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Solving heterogeneities in defibrillation for a vascular remodeling of the heart

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Atrial fibrillation (AF) is a disorder of the heart's electrical conduction system that leads to a fast and irregular heart rhythm. The prevalence of AF is in the range of 1% in the general population and affects over 33 million people globally. Current treatment options for rhythm control include interventional therapy such as ablation or pharmacotherapy with antiarrhythmic drugs (AADs). However, existing AADs lack atrial selectivity and pose a risk of inducing undesirable cardiac events, such as ventricular pro-arrhythmia. In order to improve the selectivity of the ADD repertoire, it is therefore imperative to identify and characterize new network of genes controlling rhythm in an atrial-specific manner. To address this issue, here we describe an original high-throughput platform that enables to perform large scale functional screens (siRNAs, miRNAs, and small molecules) to identify novel regulators of rhythm in hPSC-derived atrial-like cardiomyocytes (hPSC-ACMs). This new method combines high-speed kinetic imaging, voltage and calcium-sensing probes, automated fluorescence quantification and trace analysis to retrieve physiological (calcium and voltage) parameters of hPSC-ACMs biology with single-cell resolution. In sum, this platform enables the rapid functional evaluation of thousands of genes and/or small molecules on subtype-specific cardiac physiological parameters in both healthy or disease contexts. As an example of application, here we present our most recent results on the functional evaluation of 20 genes associated (rare variants and GWAS locus) with atrial fibrillation.

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