Multicentered IND-enabling Efficacy and Safety Studies Are Highly Promising For SMARD1/CMT2S Gene Therapy

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Presented by Kathrin Meyer at ASGCT, May 16th, 2022, Washington, DC

DISCLOSURES: Kathrin Meyer receives royalties from Batten Gene Therapy programs licensed to Amicus Therapeutics, Inc.; is a member of the scientific advisory board and receives consulting fees, royalties, and sponsorship for research from Alcyone Therapeutics; and receives royalties for AAV-NK methodology from Kiadis Pharma.

Loss Of Function Mutations In IGHMBP2 Cause SMARD1/CMT2S

Motor + sensory involvement

Respiratory + motor involvement

SMARD1

- Distal muscle weakness and respiratory failure
- Onset usually before 6 months of age
- Require permanent ventilation before 13 months of age (classically)

CMT2S

- Slowly progressing distal muscle weakness
- Onset usually in 1st decade (up to 60 years)
- Muscle atrophy of upper and lower limbs
- Mild sensory involvement







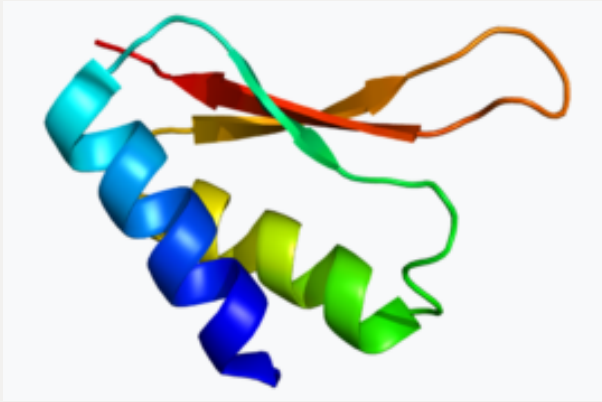

NO clear genotype/phenotype correlation

Pictures kindly provided by SMASHSMARD USA

smashSMARD

IGHMBP2 Function

- **Immunoglobulin μ-binding protein 2**
- **993 amino acids**
- **Chromosome 11**
- **RNA/DNA helicase**
- **Interacts with small RNAs (especially tRNAs – tRNA-Tyr)**
- **Mouse gene identified by Dr. Cox (Cox et al, 1998)**



IGHMBP2

Gene Therapy for SMARD1 Proof of Concept Studies

RESEARCH ARTICLE

GENE THERAPY

Gene therapy rescues disease phenotype in a spinal muscular atrophy with respiratory distress type 1 (SMARD1) mouse model

10.1126/sciadv.1500078

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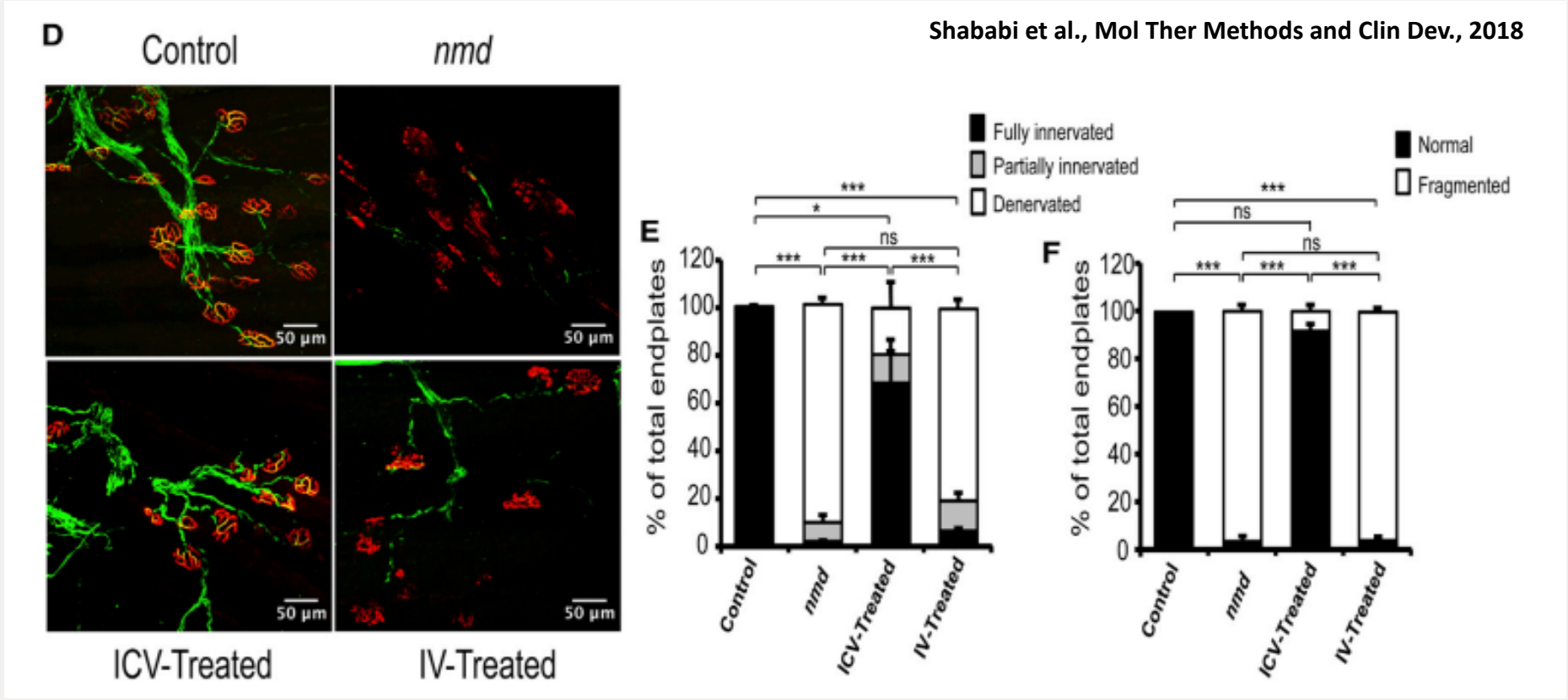
Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is an autosomal recessive motor neuron disease affecting children. It is caused by mutations in the *IGHMBP2* gene (11q13) and presently has no cure. Recently, adeno-associated virus serotype 9 (AAV9)–mediated gene therapy has been shown to rescue the phenotype of animal models of another lower motor neuron disorder, spinal muscular atrophy 5q, and a clinical trial with this strategy is ongoing. We report rescue of the disease phenotype in a SMARD1 mouse model after therapeutic delivery via systemic injection of an AAV9 construct encoding the wild-type *IGHMBP2* to replace the defective gene. AAV9-*IGHMBP2* administration restored protein levels and rescued motor function, neuromuscular physiology, and life span (450% increase), ameliorating pathological features in the central nervous system, muscles, and heart. To test this strategy in a human model, we transferred wild-type *IGHMBP2* into human SMARD1-induced pluripotent stem cell–derived motor neurons; these cells exhibited increased survival and axonal length in long-term culture. Our data support the translational potential of AAV-mediated gene therapies for SMARD1, opening the door for AAV9-mediated therapy in human clinical trials.

