



**Announcement:**

All interested members of the university community are invited to attend the Final Oral Examination for the degree of **Master of Science** of

**ZEESHAN SHAIKH**

on Monday, December 3, 2018 @ 1 p.m. in SSC 1304

**Thesis Title:** Regulatory changes in the  $\alpha$ -cardiac actin variants H88Y and F90 $\Delta$  implicated in early-onset hypertrophic cardiomyopathy

**Examination Committee:**

Dr. J. Yankulov, Dept. of Molecular and Cellular Biology (Exam Chair)  
Dr. J. Dawson, Dept. of Molecular and Cellular Biology  
Dr. T. Martino, Dept. of Biomedical Science  
Dr. D. Josephy, Dept. of Molecular and Cellular Biology

**Advisory Committee:**

Dr. J. Dawson (Adv)  
Dr. T. Martino  
Dr. A. Clarke

**Abstract:** Cardiovascular disease (CVD) impacts millions of lives worldwide with a total global healthcare cost of 47 trillion dollars a year. A commonly inherited CVD called 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 variable and little is known about the molecular pathogenesis apart from its link to mutations in genes encoding sarcomere proteins, including  $\alpha$ -cardiac actin (ACTC). My research focuses on the F90 $\Delta$  and H88Y ACTC variants implicated in early-onset HCM. Previous studies have shown that myosin activity is largely unchanged with these ACTC variants. I hypothesized that these ACTC variants adversely affect tropomyosin (Tm) regulation, decreasing cardiac contractility. Troponin (Tn) and Tm were bound to ACTC variants forming regulated thin filaments (RTFs), and both myosin ATPase assay and an *in vitro* motility assays were used to generate pCa<sub>50</sub> curves. Decreased Tm binding affinity reduced the calcium sensitivity of F90 $\Delta$  and H88Y variants. These data will contribute to a fuller understanding of the molecular pathogenesis of early-onset HCM development leading to more specific and effective treatments.

**Curriculum Vitae:** Zeeshan obtained his Bachelor of Science (Hons.) at the University of Waterloo in 2014. He began his M.Sc. in the lab of Dr. John Dawson in the fall of 2016.