THE HARTWELL FOUNDATION

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Restoration of Bioenergetic Deficiencies in Mitochondrial Disease of Skeletal Muscle

Mitochondrial disease encompasses a heterogeneous group of disorders that primarily impacts young children. The disorders originate from inherited mutations in the DNA responsible for mitochondria, the bacteria-sized organelles present in almost all living cells that are responsible for cellular respiration and generating energy (molecular ATP). It is estimated that every 30 minutes, a child is born with mitochondrial disease, with reported incidence rates in the U.S. of 1:4300 placing mitochondrial disorders as one of the most commonly inherited human diseases. Continual ATP production is critical to sustain life and, if energy levels in tissues cannot be maintained, an affected child will gradually experience accumulated tissue damage which will then rise to multisystemic decline (heart, kidney, GI) and, ultimately, culminate in the death of the child. In the most severe cases, the average life expectancy, once diagnosed, ranges from 5-10 years. Sadly, there is currently no cure or effective therapy for pediatric mitochondrial disease. There are over 25 subtypes of mitochondrial related metabolic disease in children, with new examples emerging every year. Skeletal muscle is most often affected, since its high energetic demand makes it the first to succumb. As a consequence, the typical early sign of mitochondrial disease is muscle weakness and ataxia (difficulty walking). Extensive genetic testing will then confirm the diagnosis of mitochondrial myopathy, a rare but potentially treatable disorder. Unfortunately, the disorder can be misdiagnosed as a muscular dystrophy or inflammatory myopathy, unrelated to mitochondrial dysfunction. Understanding the pathogenesis of mitochondrial disease is critical for detection and accurate diagnosis. To meet this need, I have generated three genetic mouse models that each carry a distinct mitochondrial mutation in their muscle stem cells characteristic of mitochondrial myopathy. The mice mirror the pediatric clinical presentation of impaired muscle cellular growth and performance, including insufficient energy levels. Extracting stem cells from the mitochondrial diseased skeletal muscle, followed by a high-throughput screen of molecules drawn from a novel library of 2000 biogenic compounds will enable identification of agents that can overcome the mitochondrial mutation and restore the regenerative capacity of diseased muscle cells. Promising biomolecules will then be evaluated in genetic mouse models of mitochondrial myopathy for their ability to correct bioenergetic deficiencies in muscle function. My initial screen of 200 of the compounds has already yielded three leads. I hypothesize that for any compound, the observed therapeutic rescue potential will persist in human samples maintained in cell culture. If I am successful in translating these observations to a therapy, it will be possible to restore bioenergetic deficiencies in skeletal muscle fibers from pediatric patients with mitochondrial disease, enabling them to recover their physical mobility, improve the quality of their life, and extend their lifespan.