

Disease-in-a-Dish Model for XL-MTM skeletal muscle using patient-specific iPS cells.

Dr. David Mack

University of Washington, Rehabilitation Medicine/Institute for Stem Cell and Regenerative Medicine (ISCRM)

The goals of this project are to develop an *in vitro* model system for X-linked myotubular myopathy for the purpose of identifying new compounds that can augment or enhance the AAV8-MTM1 gene therapy. Although unexpected, given the strong data coming out of the canine model, it remains possible that *complete* reversal of the disease will not be achieved in *all* patients. More importantly, the long-term effects of gene therapy in the dogs are just now becoming clear. MTM1-affected dogs treated with a normal copy of the gene show impressive muscle regeneration after more than one year, but boys with myotubular myopathy need a treatment that lasts throughout their lives. Therefore, our objective is to generate a research tool that will allow us to study human MTM1-deficient skeletal muscle in culture, and then use that platform to discover new drugs that can correct the defect in the dish. Compounds identified using this personalized medicine approach have a higher likelihood of working in the patient because the patient's own cells were used to find the drug. An added benefit will be that we can address questions from the FDA more quickly and insightfully once we have this human system operational in the lab. A future, loftier outcome from this project could be the construction of MTM1-deficient neuromuscular junctions. In collaboration with other ISCRM investigators, methods are being developed to produce not only skeletal muscle precursors but also motor neurons, with the intention of combining them in culture to better understand the excitation-contraction coupling defect in this disease.