Heart failure (HF) is a major cause of morbidity and mortality in the United States, accounting for 1 in 9 deaths and costing over $32 billion per year. Despite advancements in the clinical management of HF, the overall 5-year mortality rate has remained at over 50% for the past 10 years. This is, in part, due to current HF therapies being focused on addressing peripheral symptoms (e.g., blood pressure) instead of targeting the molecular defects within the cardiomyocyte directly. The Sarcoplasmic Reticulum (SR) Ca$^{2+}$-ATPase (SERCA) enzyme is a transmembrane protein responsible for pumping two Ca$^{2+}$ ions from the cytosol into the SR lumen to relax muscle cells (diastole), which is regulated endogenously by phospholamban (PLN). A key abnormality in HF involves insufficient SERCA expression and impaired PLN phosphorylation, synergistically leading to SERCA inactivation, and thus, decreased Ca$^{2+}$ transport in the cardiomyocyte resulting in diastolic dysfunction. It has been shown that reactivation of Ca$^{2+}$ transport resulted in improved cardiac function in HF models, validating SERCA activation as a therapeutic approach for HF. Preliminary studies conducted by the Espinoza-Fonseca and Herron groups at the University of Michigan led to the discovery and validation of HF600, a potent small molecule SERCA activator that stimulates intracellular Ca$^{2+}$ transport to reverse calcium mishandling in diseased human cardiomyocytes ($EC_{50}= 2 \, \mu M$), while also protecting the system against arrhythmia, and no apparent long-term cardiotoxicity. Through data-driven, computer-aided, fragment-based drug design, we are currently performing several hit-to-lead optimization structure-activity relationship campaigns based on HF600 to develop diverse classes of safe, effective, pharmacologically viable small molecule SERCA activators directed at cardiomyocytes to restore diastolic function in the failing heart. Our goal is to develop several small molecule, orally bioavailable HF therapeutic candidates for administration in both an acute hospital intervention and a chronically reduced cardiac function setting.