

## **Pharmacological inhibition to treat cardiomyopathy associated with muscular dystrophies**

This proposal details a comprehensive program for my career development in research on muscular dystrophies. I have planned this research program to provide the additional scientific training necessary for an independent career in academic research.

Emery-Dreifuss muscular dystrophy (EDMD) results majoritary from mutations in two genes, both encoding proteins of the nuclear envelope expressed in virtually all differentiated somatic cells. In EDMD, contractures affecting the elbows, neck extensor muscles and Achilles' tendons are the first clinical signs of the disease and appear before muscle weakness and wasting. Cardiac disease occurs in virtually all cases of EDMD. Sudden cardiac death due to ventricular dysrhythmias is common in EDMD and timely insertion of an implantable defibrillator can be lifesaving. My recent results have provided some of the only evidence explaining how mutations in these genes encoding nuclear envelope proteins cause striated muscle abnormalities. I identified that the stress-induced MAP kinases signaling pathway is activated in hearts and skeletal muscles of an animal model of EDMD and that this activation occurs prior to the appearance of symptoms, suggesting that it is a primary pathogenic mechanism. I recently provided initial proof of principle for MAP kinases inhibition as a therapeutic option to prevent or delay the onset of heart failure in cardiomyopathy caused by *LMNA* mutation. Hence, my results have shown the first connection between proteins of the nuclear envelope and a cell signaling pathways implicated in the pathogenesis of EDMD.

Orphan disorders such as EDMD are often not of interest for the major pharmaceutical companies, making such disorders an area of high unmet medical needs. I propose to develop a lead compound in-house, which could be further developed as a drug for EDMD. This molecule, if effective, could rapidly move from bench to bedside in a clinical trial for humans with EDMD. Based on my discovery on EDMD mouse model and what is known from some other studies, stress-induced signal transduction may be important in muscular dystrophies. Indeed, the integrity of the structural network in muscle cells is essential and deficiency in one of the components of the dystrophin-associated protein leads to an altered mechanical integrity of the myofiber and a predisposition to contraction-induced damage. I will test the hypothesis that alteration in components of the dystrophin associated protein complex deregulates the MAP kinase cascade, which leads to a muscular dystrophy. It is also known that the MAP kinase cascade is known to have a key role in fibroblast proliferation. Because fibrosis is a hallmark of muscular dystrophy, I will test the hypothesis that there is an existing cross talk between MAP kinase and Tgf- $\beta$  signaling. This could open perspectives for new pharmacological treatment of EDMD.