Previously Published Data Indicates CSF Delivery as Better Route of Treatment



Shababi et al., Mol Ther Methods and Clin Dev., 2018

→ **Intrathecal delivery seems to make a lot of sense for this program**

Project Sponsors

Mouse Models used in SMARD1/CMT2S Program

- **Three mouse models, spanning the entire disease spectrum**

Severity	Mouse model	Genotype	Phenotype
Severe	em3	L362del	Severe SMARD1-like paralysis, death within 21 days
Intermediate	nmd-2J	Exon 4 splice variant reduces protein expression	Intermediate SMARD1-like paralysis, death ~60-100 days
Mild	em5	Y918C modelled after patient mutation	CMT2S, sensory and motor neuropathy, death >10 months

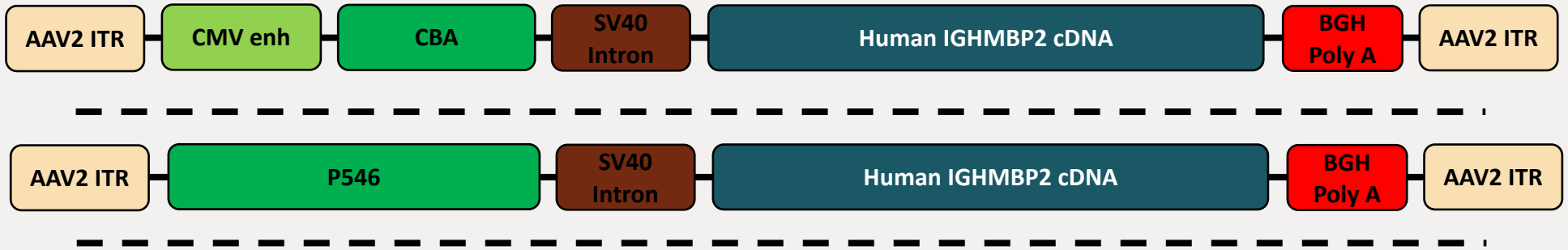
(L362del = nonfunctional truncated protein)

Promoter Selection

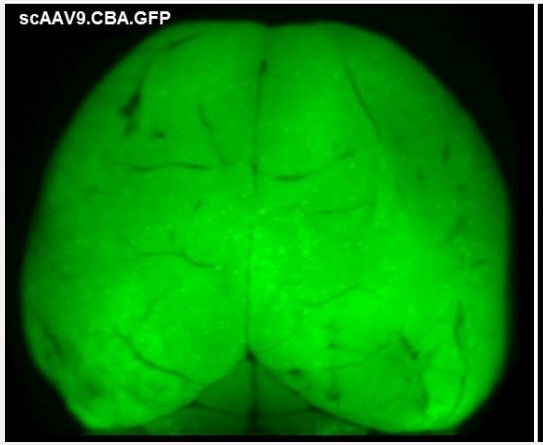
We assessed two candidate promoters for driving the expression of IGHMBP2 (see ASGCT poster #1072 - Andrea Sierra Delgado)

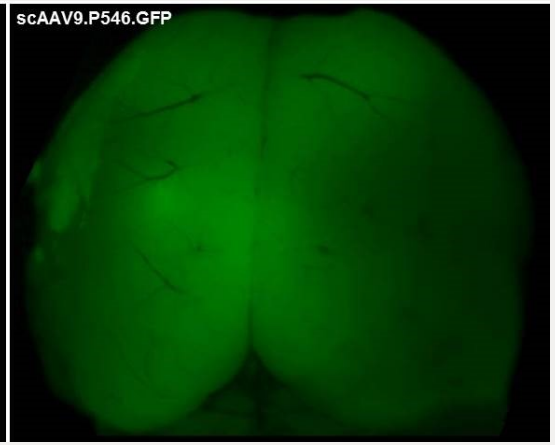
Two Different Promoters Used To Drive IGHMBP2 Expression To Vary Expression Levels

- **All mice in all studies dosed at PND1 to mimic targeting pattern seen in larger animal species**
- **Teams in all studies performed blinded**

