Successful Cardiac Gene Transfer With a Rationally Designed AAV Capsid in the Presence of Anti-AAV Neutralizing Antibodies

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INTRODUCTION

- AAV vectors serve as delivery vehicles for genomic medicines, with therapeutic success dependent on efficient targeting to the intended tissue or cell type and sustained expression of the genetic payload at desirable levels
- Pre-existing or treatment-induced anti-AAV antibodies can limit vector biodistribution and reduce transgene expression by neutralizing AAV particles and restricting tissue uptake. These antibodies pose a barrier to gene therapy by limiting patient eligibility.
- AAV-SLB101 is a proprietary, rationally engineered muscle-tropic capsid that demonstrates enhanced transduction efficiency and earlier onset of expression compared to AAV9 and AAVrh74 capsids
- Based on its rapid transduction kinetics, **we hypothesize that AAV-SLB101 may retain the ability to efficiently transduce target tissues in the presence of neutralizing antibodies**
- To test this hypothesis, we used a RAG2KO murine model passively transferred with human sera containing varying neutralizing antibody titers, and assessed the impact on AAV-SLB101 heart transduction

METHODS

- Anti-AAV-SLB101 antibodies: A total antibody (TAb) assay was used to quantify anti-AAV-SLB101 antibodies and titers were established using a statistical cut point[1,2]
- RAG2KO mice were dosed with AAV-SLB101- CK8-luciferase at a dose of 2.5E13 vg/kg and 1E14 vg/kg
- BLI (IVIS) Imaging: Mice were injected IP/SC with luciferin and imaged at peak signal time. Whole-body ROI was used to quantify total flux (photons/sec).
- Tissue Biodistribution: Genomic DNA was extracted from mouse heart and Quantitative PCR (qPCR) was performed to quantify vector copy numbers
- Luciferase Activity Assay: Tissue luciferase activity in heart tissues was measured using standard assays and is reported as relative luciferase units (RLUs)

RESULTS

1. AAV-SLB101 DEMONSTRATED HIGHER TRANSDUCTION LEVELS COMPARED TO AAV9 IN SKELETAL AND CARDIAC MUSCLE IN WT MICE AND NHPs

