Department of Molecular and Cellular Biology

Graduate Seminar MCB*6500

Friday, Feb. 10, 2017 in SSC 1511 @ 12 noon

presented by:

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Regulatory changes in H88Y and F90Δ α-cardiac actin variants implicated in early-onset hypertrophic cardiomyopathy

Cardiovascular disease (CVD) impacts millions of lives worldwide with a total global healthcare cost of 17 billion dollars a year. A commonly inherited CVD is a disease of the heart muscle called cardiomyopathy. Hypertrophic cardiomyopathy (HCM) is defined by an increase in ventricular wall thickness resulting in the abnormal relaxation of the heart, impeding systole. HCM expression is highly variable and little is known about the molecular pathogenesis of this disease, apart from its link to mutations in genes encoding sarcomere proteins. A core sarcomere protein is α-cardiac actin (*ACTC)*. This study focusses on mutations linked to early-onset HCM leading to F90Δ and H88Y *ACTC* variant proteins. These variants are found in the myosin binding site on *ACTC* sub-domain 1 (SD1). Previous research shows that myosin activity is largely unchanged with these *ACTC* variants, so another level of regulation must be affected. I believe that level is regulation of actin and myosin cross-bridge formation by tropomyosin (Tm) allosteric inhibition of myosin binding. I hypothesize that these *ACTC* variants adversely affect Tm regulation within SD1 causing an overall decrease in cardiac contractility. Troponin (Tn) and Tm will be complexed with *ACTC* variants forming regulated thin filaments (RTFs). Changes in the calcium sensitivity of RTFs interactions with myosin will be measured at different Ca^{2+} concentrations using a colorimetric myosin ATPase assay and an *in-vitro* motility assay to generate pCa curves. A decreased Tm binding affinity will reduce the calcium sensitivity of F90Δ and H88Y variants. This study will provide insight into the role of actomyosin regulation in the molecular pathogenesis of early-onset HCM.