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Peptide-displaying chimeric AAV vectors with increased skeletal muscle potency and specificity for systemic gene therapy

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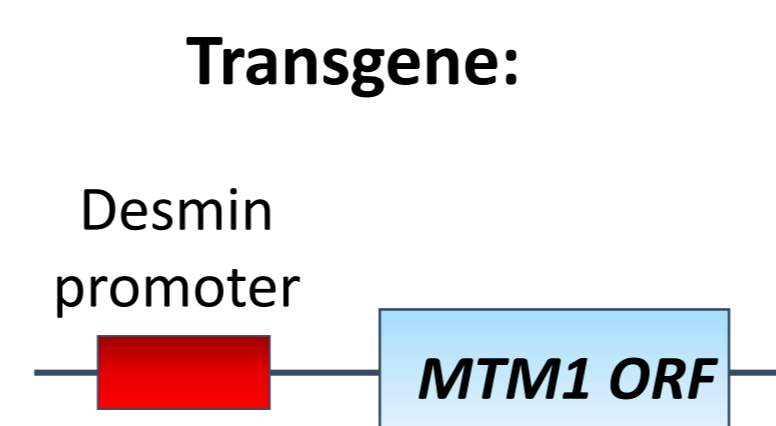
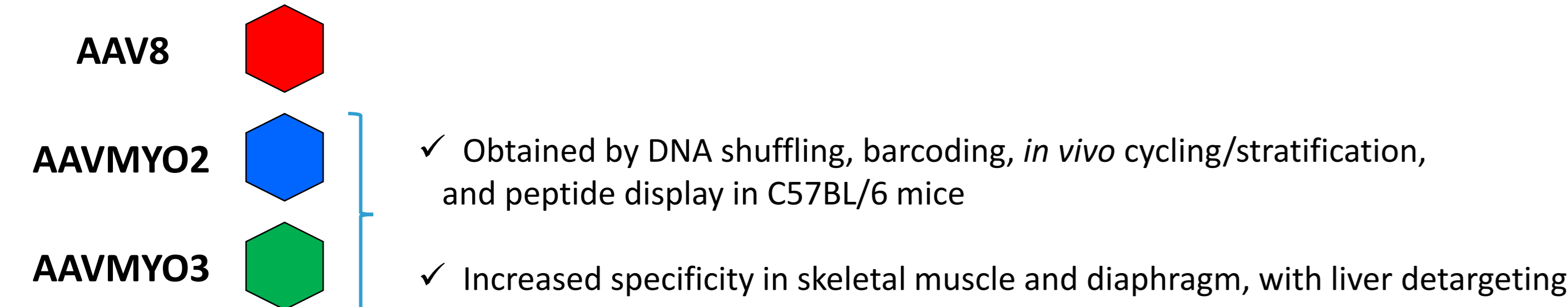
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⁵ German Center for Infection Research (DZIF) and German Center for Cardiovascular Research (DZHK), partner site Heidelberg, Germany

INTRODUCTION:

Bioengineering of adeno-associated viral (AAV) vectors is a pivotal strategy for developing next-generation gene therapies for human disorders. In the present study, we assessed the efficacy of two novel AAV vectors, AAVMYO2 and AAVMYO3, which are composed of hybrid capsids and a small VP1 peptide insertion, in a mouse model of myotubular myopathy, a fatal pediatric disease affecting skeletal muscles that is caused by loss-of-function mutations in the MTM1 gene.

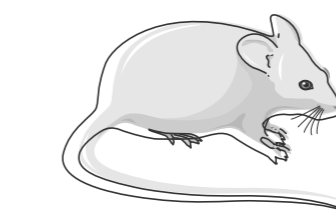
METHODS:



Dose-response:

1^e14 vg/Kg
2^e13 vg/Kg
4^e12 vg/Kg

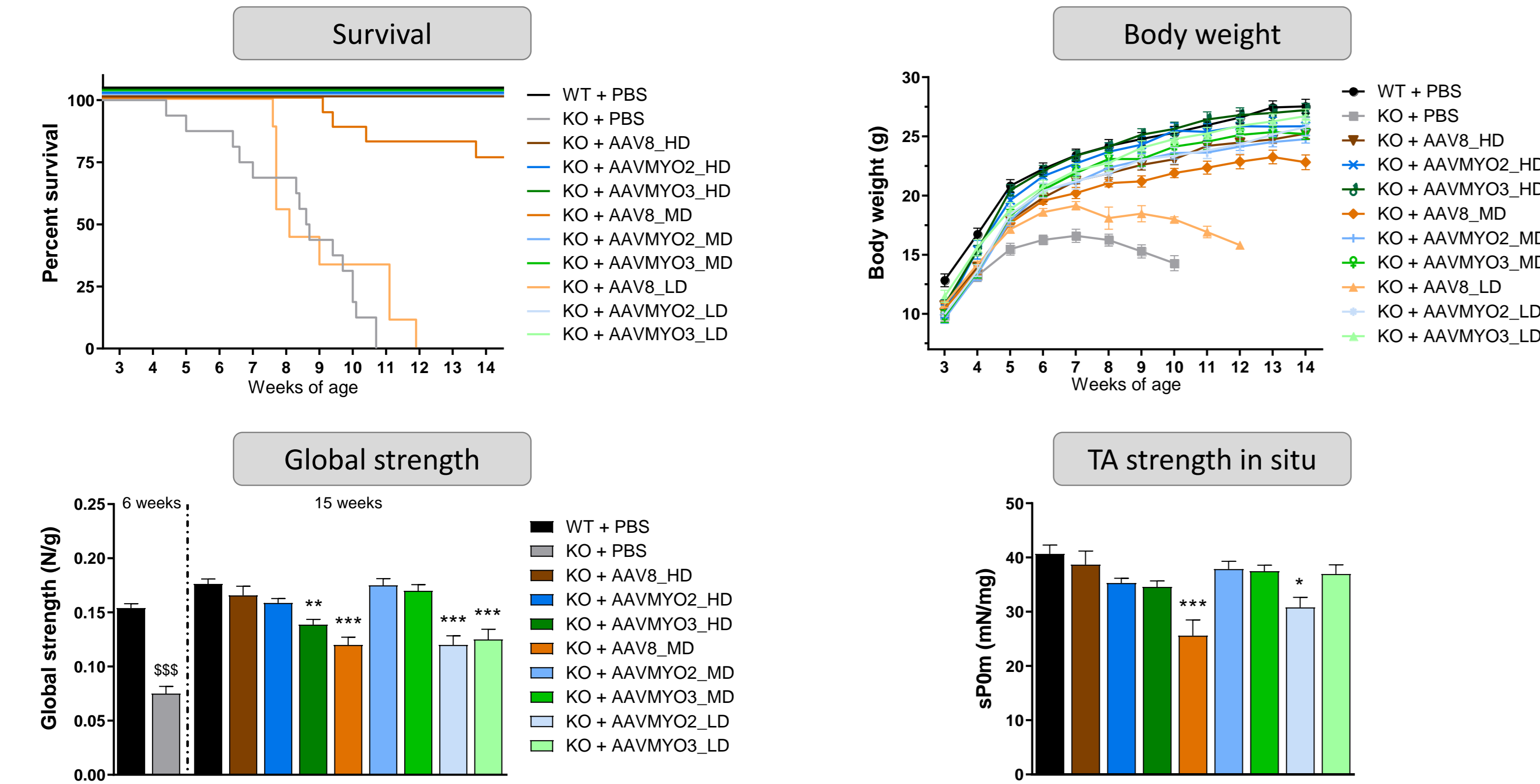
Mtm1 KO mice



3 weeks 6 weeks 15 weeks

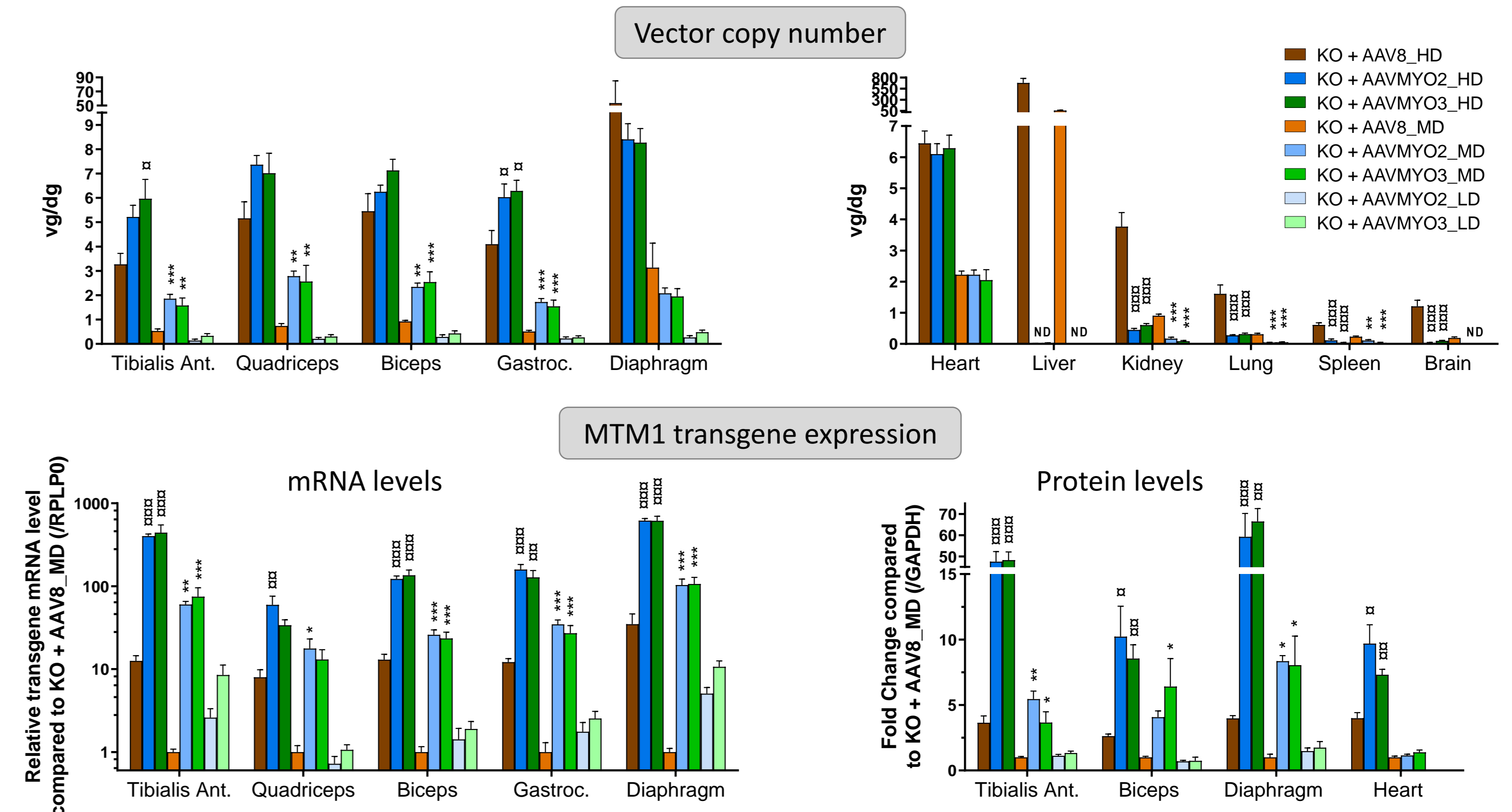
IV Injection WT/KO Functional analysis Functional analysis and tissue harvesting

RESULTS - Gene therapy of myotubular myopathy:



