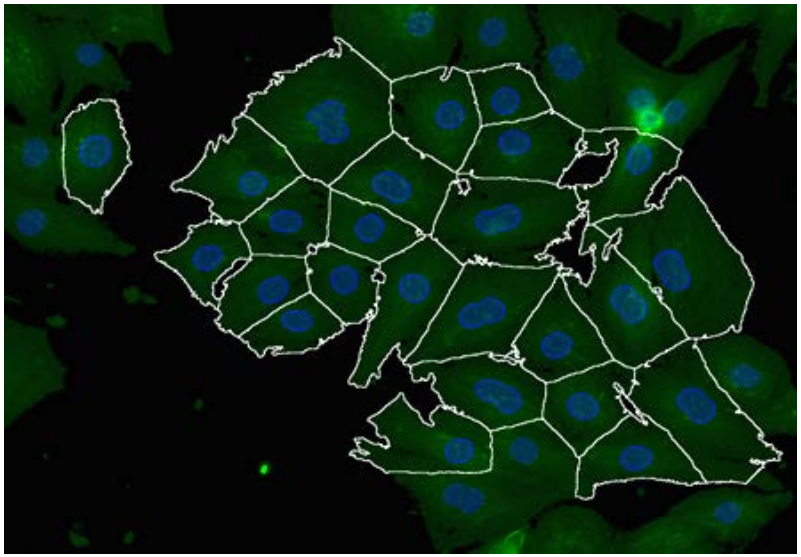
Cardiac Systems Biology Lab



Heart function and failure are controlled by complex signaling and transcriptional networks that are just beginning to be mapped out. Our lab combines computational modeling and live-cell microscopy to identify these molecular networks and understand how they mediate cell decisions. We are tackling a number of unexplained cellular decisions that are fundamental to the development of heart failure. For example, after myocardial infarction, what causes a given myocyte to choose enhance contractility, growth, or death? Why do certain stresses cause myocyte lengthening, while other stresses increase myocyte thickness? Why are certain forms of heart growth reversible while others are irreversible? Answers to these basic science questions are being translated into novel strategies to re-engineer the failing heart.

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"Using engineering approaches to understand and control how the heart responds to stress."

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β-Adrenergic Signaling and Beta Blockers in Heart Failure

Do beta blockers work by suppressing or resensitizing the β-adrenergic pathway? Would patients with receptor polymorphisms benefit from personalized therapies? We are coupling integrated models of signaling and contractile function with video microscopy of Ca^{2+} dynamics.

cAMP/PKA Compartmentation

cAMP and PKA are central hubs transmitting signals from dozens of receptors to hundreds of effectors. We are studying how compartmentation (subcellular localization) cAMP and PKA determines the input/output specificity of the signaling network. Key methods are imaging genetically-encoded FRET biosensors and computational models with realistic cellular geometries. Dysregulated cAMP compartmentation is a key element of heart failure.

Cardiac Hypertrophy

Dozens of pathways are implicated in cardiac myocyte growth, but little is known about the quantitative contribution of these pathways to myocyte shape, reversibility, sarcomeric organization, or many other factors affecting the progression of heart failure. We are combining high-throughput microscopy, automated image processing, and large-scale network modeling to address these challenges.

Crosstalk between Signaling Networks and Cardiac Electrophysiology

Overstimulation of β-adrenergic signaling is a common trigger of cardiac arrhythmia. Electrical and Ca^{2+} signals also activate their own pathways such as Ca^{2+}-calmodulin-dependent protein kinase (CaMKII), which can synergize with the β-adrenergic pathway to modulate short and long-term heart function.

RECENT RESEARCH DEVELOPMENTS

- Developed a large-scale computational model, which revealed the cellular logic of the biochemical networks regulating cardiac hypertrophy (J. Biol. Chem. 2012).
- Developed an automated microscopy and image analysis platform to study the dynamics and reversal of myocyte hypertrophy (J. Mol. Cell Cardiol. 2012).

RECENT GRANTS

- NIH – Multi-scale Systems Model of Murine Heart Failure
- NSF – Accelerating Simulations Using CPU + FPGA
- NIH – Quantitative Analysis of cAMP Compartmentalization in Heart

SEAS Research Information
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