"In vitro perspectives of novel therapeutics for actin variants in dilated and hypertrophic cardiomyopathy"

Cardiomyopathies are a form of heart disease that are associated with the dysfunction of the ventricular myocardium. This can cause a reduction in cardiac output, eventually leading to progressive heart failure. Two of the main forms of cardiomyopathies are dilated (DCM) and hypertrophic (HCM), where DCM is characterized by thinning of the left ventricular walls and an increase in left ventricular volume. Opposingly, HCM is characterized by thickening of the ventricular walls and a reduction in left ventricular volume. Mutations in sarcomere proteins are one of the most common causes of cardiomyopathies, with many actin mutations implicated in this disease. Characterization of these variant sarcomere proteins allows for determination of the molecular mechanisms causing HCM and DCM and treatment capable of targeting these changes. The current treatment strategies do not cure the disease, but rather reduce the symptoms and decrease mortality. However, novel therapeutics such as Mavacamten and Omecamtiv mecarbil are capable of targeting the molecular mechanisms of cardiomyopathies and provide a promising outlook on future treatment options. It is the aim of my work to provide in vitro characterization of specific actin variants T126I and H88Y which have been implicated in cardiomyopathies and determine the optimal dose of these novel therapeutics that is required to correct the function of specific actin variants. This work will aid in developing treatment strategies optimal for each individual based on their causative genetic mutation, which will be a promising achievement towards reducing the global burden of this disease.