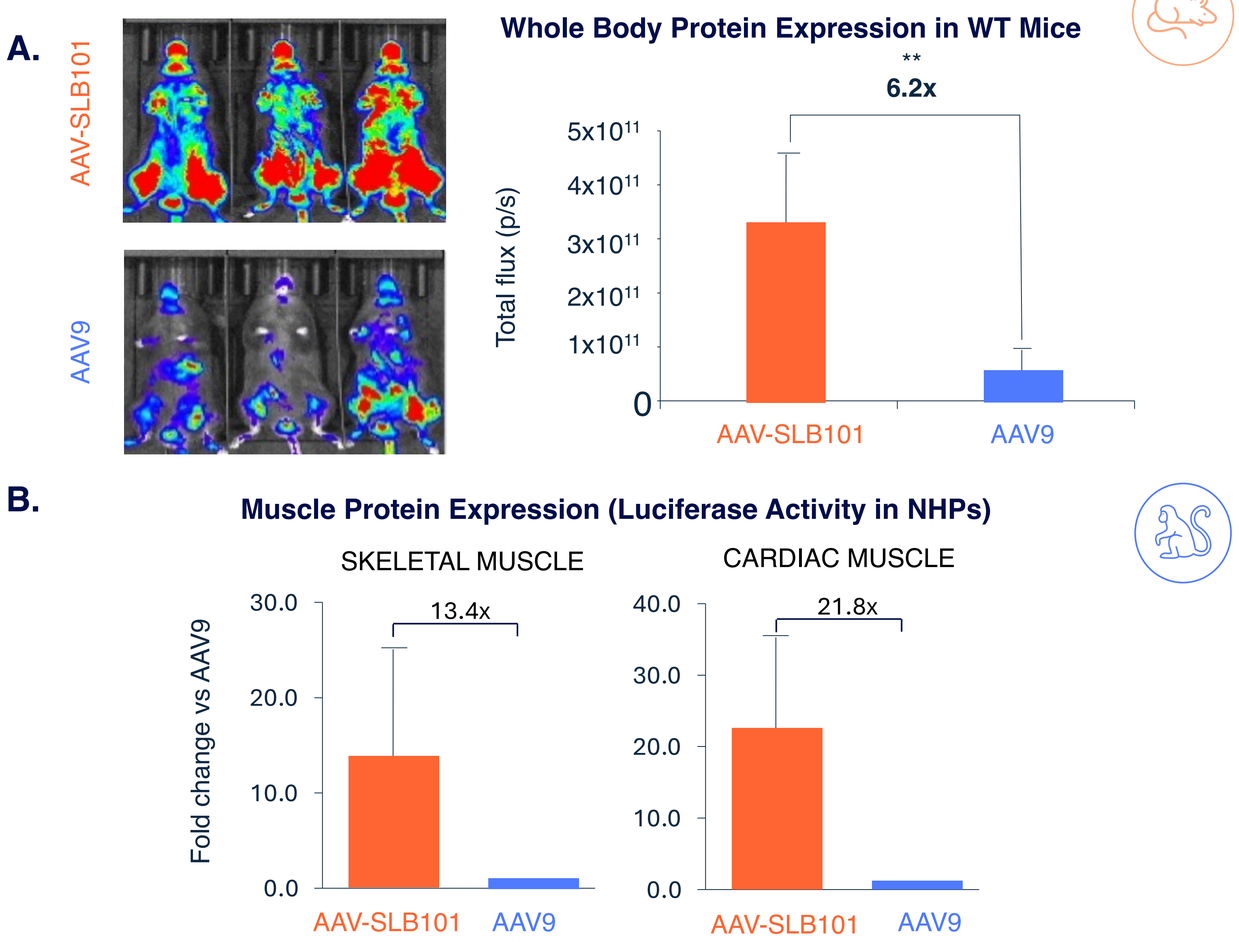


Figure 1. A) In life whole body luminescence image quantification shows significantly higher transduction at day 15 for WT mice dosed with AAV-SLB101 vs AAV9 at 3E14 vg/kg. **B)** Day 29 luciferase expression (RLUs) in isolated skeletal muscle and heart tissues from NHPs administered systemically with $5x10^{13}$ vg/kg of AAV-SLB101 or AAV9. NHP, nonhuman primate; WT, wild type. **p<0.005.

