Congenital muscular dystrophies (CMDs) are rare genetic disorders of the striated muscle, which per definition, manifest clinically at birth or early infancy. CMDs are genetically and phenotypically heterogeneous and comprise disorders caused by several different genes; among them is LMNA encoding nuclear A-type lamins. In CMD caused by LMNA (i.e., L-CMD), children also develop dilated cardiomyopathy. Dilated cardiomyopathy is characterized by dilatation and systolic dysfunction of the left or both ventricles. The ventricular walls become thin and stretched, compromising cardiac contractility and resulting in altered left ventricular function. Despite current strategies to aggressively manage dilated cardiomyopathy, the disorder remains a common cause of heart failure and a prevalent diagnosis in individuals referred for cardiac transplantation. Therefore there is a need to assess heart dysfunction early in the L-CMD patients’ follow-up. The mechanism through which mutated lamins cause cardiac dysfunction remains obscure.

Studies have indicated that nicotinamide adenine dinucleotide (NAD) content is a critical determinant for heart function and structure. We will ask here, whether NAD⁺ salvage pathway is altered and could play a role in the development of dilated cardiomyopathy caused by LMNA mutations in L-CMD. In preliminary work, we recently showed significantly reduced cardiac NAD⁺ content in L-CMD compared to control. One could thus hypothesize that pathogenic nuclear A-type lamins mutants alter the metabolism of NAD⁺ and lead to molecular cascade of events leading to cardiac dysfunction. This project will test the novel hypothesis that abnormal modulation of NAD⁺ in L-CMD leads to alteration of molecular mechanism (PARylation,…). This may cause cardiomyopathy. Positive results will break new ground for future work in developing novel treatment for cardiac involvement in L-CMD.