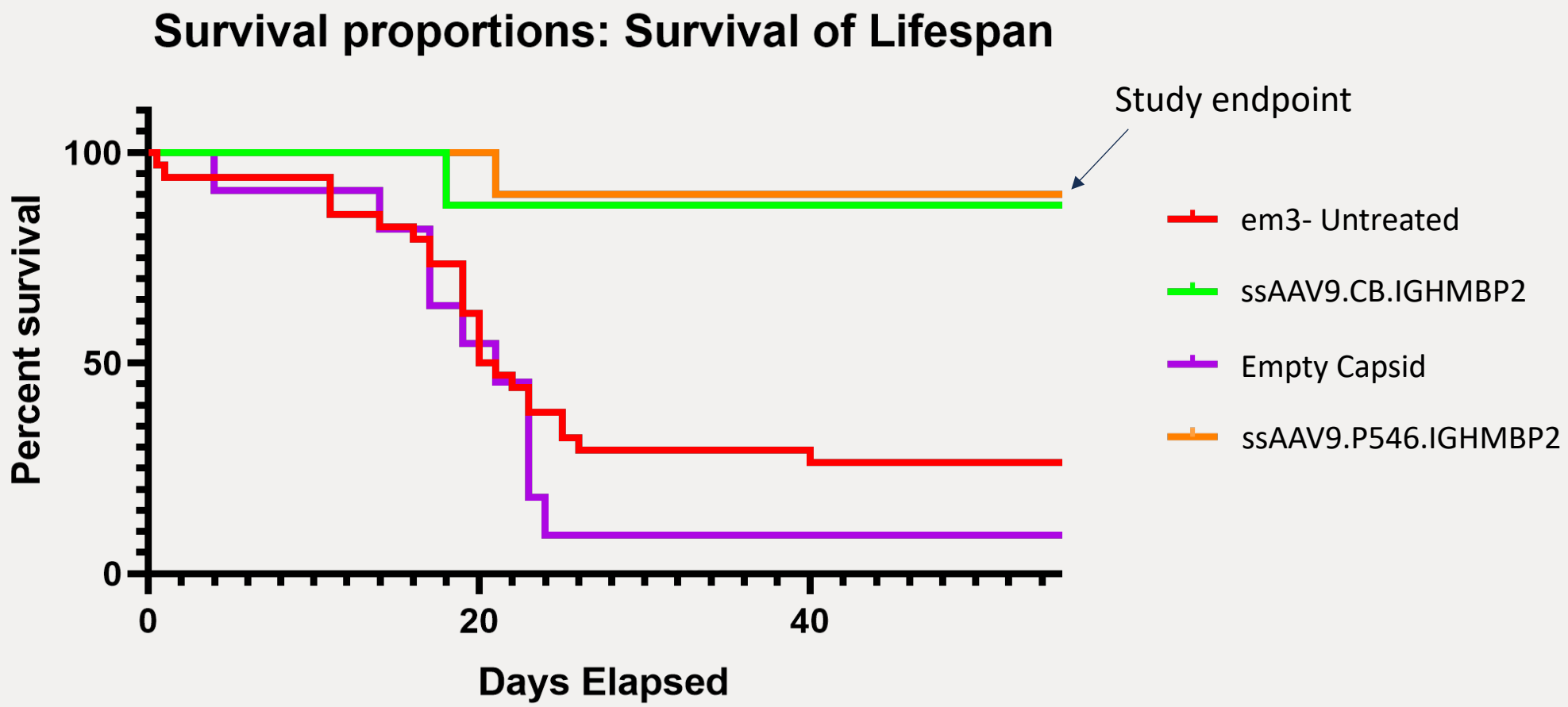


Empty viral particles

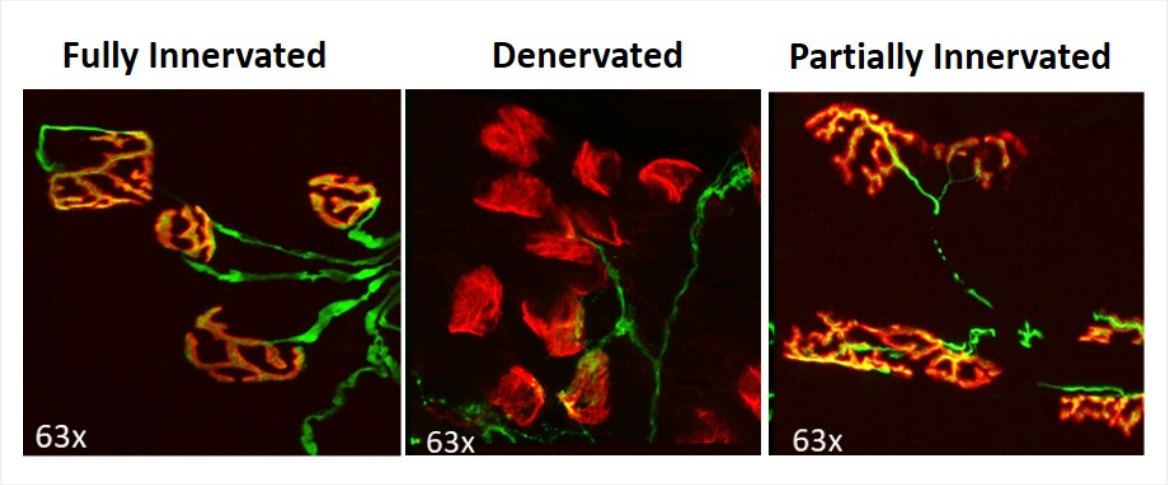


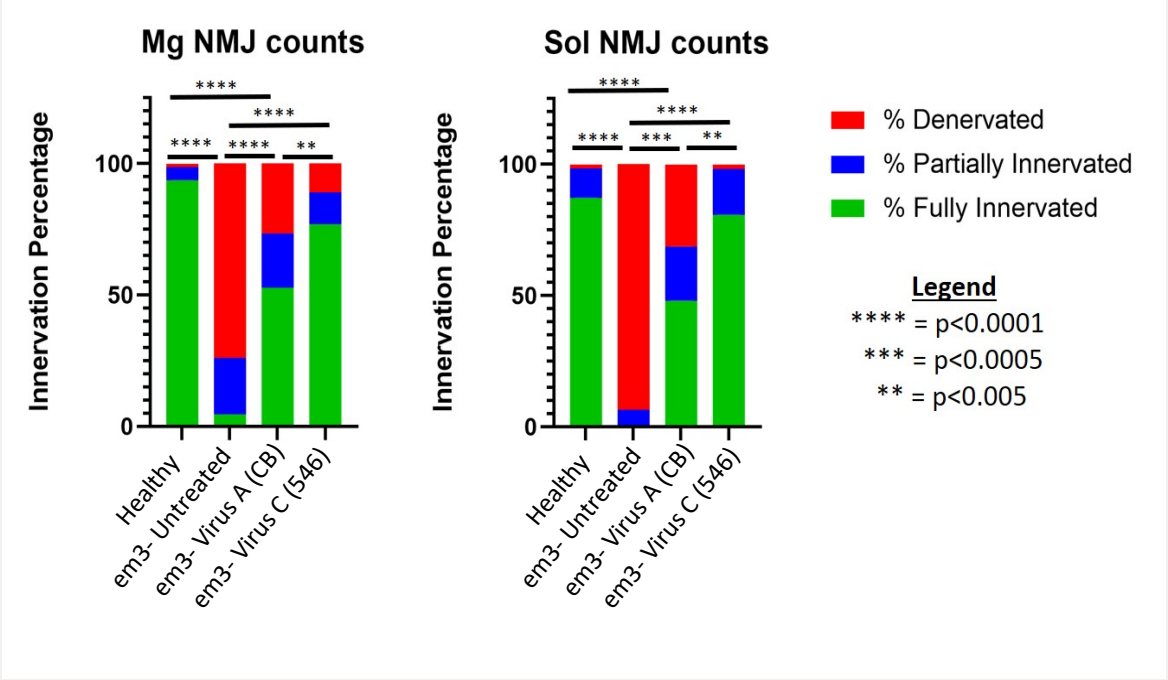


