Dr. Howard Worman

We have developed a novel technology to prevent or treat cardiomyopathy by inhibiting the ERK and JNK signaling branches of the MAP kinase pathway. We have been studying a mouse model (Lmna H222P mice) of an inherited cardiomyopathy caused by mutation in the LMNA gene encoding A-type nuclear lamins. We carried a genome-wide gene expression analysis in the hearts of these mice using Affymetrix GeneChips and a bioinformatics analysis to show abnormal activation of the ERK and JNK signaling branches of the MAP kinase pathway. We next showed that treatment with an "off the shelf" ERK signaling inhibitor, administered prior to the initiation of disease, prevented cardiomyopathy in these mice (see attached - Muchir et al. Hum. Mol. Genet. 2009;18:241-247). More recently, we obtained similar results with an "off the shelf" JNK inhibitor. Of importance from a practical therapeutic point of view, we have also shown that inhibition of ERK or JNK signaling with these inhibitors im
proved cardiac function at an age when cardiac structure and function are already abnormal. Treatment resulted in an increased ejection fraction (superior heart function), decreased dilatation of the left ventricle and decreased heart fibrosis (scar tissue) compared to placebo (manuscript in preparation). These results lead to filing a patent on May 1, 2009 entitled "Methods for treating and/or preventing cardiomyopathies by ERK or JNK inhibition" with International Patent Application No. PCT/US09/42614 (filing document attached). The inhibitors we have used, while providing critical proof-of-concept data for the technology, are not suitable for use in humans because of suboptimal pharmacokinetic properties and possible "off target" effects. We are now seeking to obtain additional preclinical data with the ultimate goal of moving our research from experimental animals to man. Specifically, we have a three-pronged strategic approach to: 1) test in our Lmna H222P inherite
d cardiomyopathy mouse model inhibitors of ERK signaling that have already been administered to human subjects, 2) start our own medicinal chemistry program to improve existing molecules for a novel indication and obtain our own composition of matter intellectual property and 3) expand our proof-of-concept preclinical research to more common causes of cardiomypathy with the aim of expanding the potential market for our technology.