

Systemic Administration of a Rationally Engineered Vector POLARIS-101™ Leads to Successful Transduction of Non-Human Primate Tissues in The Presence of Neutralizing Antibodies; Implications for Gene Therapy and Immune Evasion Strategies

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INTRODUCTION

- Neutralizing antibodies (NAbs) reduce transgene expression thereby restricting patient eligibility for AAV gene therapy treatment.
- Strategies to overcome NAbs, including immunomodulation, are complex and may increase treatment burden.
- Capsids that evade neutralization may enable transduction in seropositive patients and expand access to gene therapy.
- POLARIS-101™ (formerly known as AAV-SLB101) is a rationally engineered capsid that is currently being evaluated in clinical trials for Duchenne muscular dystrophy.
- Here, we evaluated the impact of NAbs on POLARIS-101™ mediated vector transduction using seropositive non-human primates.

METHODS

Study Design

- Cynomolgus macaques were stratified by baseline anti-POLARIS-101™ neutralizing antibody (NAbs) titers.
- Animals a single systemic dose of POLARIS-101™ (1×10^{14} vg/kg), a recombinant adeno-associated virus vector expressing microdystrophin from a muscle-specific promoter.

Neutralizing Antibody (NAb assay)

- Anti-AAV-POLARIS-101™ NAbs were measured using a cell-based neutralization assay.
- Titers <1:5 were considered negative.

Transgene Expression

- Microdystrophin protein expression in skeletal muscle was quantified by LC-MS (Liquid Chromatography Mass Spectrometry)- based proteomic analysis.

Biodistribution

- Vector genome copies in tissues and serum were quantified by qPCR following DNA extraction.

POLARIS-101™ ADMINISTRATION TO SEROPOSITIVE MACAQUES

Study Design Overview

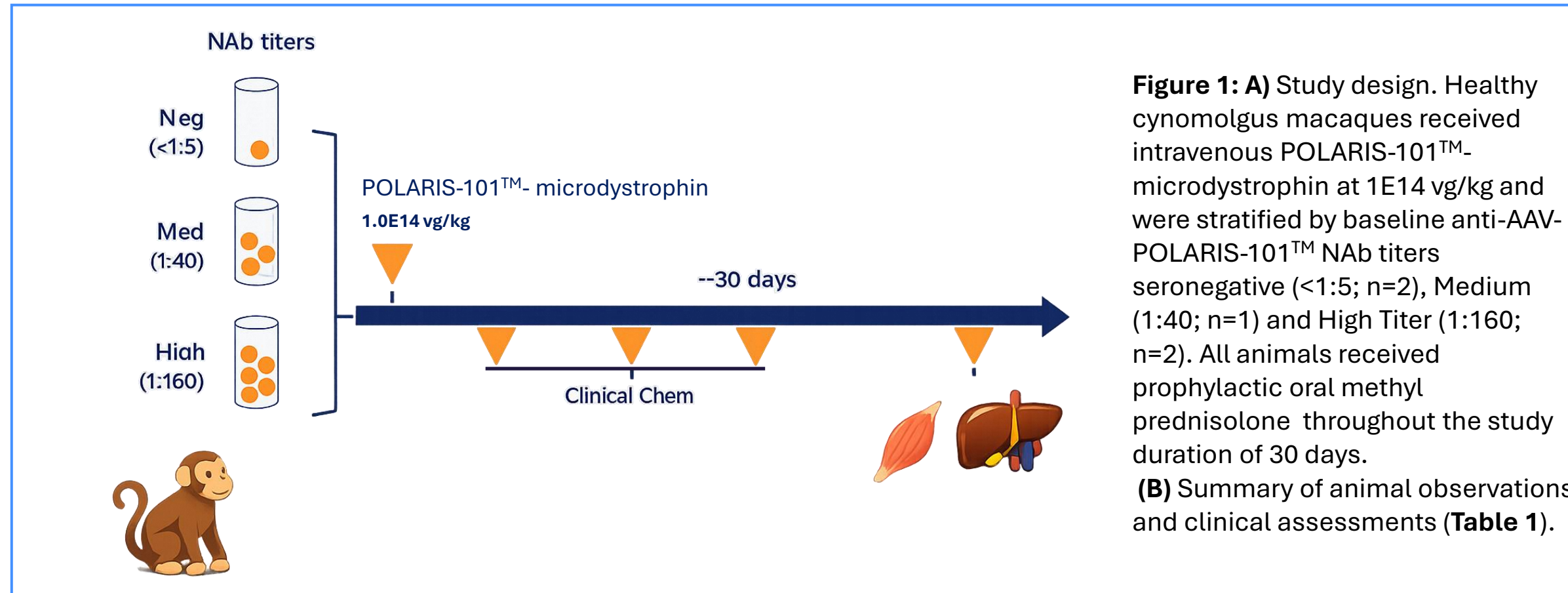
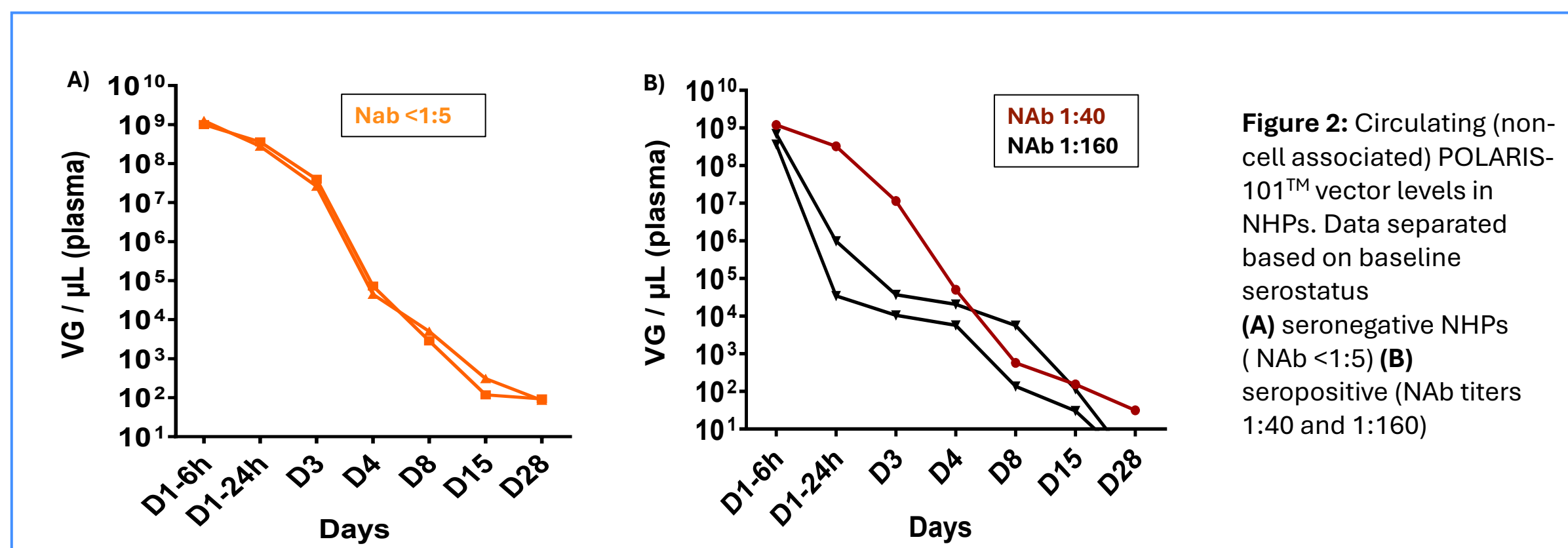