2. RAPID ONSET OF AAV-SLB101 TRANSGENE EXPRESSION COMPARED TO AAVRH74 AND AAV9

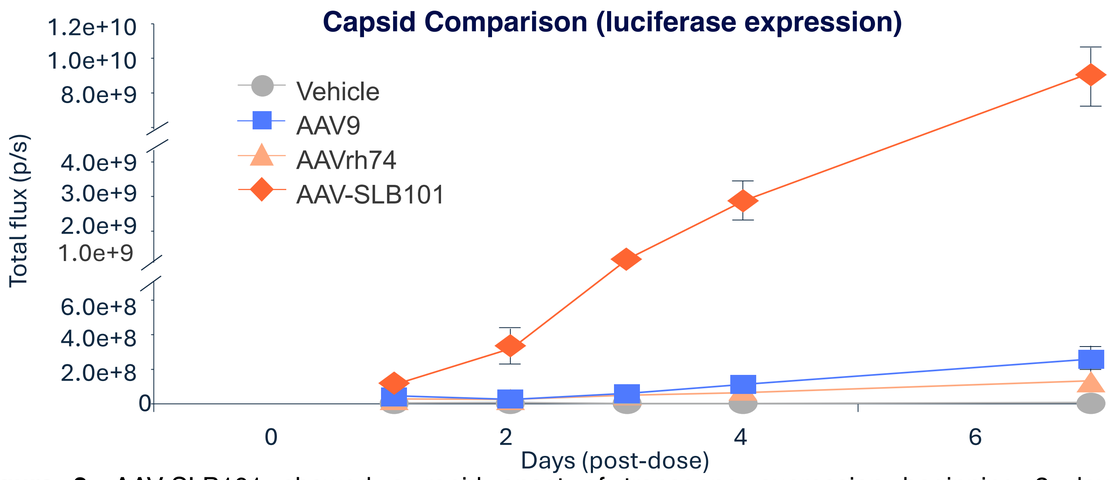
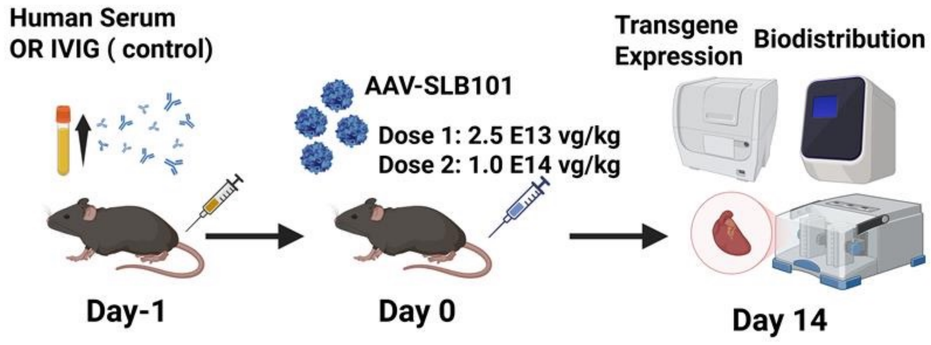


Figure 2. AAV-SLB101 showed a rapid onset of transgene expression beginning 2 days after administration that was several fold higher by day 7 when compared to AAVrh74 (74x) and AAV9 (38x) at a dose of 5E13 vg/kg.

RESULTS (cont'd)

3. ASSESSMENT OF AAV-SLB101 TRANSDUCTION EFFICIENCY IN A RAG2KO MOUSE MODEL CARRYING HUMAN NEUTRALIZING ANTIBODIES



GROUP	TITER	HUMAN ID
1	<1:5	Negative Control Human Donor
2	Low	Human Donor 1
3	Low-Mid	Human Donor 2
4	Mid	Human Donor 3
5	Mid-High	Human Donor 4
6	High	Human Donor 5
7	2 g/kg IVIG	Positive Control

Figure 3. Human serum from five healthy donors containing varying titers of anti-AAV-SLB101 antibodies was intravenously administered to RAG2KO mice (N=5/group), an immunocompromised strain lacking mature T and B lymphocytes. This model enabled assessment of AAV-SLB101 transduction in the presence of human neutralizing antibodies without interference from murine adaptive immunity.

