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Rescue of SMARD1 Mouse Model with use of AAV9-IGHMBP2 Gene Therapy

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is an infantile autosomal recessive motor neuron disease. SMARD1 is caused by loss-of-function mutations in the ubiquitously expressed immunoglobulin helicase μ-DNA binding protein 2 (IGHMBP2). The lack of functional IGHMBP2 leads to increased vulnerability to motor neuron death which leads to neuromuscular junction (NMJ) denervation and reduced muscle fiber size. There is no effective treatment for SMARD1; patients rely on mechanical ventilators and other palliative care measures. Recently, we have developed a mouse model with the first patient-derived mutation, D564N (Ighmbp2$^{D564N/D564N}$) using the CRISPR/Cas9 System. The D564N mutant mice have severe phenotypic abnormalities including reduced lifespan, weight gain, motor function, and respiratory defects. Additionally, the mice possess selective muscle vulnerability with the gastrocnemius being a severely impacted muscle to denervation and fiber size.

Objective: We wanted to determine if this new model was able to be rescued by gene therapy. We utilized gene replacement therapy by employing an adeno-associated viral vector stereotype 9 (AAV9) carrying full-length IGHMBP2 to see if it will rescue the severity of the D564N mice. Preliminary results of treated D564N mutant mice revealed an extension of lifespan and motor function. AAV9-IGHMBP2 gene therapy also improved important cellular pathology features. By further analyzing the phenotypic and cellular features, we can evaluate the extent the D564N mice are rescued with gene replacement therapy. This will provide a better context to determine if AAV9-IGHMBP2 is a viable treatment option for patients, and can lead to future developments of treatments.