Table 1. Animal Observations suggest POLARIS-101™ was well tolerated in seropositive NHPs

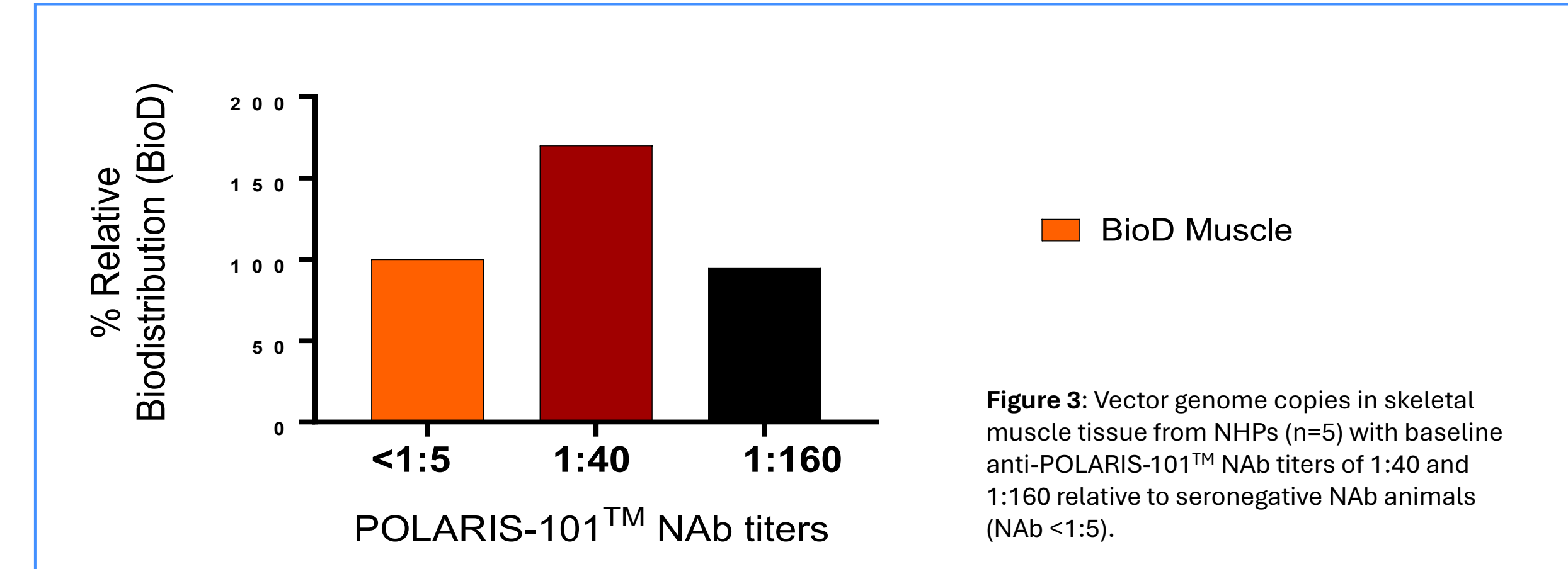
Clinical Assessment	Observations
Mortality	No mortality occurred during the study
Clinical Pathology	No vector related SAEs
Body Weights	Body weights remained normal
Gross Pathology (Necropsy)	No vector related macroscopic findings
Organ Weights	Organ weights were comparable across animals

