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

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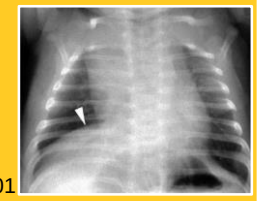
## Introduction

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. 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.

## Figure 1 - Clinical Manifestation

- Onset 6-12 months of age
- Diaphragm paralysis
- Distal to proximal spread of muscle paralysis
- No treatment options



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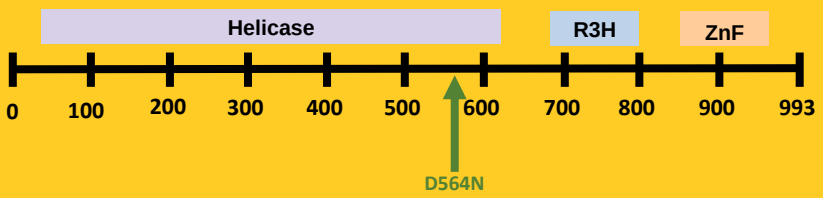
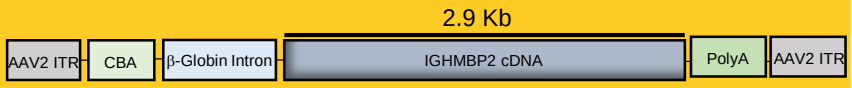
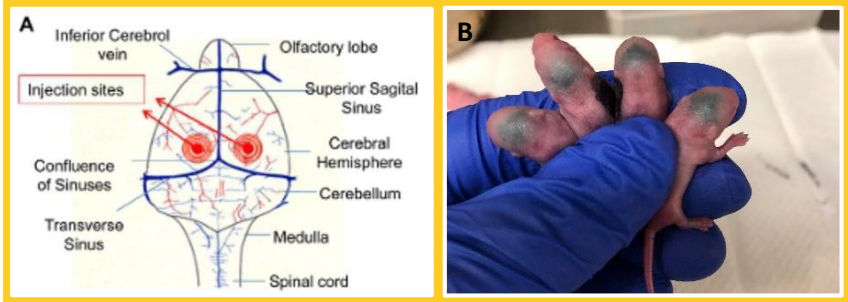
## Figure 2 - IGHMBP2 Function Domains - D564N Mutation