AAV9.IGHMBP2 Strongly Improved Life Span Of Em3 Mice Independent of Promoter Choice



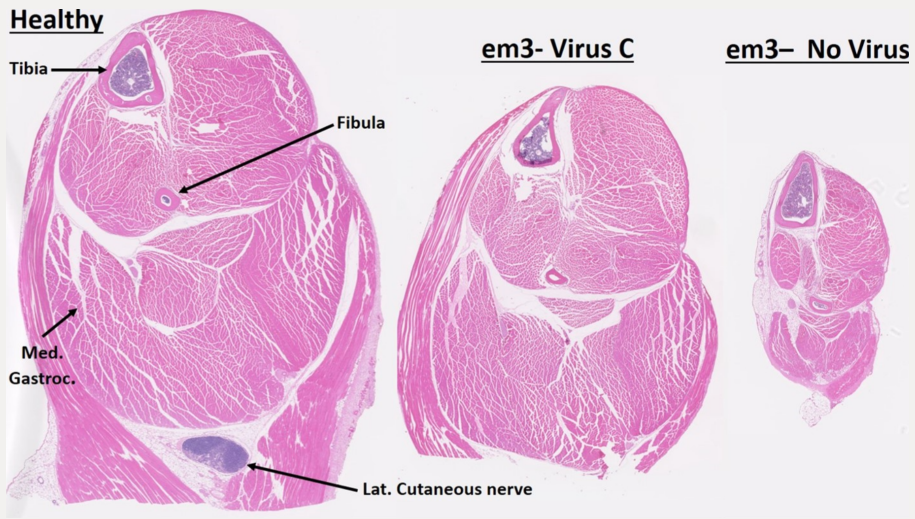
AAV9.P546.IGHMBP2 Displayed Stronger Effect On Innervation