Rapid POLARIS-101™ Vector Clearance That Is Accelerated In Presence Of Neutralizing Antibodies

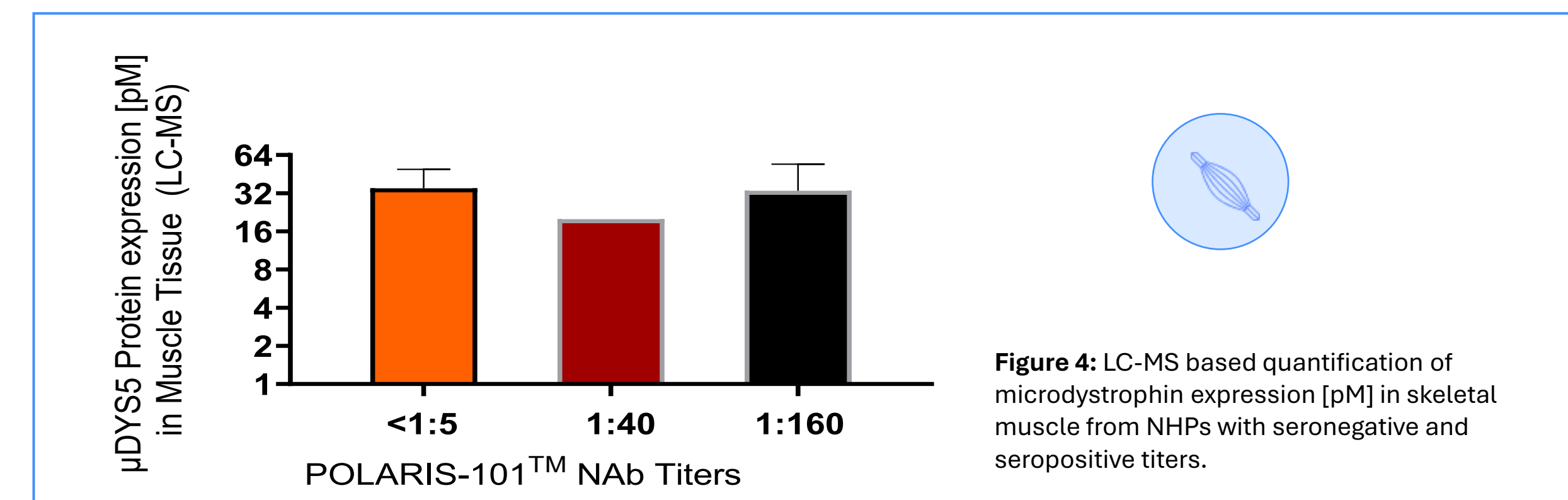


SUCCESSFUL POLARIS-101™ TRANSDUCTION IN SEROPOSITIVE MACQUES

Successful Biodistribution To Skeletal Muscle Of Seropositive Animals



Microdystrophin Transgene Expression Was Similar Between Seronegative And Seropositive Animals With High Titer Antibodies



CONCLUSIONS

- POLARIS-101™ dosing of seropositive animals was not associated with any with adverse safety findings.
- Vector biodistribution and expression in muscle tissues were comparable between seropositive and antibody naïve control animals.
- Microdystrophin expression levels were similar between naïve NHPs (<1:5) and seropositive NHPs with high NAb titers (titers 1:160).
- These findings demonstrate that POLARIS-101™ can achieve effective transduction in the presence of pre-existing NAbs.
- Results are consistent with prior preclinical studies and support the potential of POLARIS-101™ to overcome NAb-mediated barriers to gene therapy delivery.