High-content microscopy for systems pharmacology of cardiac fibrosis and regeneration

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Cardiac signaling networks control the response of the heart to a variety of pathological stresses, many of which result in heart failure. The complexity of these networks often hinders our ability to predict and fully understand the impact of therapeutic interventions. In this talk, I will discuss two projects in which we are using high content microscopy together with computational models to address these challenges of prediction and systems-level understanding. First, I will introduce our large-scale computational models of the cardiac fibroblast signaling network. Integration of this model with drug-target interaction databases permits virtual screening for therapeutic strategies to control cardiac fibrosis, which we are validating using high-content microscopy. Alternative approaches may be needed when there is little prior knowledge of relevant signaling pathways, such as in cardiac regeneration. In the second half of the talk, I will describe our phenotypic screening to identify compounds that enhance proliferation of human iPSC-derived cardiomyocytes. In both fibroblast and cardiomyocyte regeneration projects, closing the loop between modeling and experiment is essential for prioritization and mechanistic understanding of therapeutic strategies.