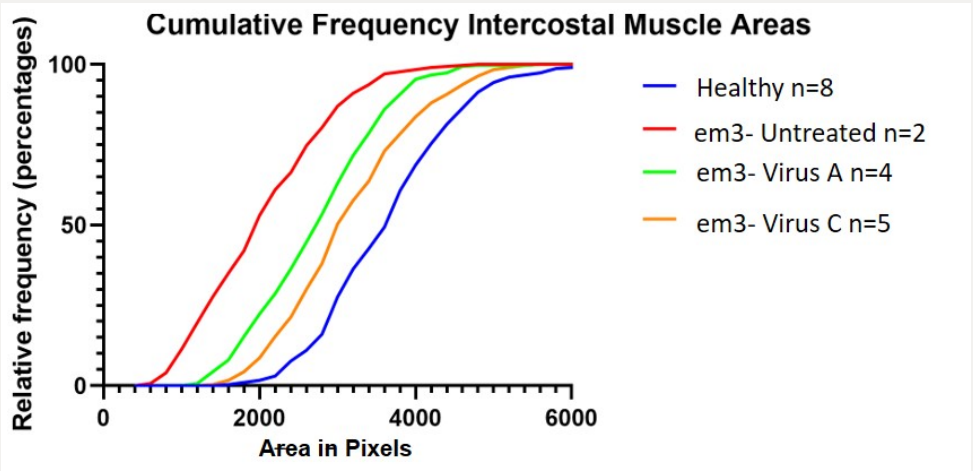


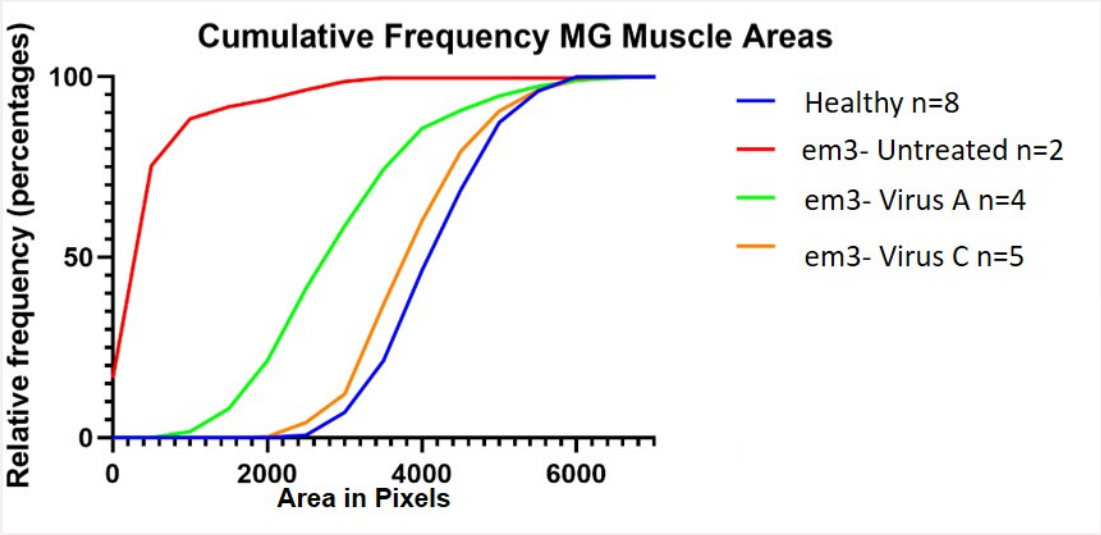


→ **70-80% Fully innervated NMJs**

Promoter-dependent Increase in Muscle Mass







Virus A= ssAAV9.CB.IGHMBP2

Virus C= ssAAV9.P546.IGHMBP2

→ **Same result also found in heart**

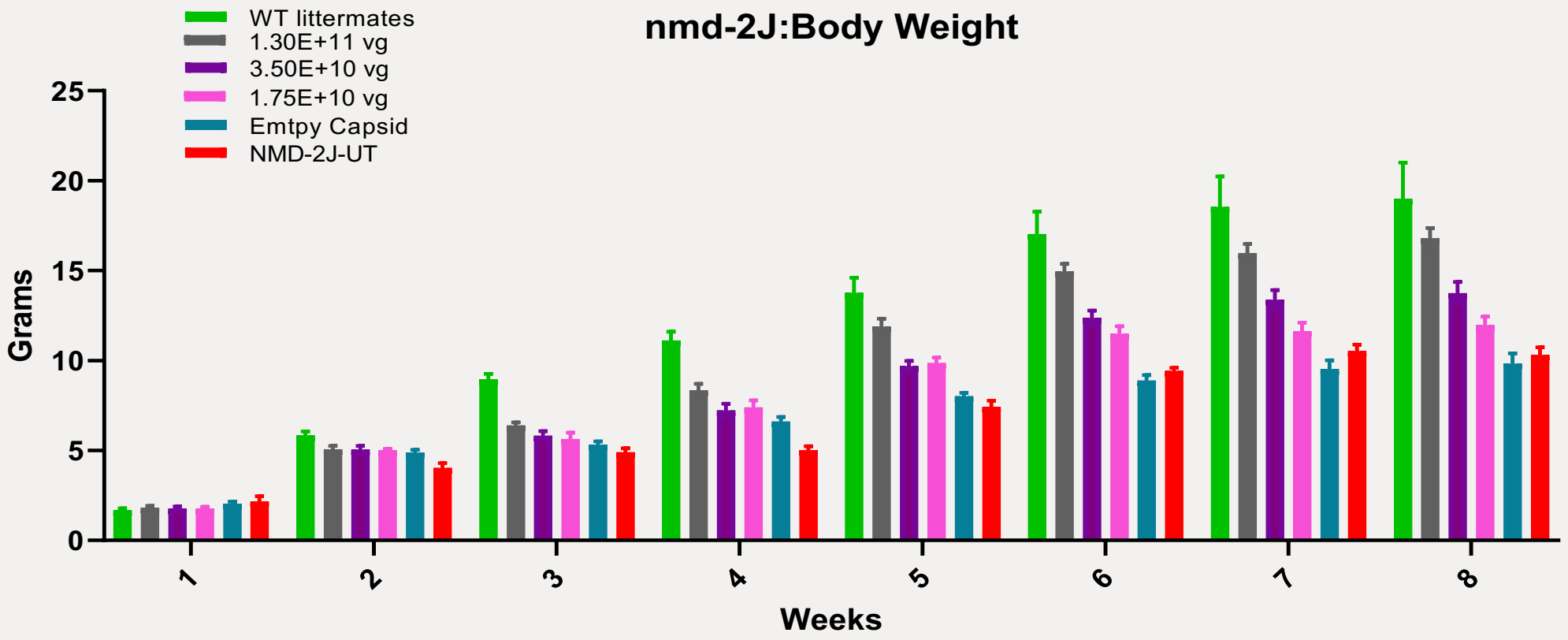
Summary of Promoter Comparison Findings

- **Both promoters work well in all 3 mouse models (ASGCT Poster #1072)**
- **P546 slightly better in the most severe mouse model in rescue of strength, axon diameter, and NMJ innervation**
- **No apparent difference in promoter performance in intermediate nmd-2J and mild Em5 mice**