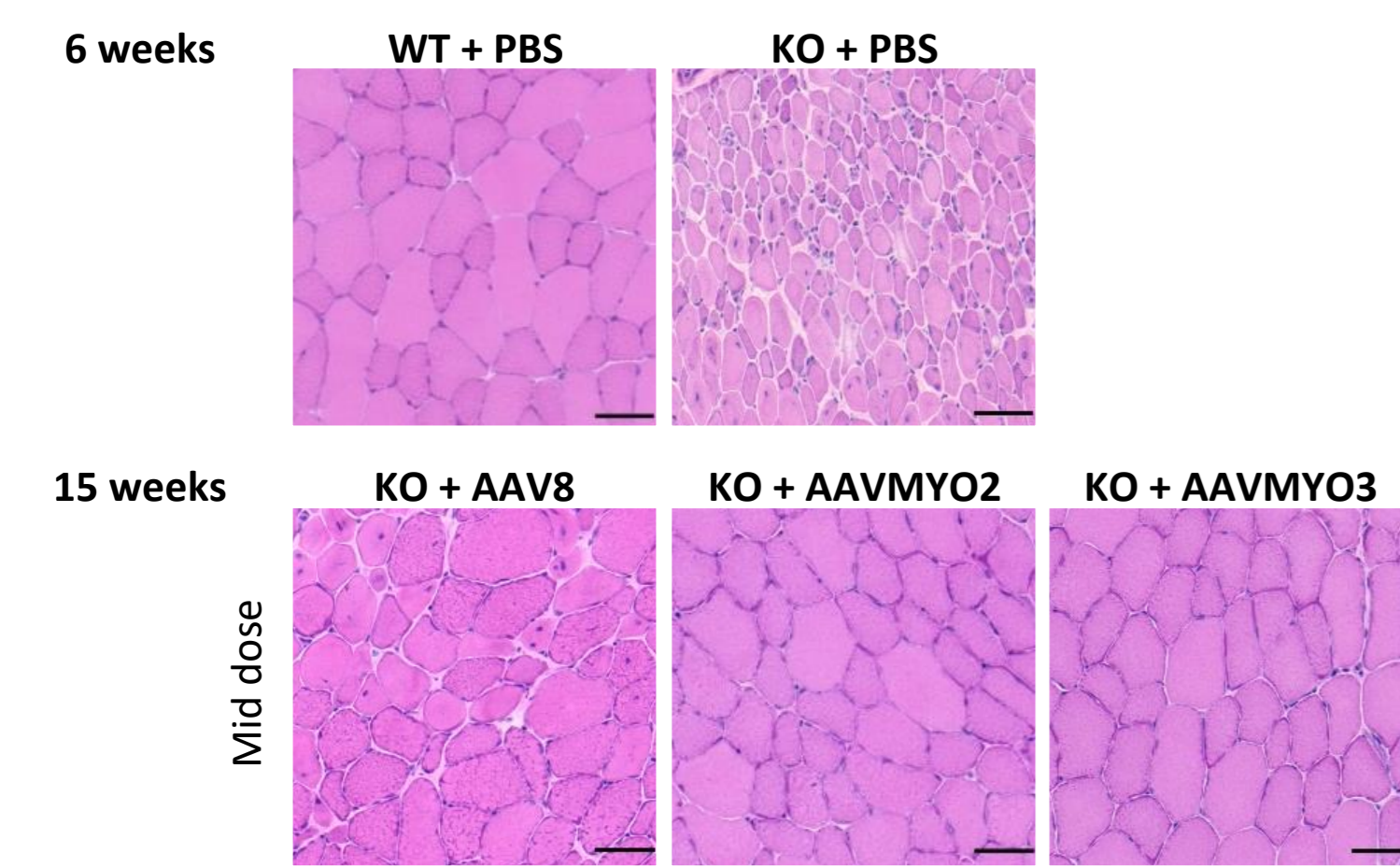
Intravenous administration of AAVMYO2- or AAVMYO3-MTM1 vectors prolongs lifespan and increases body weight and strength of *Mtm1*-KO mice

