.

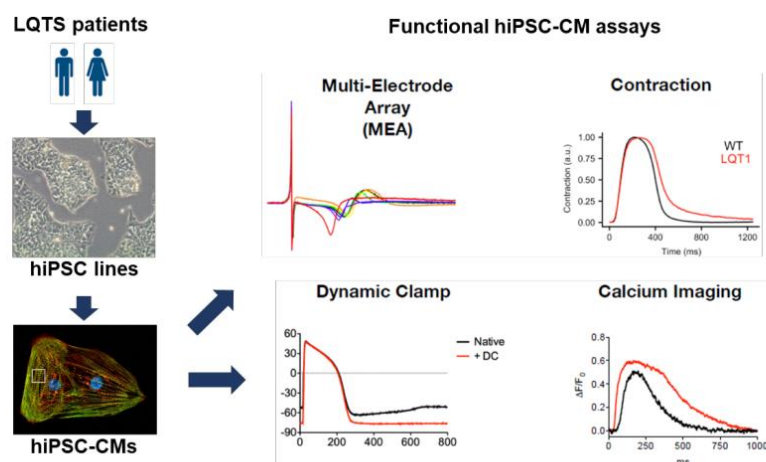


Figure 3. Overview of generation and phenotyping of human iPSC-derived cardiomyocytes