Dose Response Studies with AAV9.P546.IGHMBP2

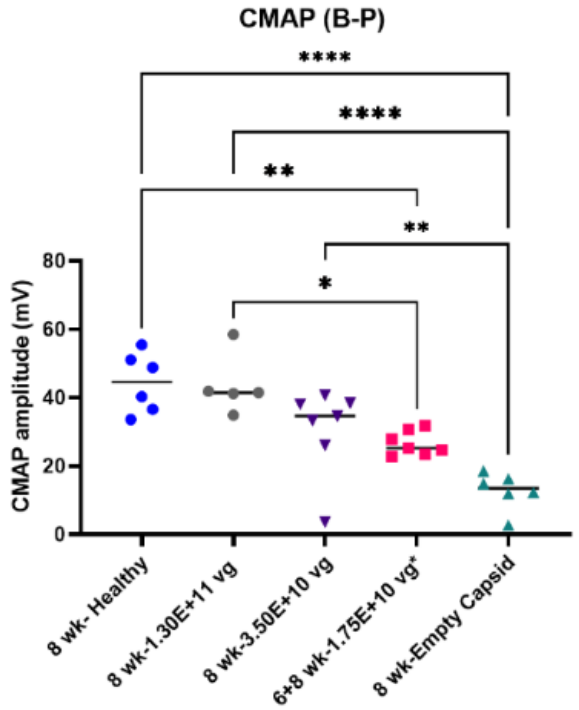
- **Doses were chosen to bracket the initial single-dose efficacy study**
- **Dose response was performed in all three mouse models**
- **The following slides mainly focus on results from the NMD-2J intermediate mouse model**

Dose-Dependent Weight Development in NMD-2J Mice Post Treatment with AAV9.P546.IGHMBP2

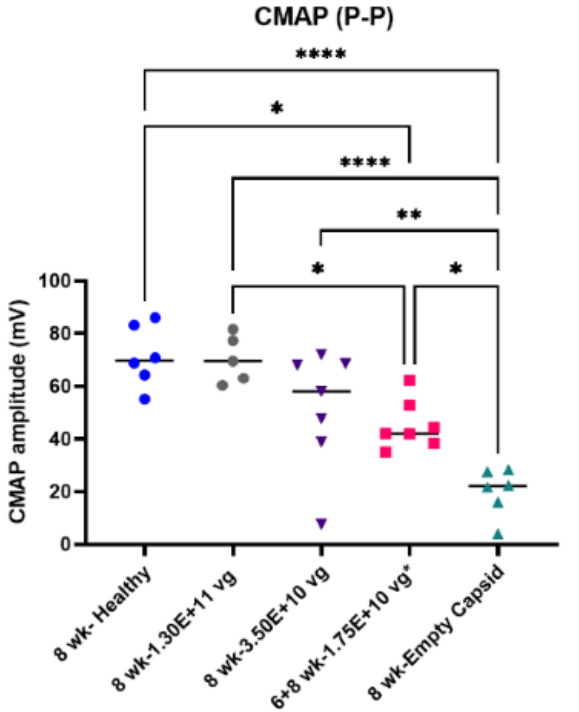


→ **Males show a slightly more severe disease progression compared to females**

Dose-Dependent Improvement in CMAP and MUNE in AAV9.P546.IGHMBP2 Treated Animals



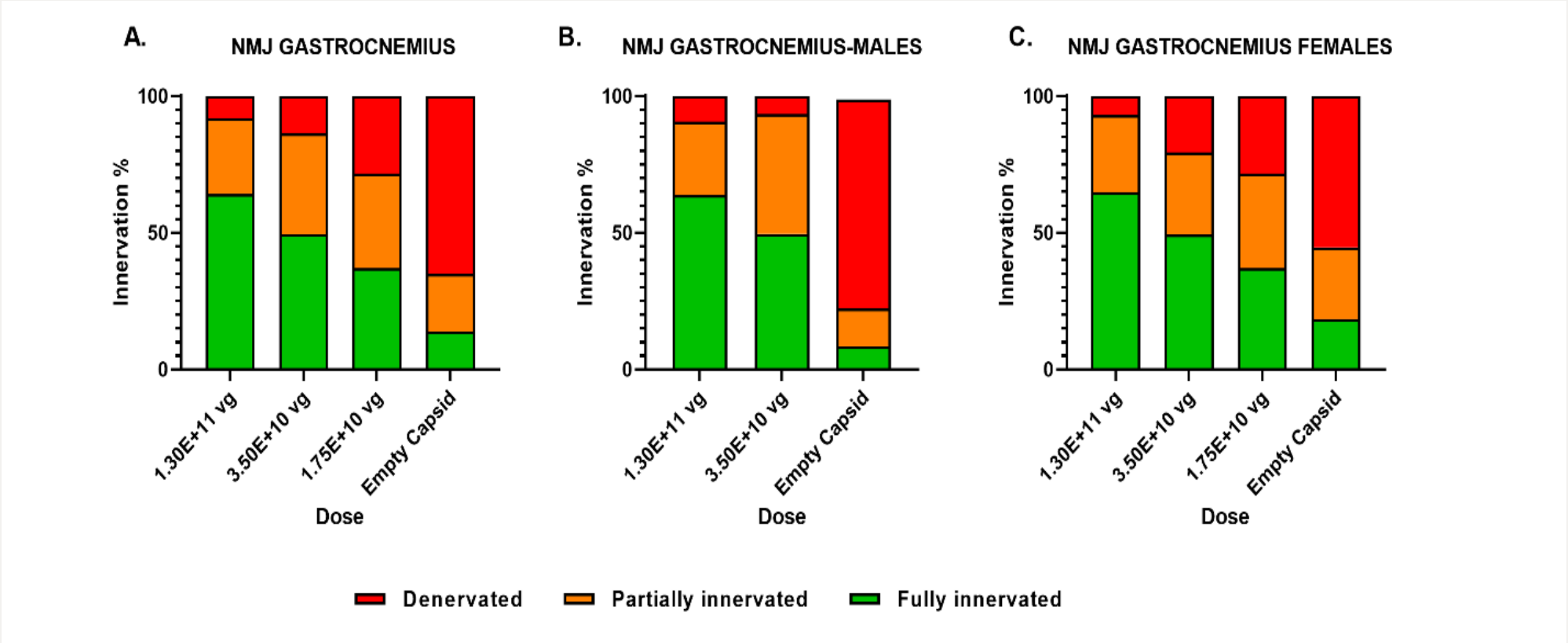
*1.75E+10 vg males analyzed at 6 weeks and 1.75E+10 vg females analyzed at 8 weeks



