

Project Title: Modulation of Heat Shock Proteins B8 by Colchicine: Example for Neurodegenerative Diseases Therapy

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Mutations in HSPB8 gene have been associated with debilitating disease, like Charcot-Marie-Tooth (CMT) diseases, distal hereditary motor neuropathy and myopathy, as recently reported by our group. Unfortunately, there is no treatment for these diseases. In vitro assays have shown that HSPB8 myopathy mutation caused a 60% reduction of HSPB8 protein expression level in patients compared with controls and abnormal autophagy and TDP43 pathology. These characteristics have also been found in other neurodegenerative disease (Amyotrophic Lateral Sclerosis, Alzheimer, Parkinson, Huntington disease). HSPB8 has a crucial activity for motor neuron function and exerts a protective role against misfolded protein accumulation in cells. Colchicine is an available FDA approved drug that has been proven to increase HSPB8 expression in neuronal cell models. Our preliminary studies indicate that in patient fibroblasts, a dose of 0.5uM of colchicine improves the disease pathology.

We hypothesize that colchicine by potentially enhancing the expression of HSPB8 may restore autophagy to normal level and block TDP-43 accumulation/ mislocalization in patient fibroblasts/myoblasts and mouse model. This increase in HSPB8 is expected to translate to improvement of the muscle disease. The ultimate objective is to conduct a clinical trial for efficacy of colchicine in HSPB8 patients and patients with related diseases based on these preclinical studies indicating that it is safe and effective.