Examining Effect of Ca2+ Sensitizers on Contractility in Engineered Heart Tissues
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Profound advances in biotechnology and tissue engineering have brought about new innovations in regenerative medicine; one major target is cardiac tissue, which is irreversibly damaged in cardiovascular disease. An engineered heart tissue (EHT) platform has the ability to detect small changes in force in real-time. Our EHT platform is a high-throughput, silicone-based device that produces dozens of engineered heart tissues, which self-assemble around two elastomeric micro-pillar cantilevers. This is a flexible platform that can be expanded to more completely capture cardiac function by interrogating different mechanical states.

This summer, under the guidance of Dr. Kenneth Margulies, I was involved in adding new functionality to our existing platform and analyzing the effect of a calcium sensitizing drug with this adaptation. Specifically, my goals were to develop and implement a system to modulate tissue length through magnetic tweezers, and to screen the system by analyzing the calcium sensitizing effect of omecamtiv mecarbil, a myosin activator currently pursued for heart failure treatment, on neonatal rat EHTs. This system simulates in vivo stresses such as preload, and opens the door for the pharmacological study of human cardiomyopathy mechanics.

This project exists at the interface between many fields, such as cardiac tissue bioengineering, physiology, microscopy, micro-fabrication, and physics. In order to control and manipulate mechanics such as preload on the micro-scale not only did I help to design a magnetic tweezer setup, but I also developed the methodology to embed the necessary inducing agent, carbonyl iron, into our existing silicone based device through a cast-mold technique. Currently, our design utilizes permanent magnets; however, future work will involve creating a tunable electromagnet to apply varying magnetic field gradients. Nonetheless, I have shown that the iron-embedded pillars can be externally probed by magnets to apply force and change tissue length. Later, I hope to use this platform to develop a comprehensive length-tension analysis for EHTs.
I also learned much about cardiovascular biology, including practical cell culture techniques involving neonatal rat myocytes and induced pluripotent stem cells differentiated into cardiomyocytes (iPS-CMs). My analysis, which employed live-cell imaging with the calcium indicator Fluo-3 to measure calcium transients in electrically stimulated EHTs, utilized confocal microscopy and Fourier transforms. This technique will allow me to test my hypothesis that omecamtiv mecarbil shifts the length-tension curve upwards, but does not raise intracellular calcium levels in our 3D in vitro EHT model.

This experience provided a meaningful insight into the field of biomedical research, and allowed me to understand and practice useful laboratory techniques. The ability to design my own experiments and analyze data helped me develop a greater sense of independence in research. Overall, I genuinely enjoyed my research, and I plan on continuing the project into the semester.