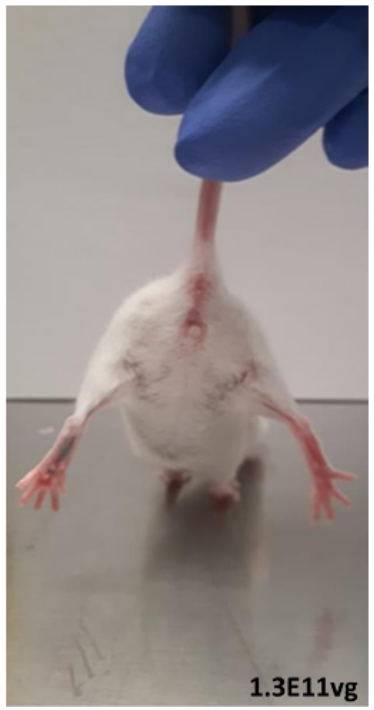
*1.75E+10 vg males analyzed at 6 weeks and 1.75E+10 vg females analyzed at 8 weeks

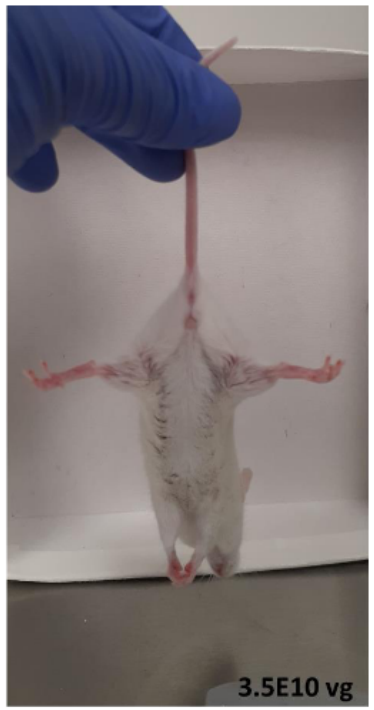
→ **Potential Translational Biomarker**

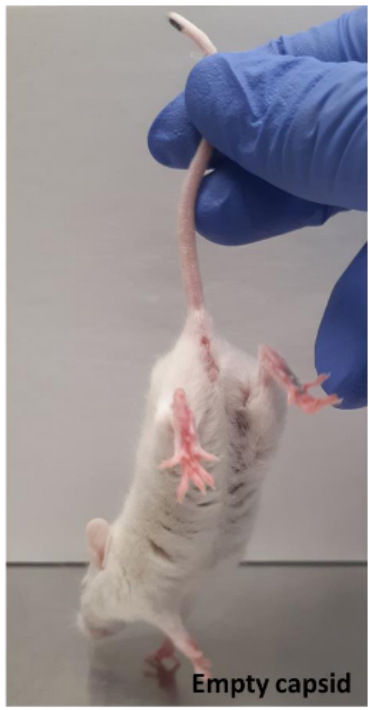
Dose-Dependent NMJ Innervation in NMD-2J Mice



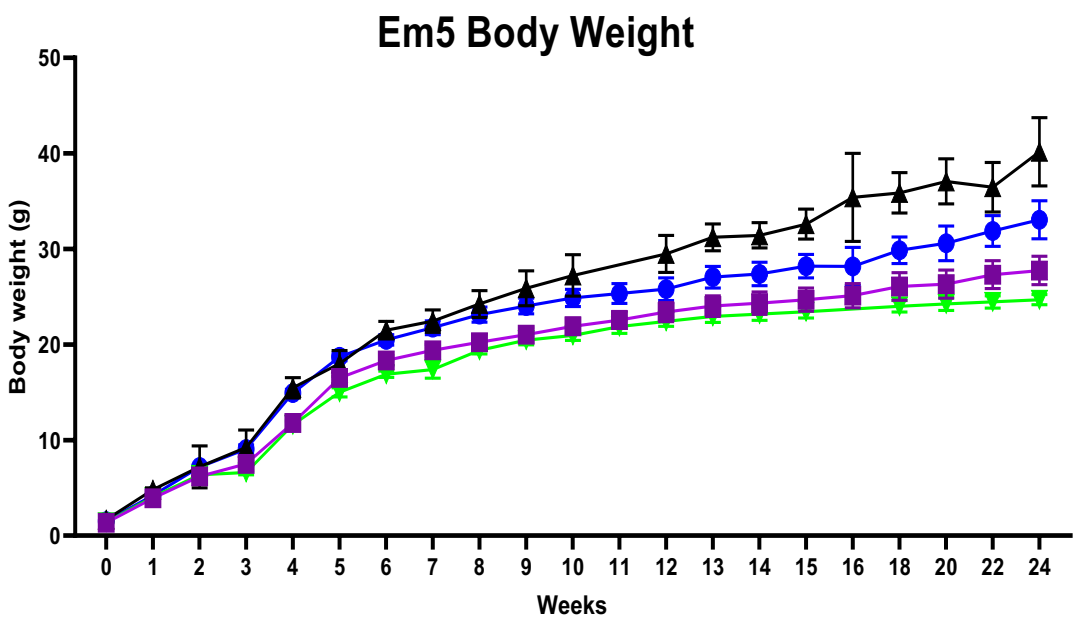
Dose-Dependent Rescue of Clasping Defect