RESULTS – Biodistribution of chimeric vectors

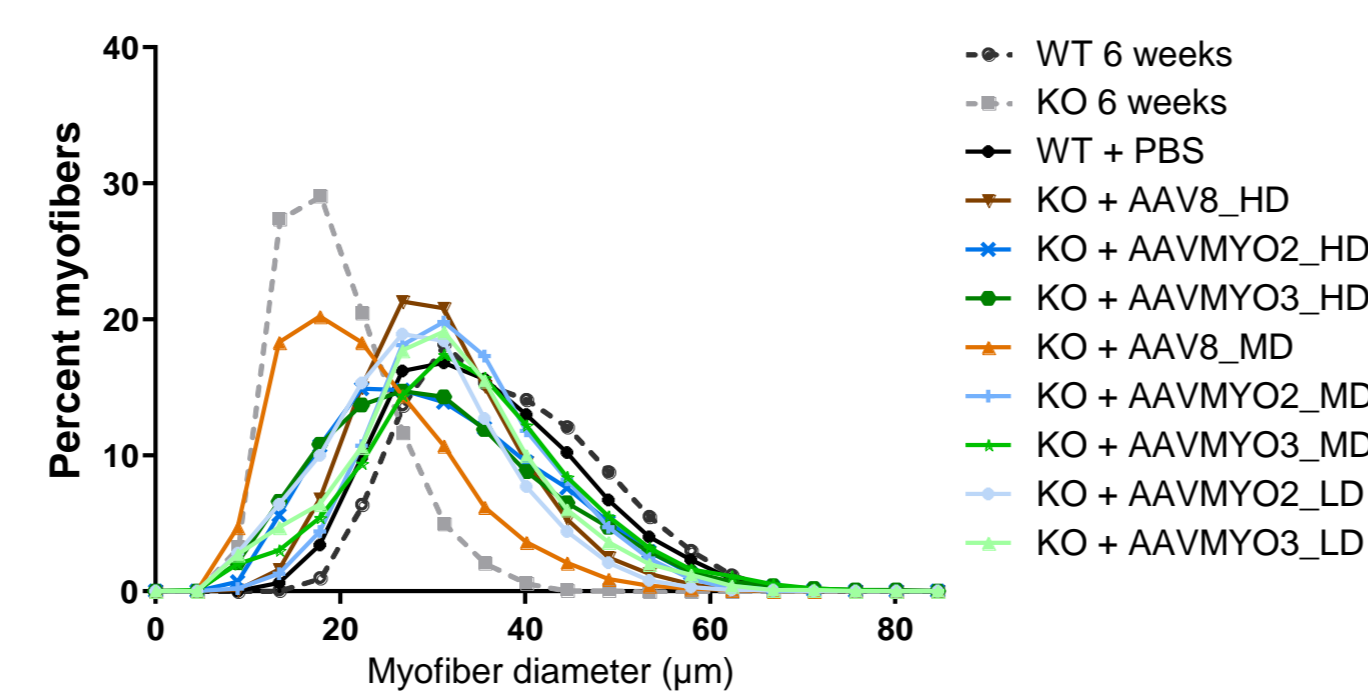


IV administration of AAVMYO2 and AAVMYO3 vectors results in increased transduction of skeletal muscles and liver detargeting

