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Bioengineered AAV vectors with increased skeletal muscle potency and specificity for systemic gene therapy

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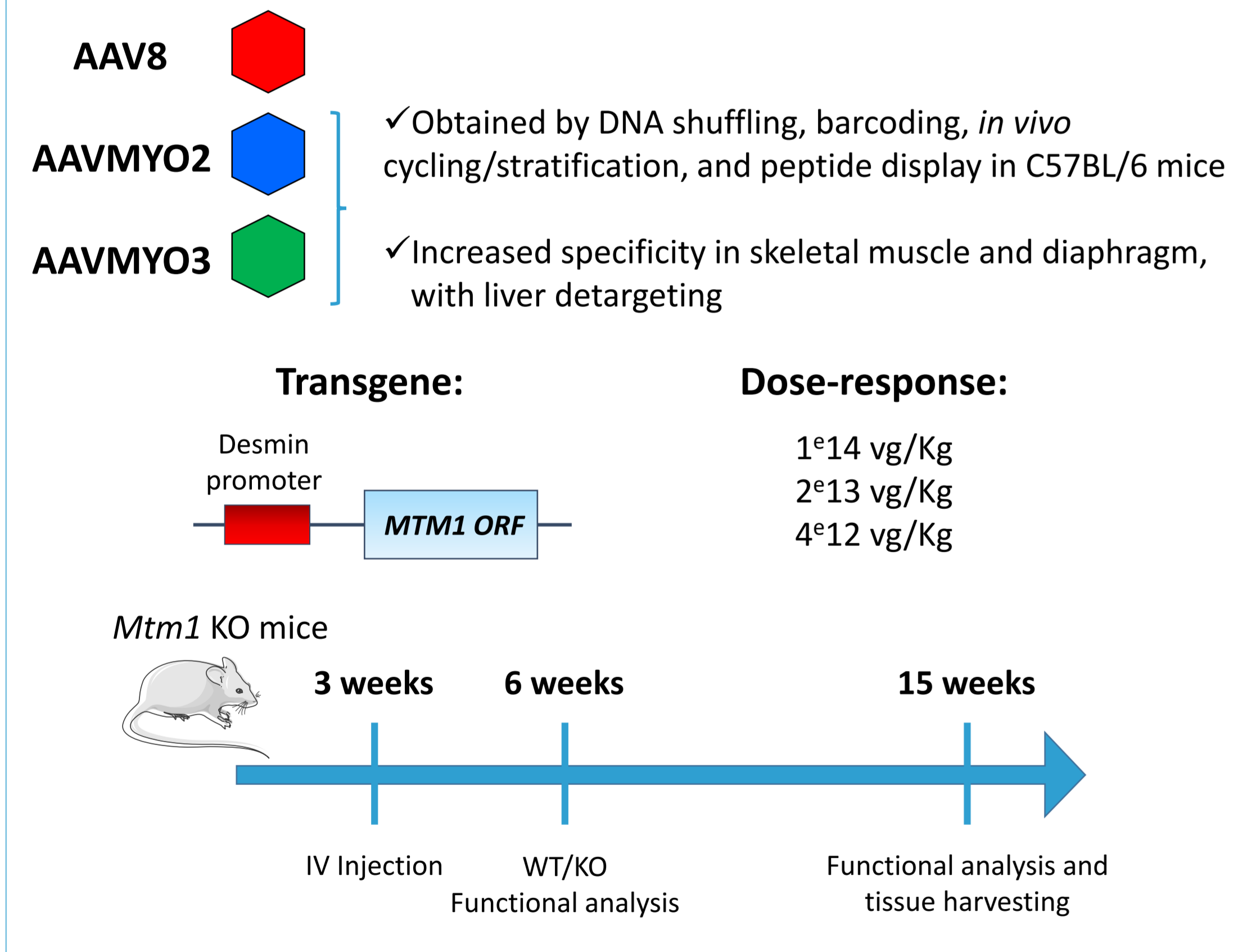
⁵ German Center for Infection Research (DZIF) and German Center for Cardiovascular Research (DZHK), partner site Heidelberg, Germany