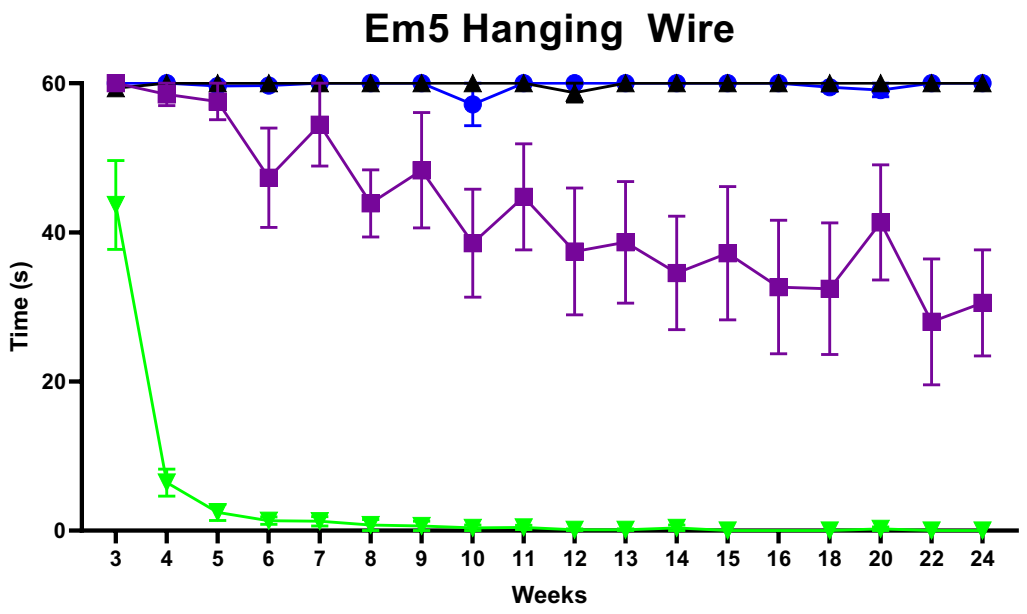






Similar Doses Needed for Optimal Treatment Effect in Mild Em5 Mouse Model





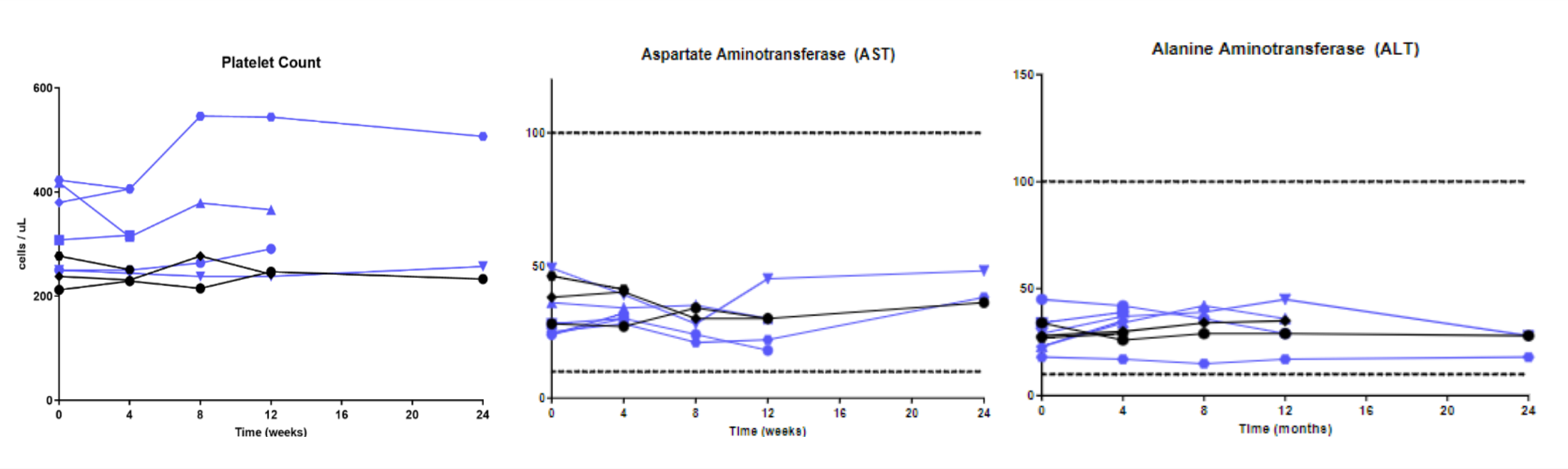
→ **Likely important factor = number of cells targeted**

Summary Dose Response Studies

- **Effect is highly dose-dependent in all three mouse models**
- **Milder mouse models do not require lower dose for efficacy – number of cells targeted likely the key**
- **Data is highly promising and indicates AAV9.P546.IGHMBP2 treatment should be applicable for both SMARD1/CMT2S caused by loss of function/reduced function of the IGHMPB2 protein**

Safety Studies in Mice and Non-human Primates

- **Dose-Response research grade viral vector in wild type mice**
- **Single-Dose research grade viral vector in non-human primates (6 animals vs. 3 PBS injected animals)**
- **Two-Dose clinical grade viral vector in wild-type mice**
- **Two-Dose clinical grade viral vector efficacy side-by-side comparison to research grade material in Em3 mice**



Safety Studies in Mice and Non-human Primates

→ **No concerns found in hematology, serum chemistry, histopathology or behavior**

- **Up to 1 year post injection in mice**
- **Up to 6 months post injection in NHPs**

→ **No histopathological findings that would indicate non-tolerability**

- **Treatment did not induce lesions in any tissue analyzed**
- **Treatment was associated with AAV class-related, previously-described changes (such as mononuclear cell infiltration in brain around meninges and in spinal cord and in some DRGs) at minimal non-concerning levels**
- **In isolated DRGs in some animals, very limited cell necrosis was found as previously described by Dr. Wilsons group. The findings were very minimal and classified as non-adverse by an experienced third-party veterinary pathologist**

Phase I/II Clinical Trial of ACT-401

- **IND application for ACT-401 has been approved by the US FDA**
- **Clinical trial initiated**
- **Immediate, high response rate and high level of interest from affected families**
- **Trial currently actively enrolling**
- **Treatment so far safe and well tolerated**

- **Sponsor: Megan Waldrop, MD**

Acknowledgements

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