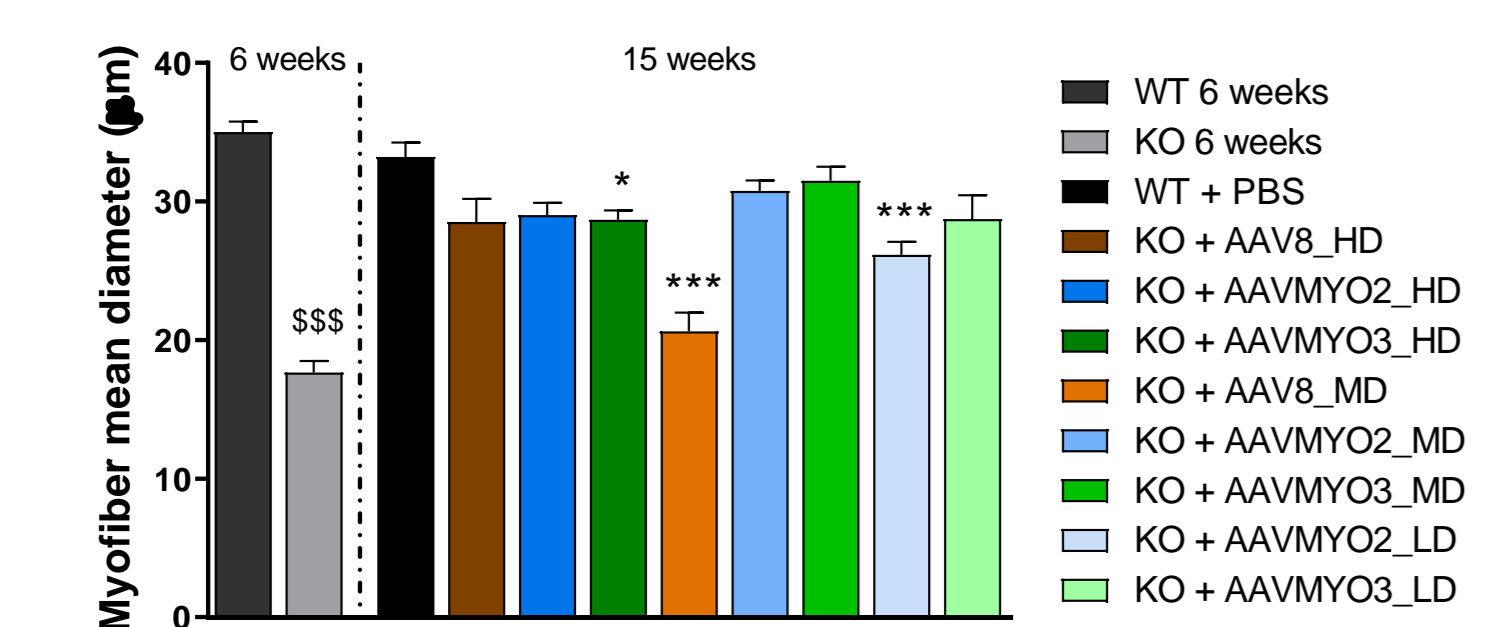
HE staining



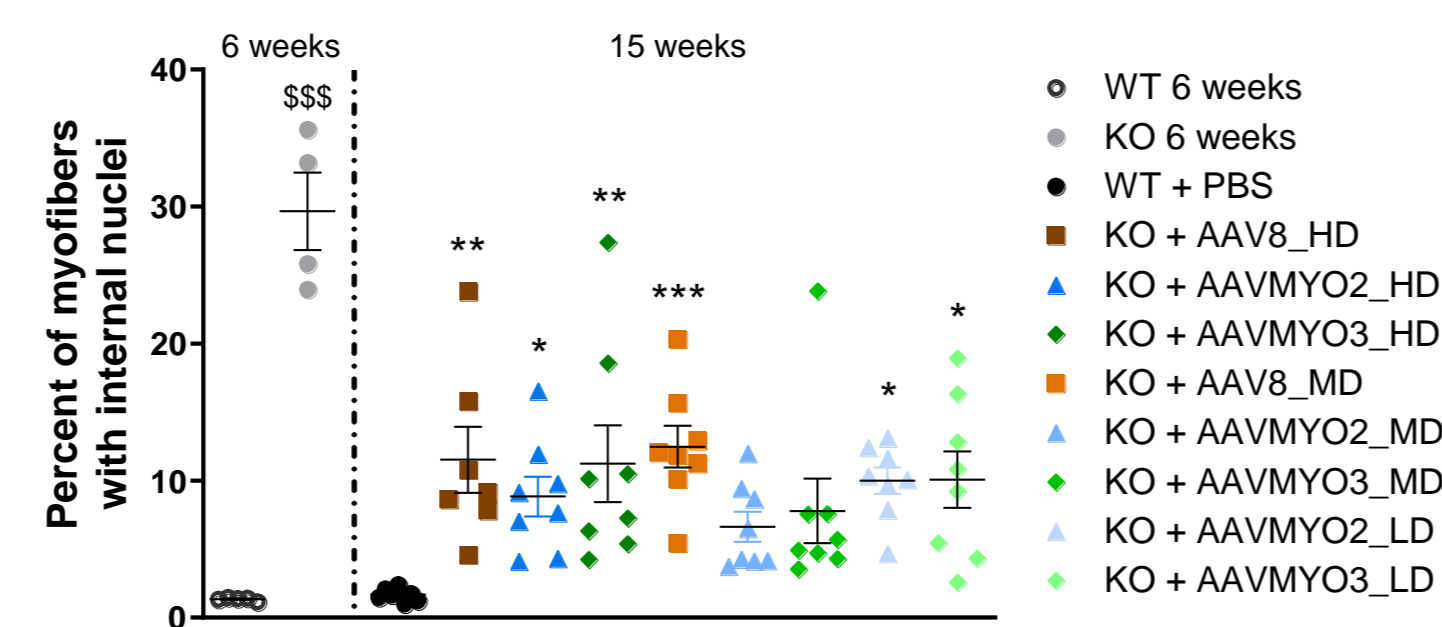
TA myofiber diameter frequency distribution



