Dr. Howard Worman

Dilated cardiomyopathy is the life-threatening feature of Emery-Dreifuss muscular dystrophy. Although implantable pacemakers and defibrillators can respectively prevent death from heart block and ventricular dysrhythmias, patients eventually develop heart failure for which there is no curative treatment and cardiac transplantation is ultimately necessary. Our long-term objective is to develop drug treatment for the dilated cardiomyopathy that occurs in Emery-Dreifuss muscular dystrophy and related disorders resulting from mutations in the same genes. We have previously shown abnormal activation of the JNK and ERK branches of the MAP kinase signaling cascade in hearts of Lmna H222P mice, a model of autosomal Emery-Dreifuss muscular dystrophy. As part of a previous MDA Research Grant, we have treated these mice with compounds that inhibit ERK and JNK and both prevented the development of cardiomyopathy and improved cardiac ejection fraction when given after deterioration had already occurred. We therefore hypothesize that ERK and JNK inhibition can be developed into treatment for cardiomyopathy in human subjects with Emery-Dreifuss muscular dystrophy. In this project, we propose to carry out additional preclinical testing in mice with the ultimate goal of developing a therapy for humans. Specific Aim 1 is to extend our results using “first generation” ERK and JNK pathway inhibitors to additional drugs in these classes to confirm specificity of their ability to prevent and improve cardiomyopathy. As a potential prelude to future human clinical trials, we will include ERK pathway inhibitors that have already been given to human subjects. Specific Aim 2 is to extend our findings in Lmna H222P mice to additional mouse models of Emery-Dreifuss muscular dystrophy. We will examine mice with two other mutations that cause Emery-Dreifuss muscular dystrophy in humans (Lmna N195K and Lmna-delta32) for abnormal activation of ERK and JNK in hearts. As controls, we will examine mice with cardiomyopathy caused by genetic mutations responsible for other muscular dystrophies that cause heart damage by different mechanisms. As part of Aim 2, we will also examine skeletal muscle for abnormal ERK and JNK activation and, if detected, determine if the inhibitors reverse it. In Specific Aim 3, we will determine if administration of ERK or JNK inhibitors to mouse models of Emery-Dreifuss muscular dystrophy have toxicities that could limit their use. Overall, the proposed studies have significant implications for developing drug treatment for the life-threatening complication of a neuromuscular disease in the MDA Program.