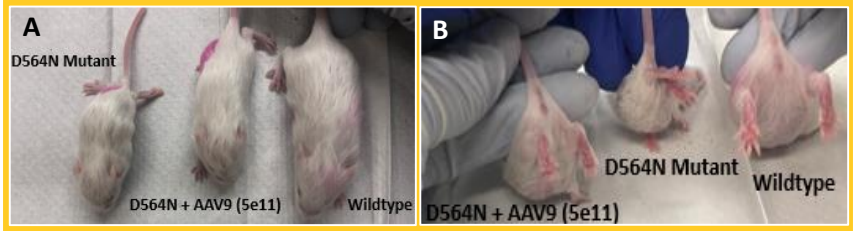

## Figure 3 - ssAAV9-IGHMBP2 Viral Construct



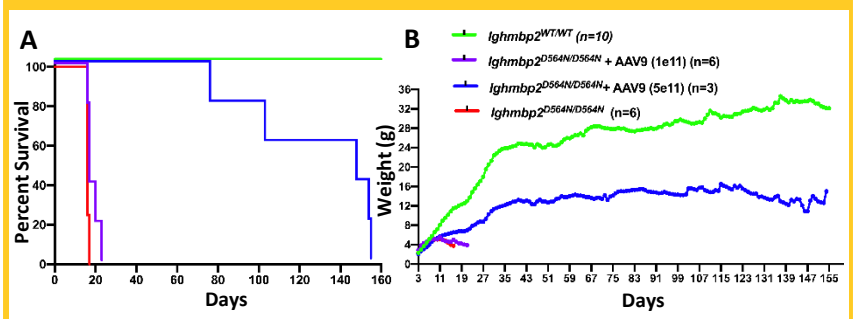

## Figure 4 - Intracerebroventricular Injection



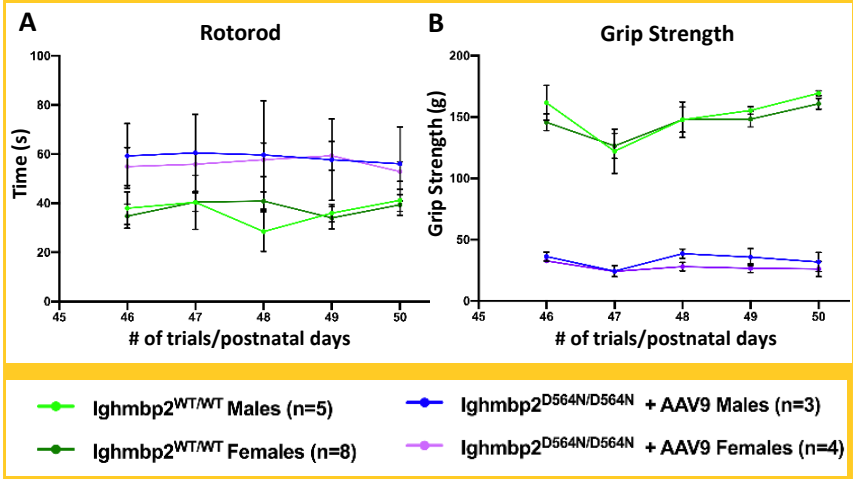

## Figure 5 - ssAAV9-IGHMBP2 Treatment Improves Phenotype



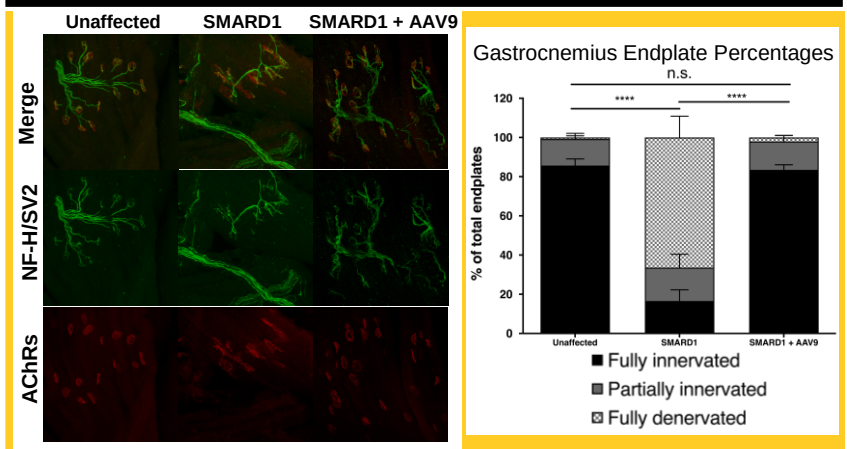

## Figure 6 - ssAAV9 Improves Survival and Weight Gain



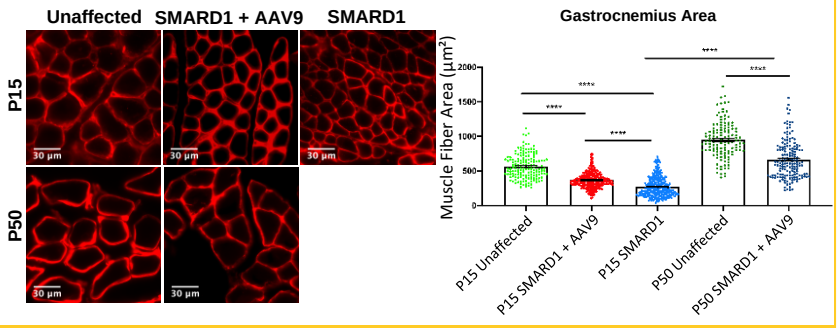

## Figure 7 - ssAAV9-IGHMBP2 Improves Motor Function




## Figure 8 - ssAAV9-IGHMBP2 Improves Innervation




## Figure 9 - ssAAV9 Improves Muscle Fiber Size




## Conclusion and Future Directions

- AAV9-IGHMBP2 Improves survival, weight gain, and motor function.
- AAV9-IGHMBP2 increases muscle fiber size and innervation in the gastrocnemius muscle.
- Cellular pathology for lumbar spinal cord motor neurons still need to be analyzed. Other muscle groups need to be analyzed.
- If gene therapy on a patient-derived mutation treats SMARD1 patients, it can potentially lead to the development of treatments.
- This project can be furthered by determining drug dosages, route of administration, and time points for treatment.

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