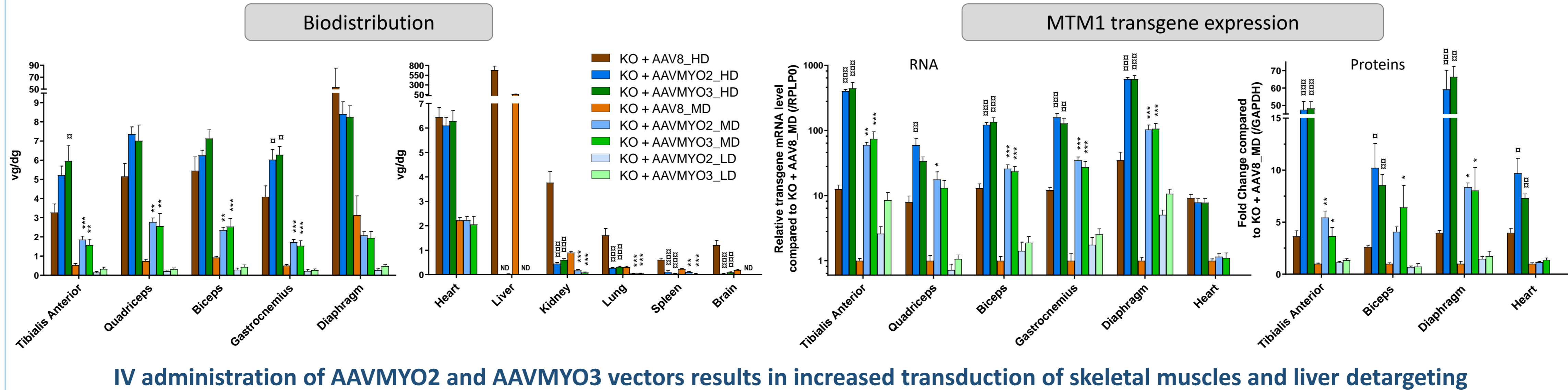
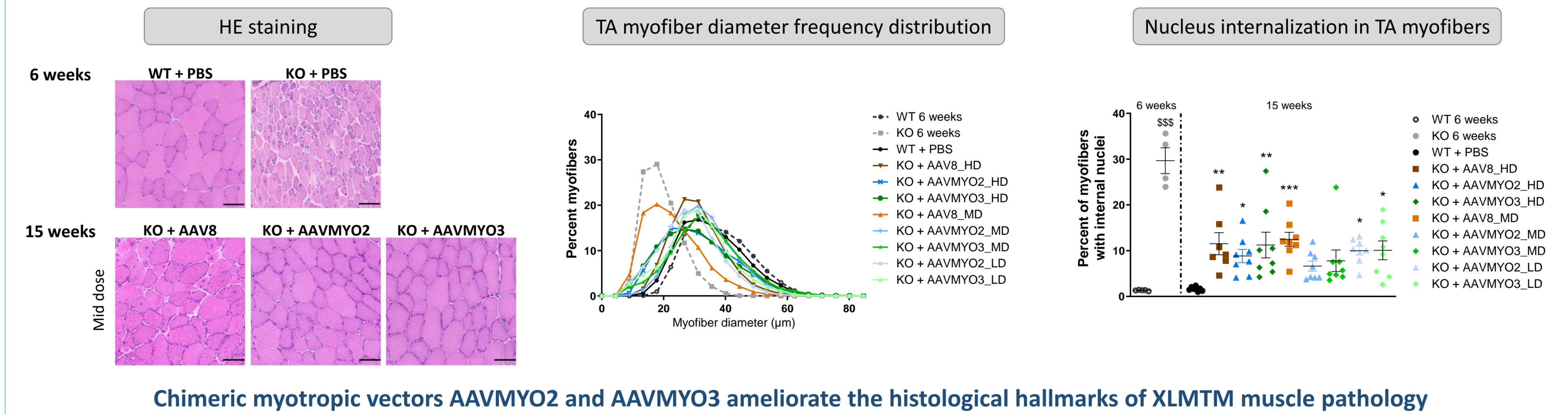
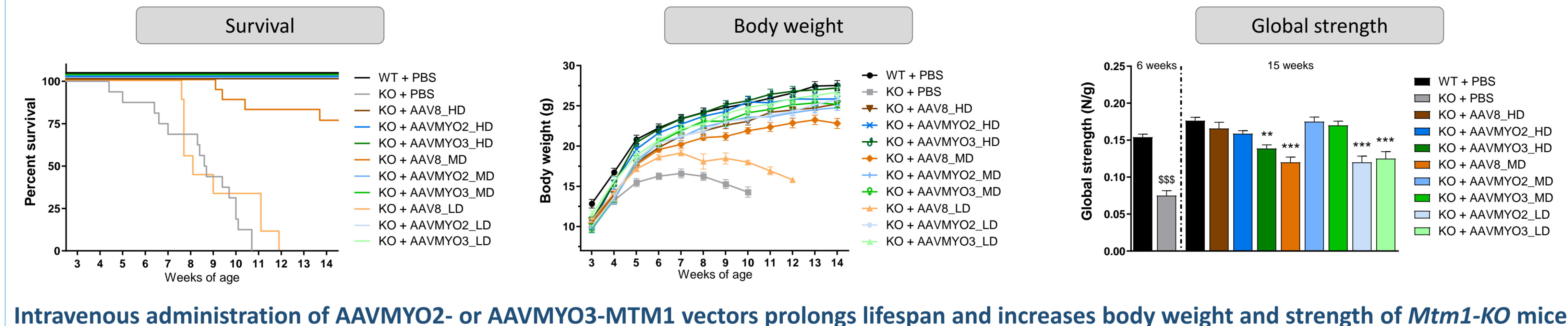
INTRODUCTION:

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.

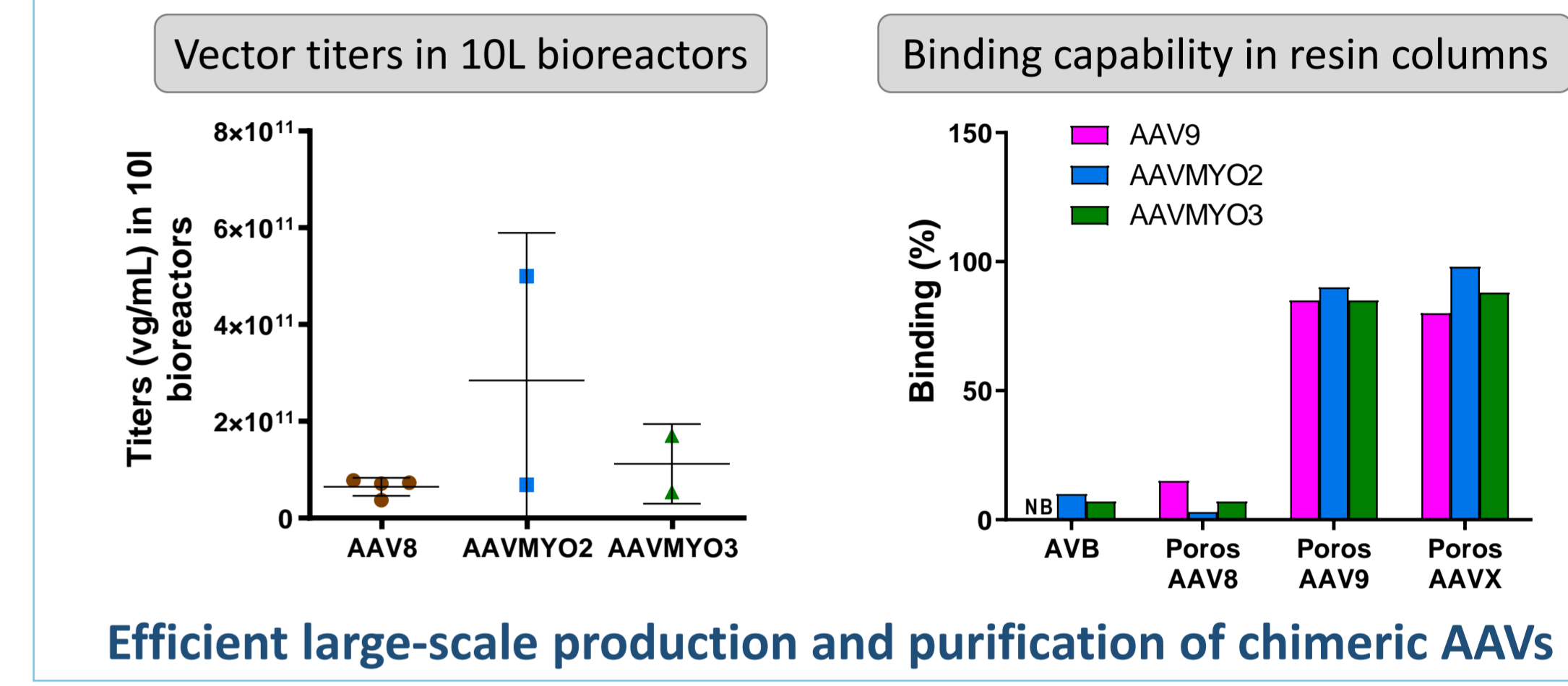
METHODS:



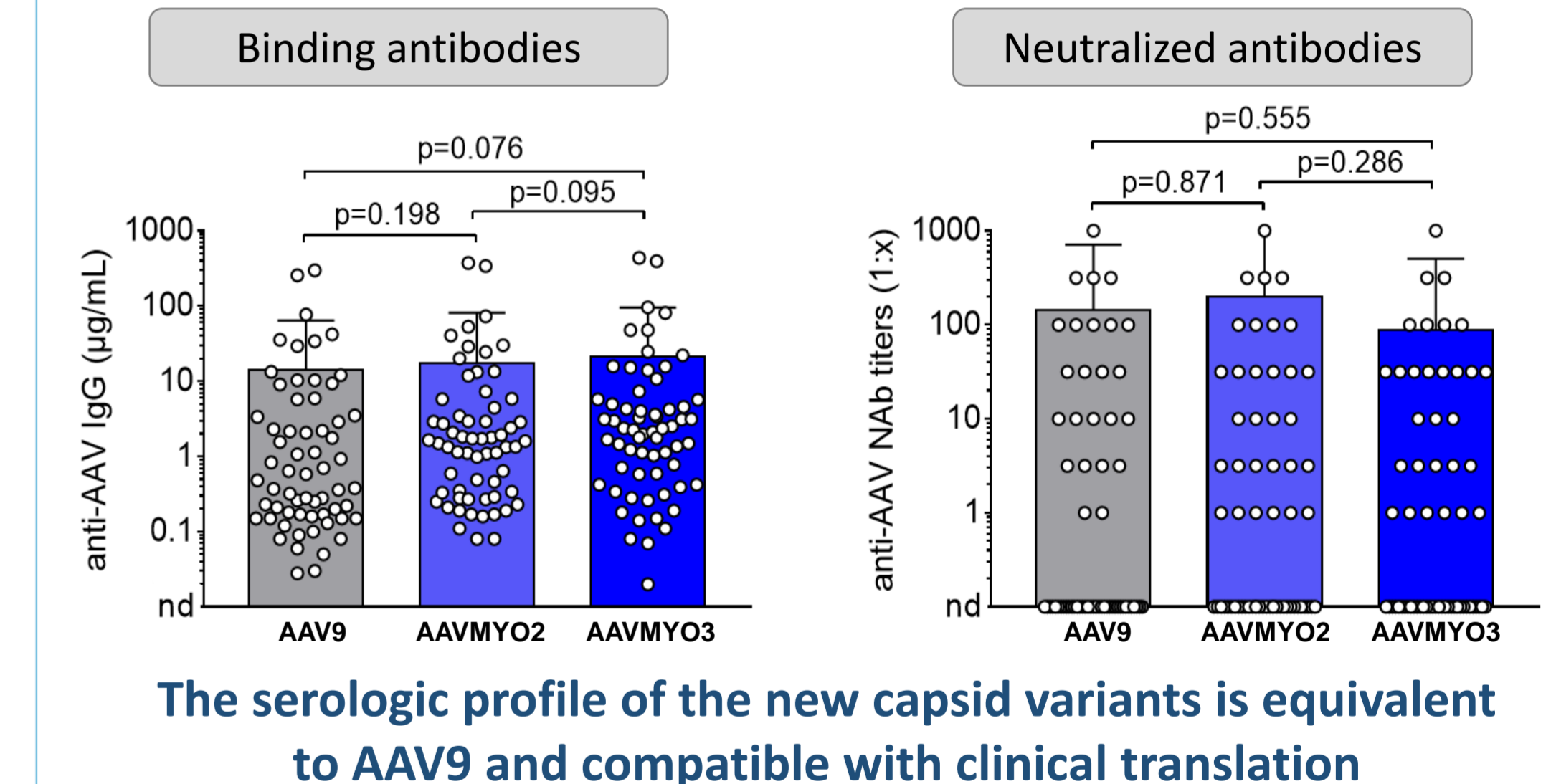
RESULTS - Gene therapy of myotubular myopathy:



RESULTS - AAV production:



RESULTS - AAV seroprevalence:



CONCLUSIONS:

- Intravenous administration of either AAVMYO2- or AAVMYO3-MTM1 vectors at 2x10¹³ 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.

