**Dr. Howard Worman**

Mutations in the *LMNA* gene encoding A-type nuclear lamins cause dilated cardiomyopathy. Patients may have an isolated cardiomyopathy or it may be in association with skeletal muscular dystrophy. We have discovered increased extracellular signal-regulated kinases 1 and 2 (ERK1/2) activity in hearts from mice with the *Lmna* H222P mutation that develop cardiomyopathy. Based on this discovery, our therapeutic hypothesis is that inhibition of ERK1/2 signaling can be used to treat patients with cardiomyopathy caused by *LMNA* mutations. Specifically, we propose inhibiting mitogen-activated protein kinase/ERK kinase 1/2 (MEK1/2), the enzyme that activates ERK1/2, to treat this rare disease. Recently, we have shown that the MEK1/2 inhibitor most advanced in human clinical trials for cancer, selumetinib, is efficacious in the $Lmna^{H222P/H222P}$ mouse model of cardiomyopathy, leading to improved parameters of cardiac function and reduced cardiac fibrosis. In this project, we will further assess the efficacy of selumetinib on the cardiac conduction block that occurs in *LMNA* cardiomyopathy and the $Lmna^{H222P/H222P}$ mice. In addition, we will carry out studies in $Lmna^{H222P/H222P}$ mice to determine the most optimal selumetinib dose effective for cardiomyopathy and with minimal toxicity. The overall goal is to use the preclinical data obtained in this project to help advanced selumetinib or a very similar MEK1/2 inhibitor to human clinical trials for cardiomyopathy caused by *LMNA* mutations.