TA myofiber mean diameter



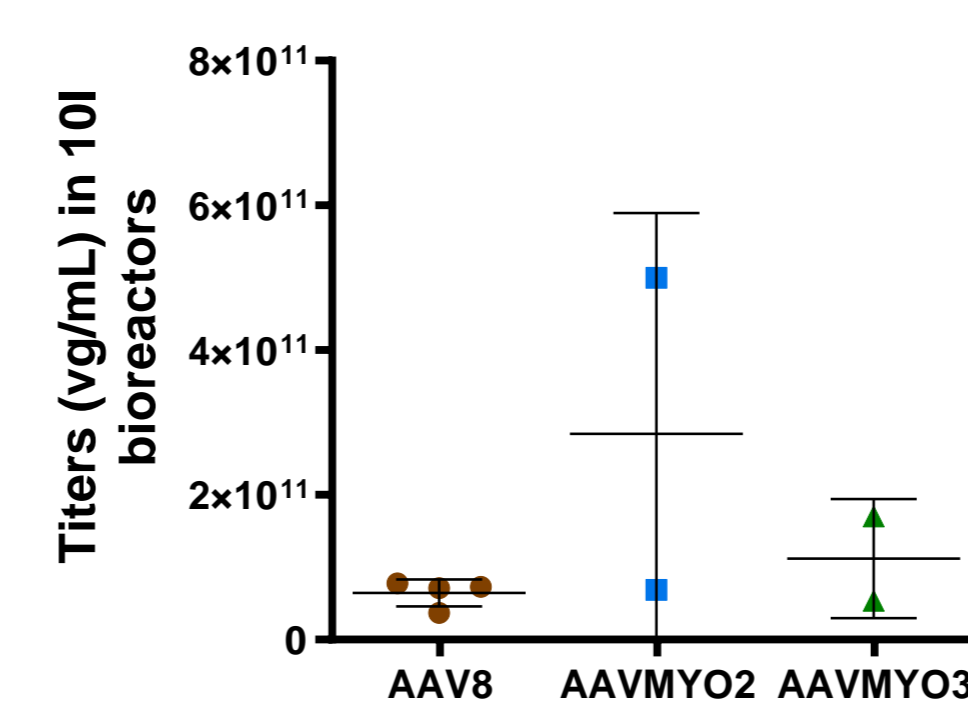
Nucleus internalization in TA myofibers



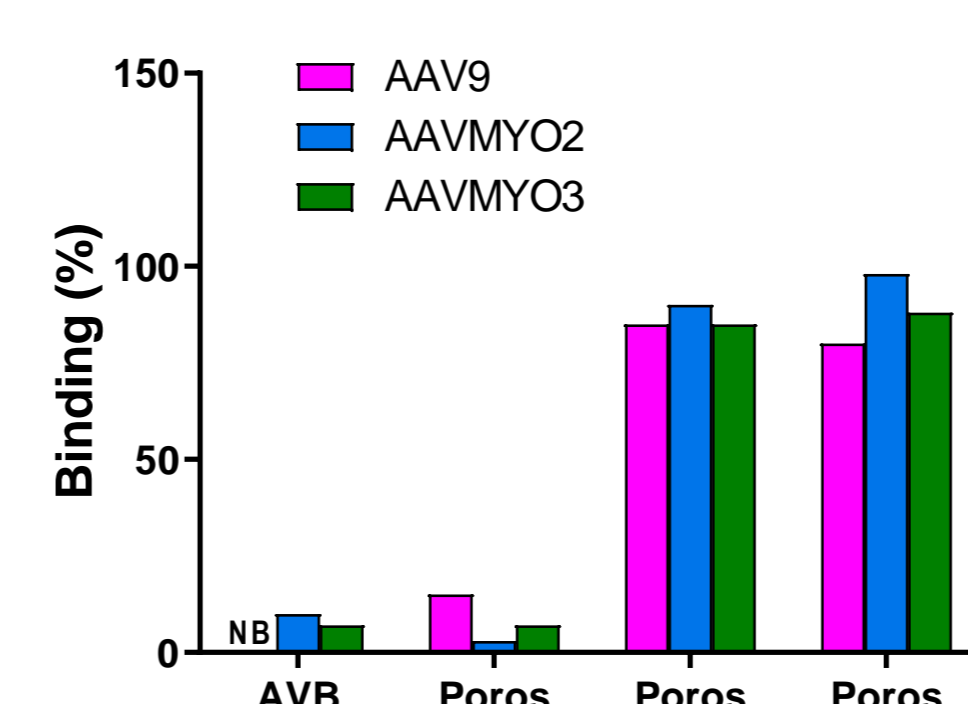
Chimeric myotropic vectors AAVMYO2 and AAVMYO3 ameliorate the histological hallmarks of XLMTM muscle pathology

RESULTS - AAV production:

Vector titers in 10L bioreactors



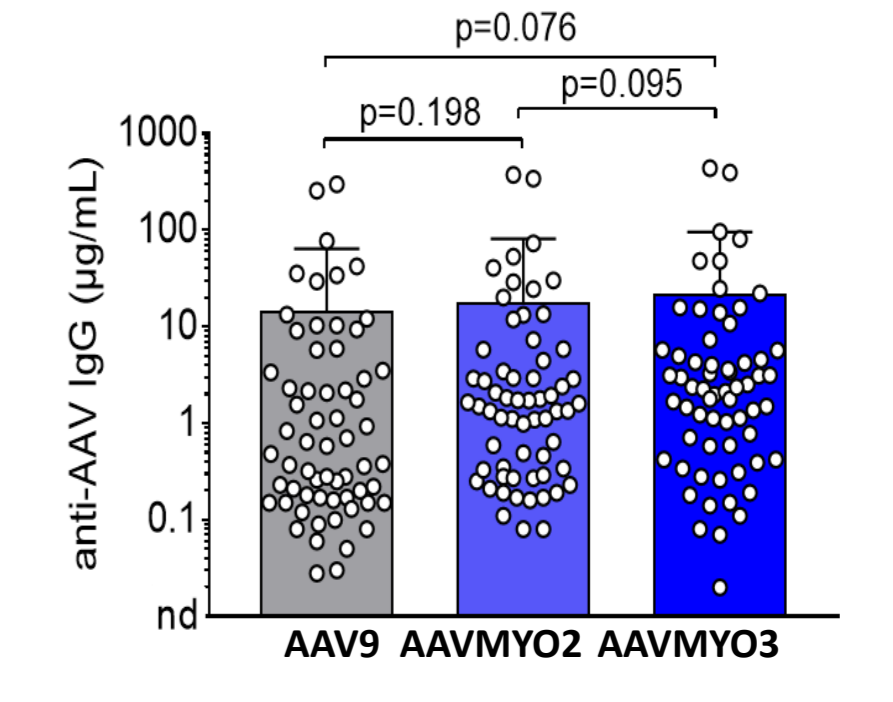
Binding capability in resin columns



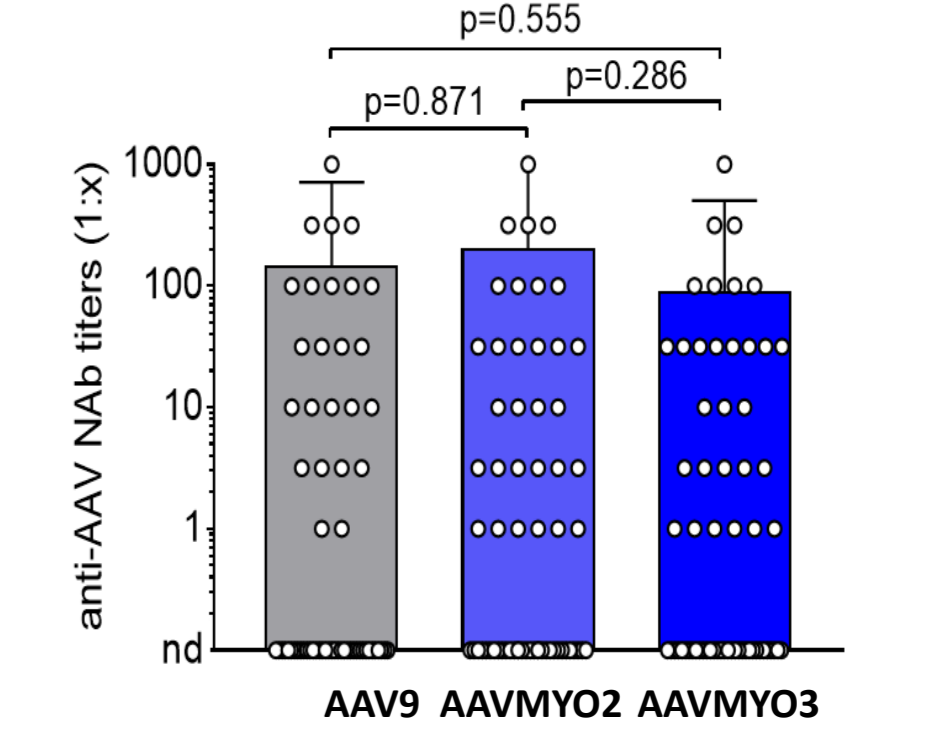
Efficient large-scale production and purification of chimeric AAVs

RESULTS – AAV seroprevalence:

Binding antibodies



Neutralized antibodies



The serologic profile of the new capsid variants is equivalent to AAV9 and compatible with clinical translation

CONCLUSIONS:

- Intravenous administration of either AAVMYO2- or AAVMYO3-MTM1 vectors at 2×10^{13} vg/kg in *Mtm1*-KO mice **prolonged their lifespan** and resulted in **increased muscle mass and strength**, and in **liver transduction detargeting**.
- We show **efficient large-scale production and purification** of AAVMYO2 and AAVMYO3, and data on their **seroprevalence** in a cohort of human sera.
- Our findings indicate that these novel vectors are potent in **rescuing the phenotype** of myotubular myopathy in mice, and hold **great potential for gene therapy of other inherited disorders affecting skeletal muscles**.