4. DOSE-DEPENDENT AAV-SLB101 TRANSDUCTION IN HEART IN THE PRESENCE OF NEUTRALIZING ANTIBODIES

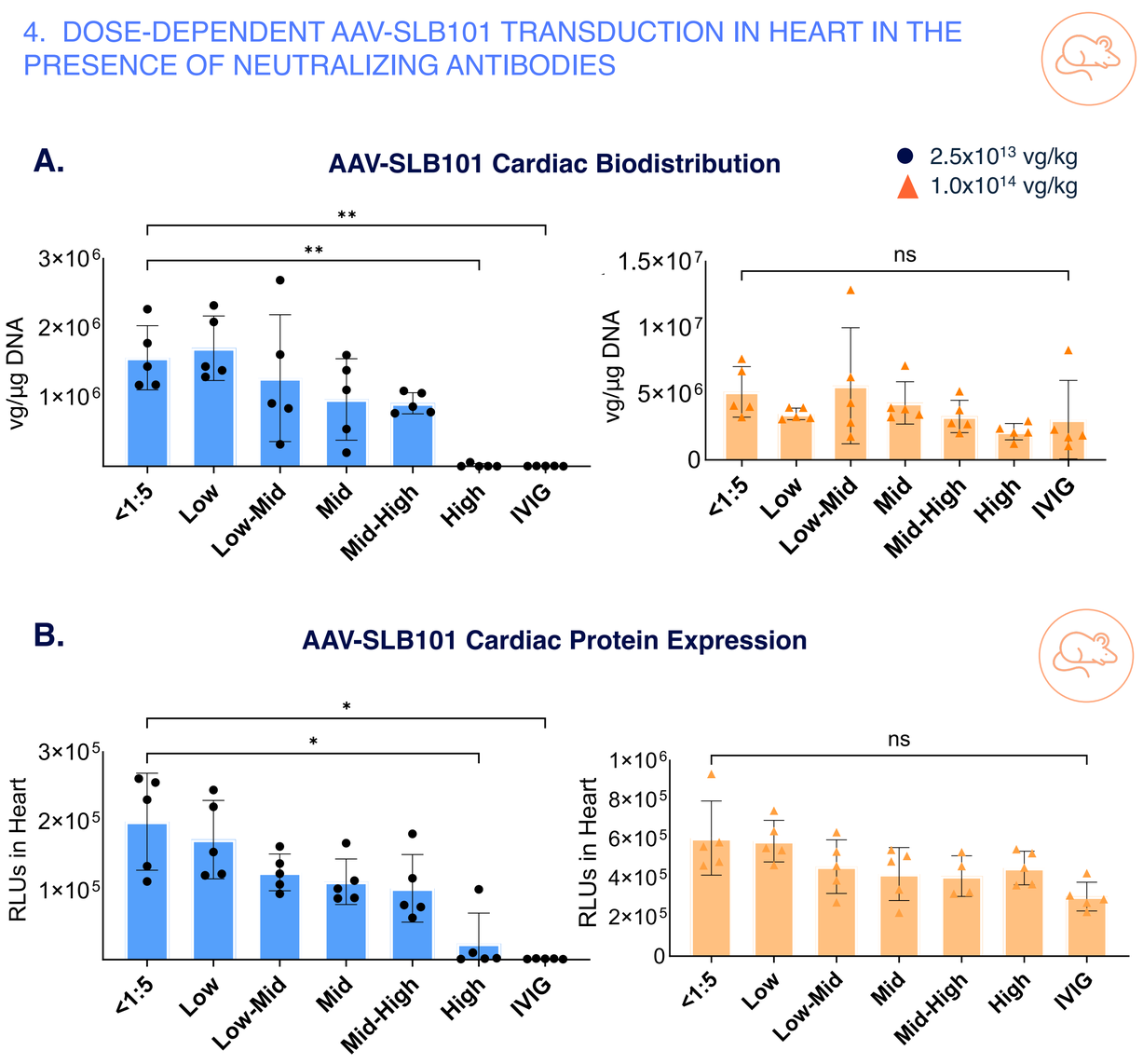


Figure 4. AAV-SLB101 heart biodistribution **(A)** and transgene expression **(B)** in animals transduced with AAV-SLB101 at a dose of $2.5x10^{13}$ vg/kg (left panels) or $1x10^{14}$ vg/kg (right panels). RLU, Relative light units; IVIG, intravenous Immunoglobulin; statistical significance (One way ANOVA). *p<0.05; **p<0.001.

CONCLUSIONS

- Our engineered AAV-SLB101 capsid achieves cardiac biodistribution and transgene expression even in the presence of pre-existing neutralizing antibodies, overcoming a key barrier to gene therapy and supporting broader patient eligibility
- Ongoing studies are characterizing AAV-SLB101's rapid cardiac transduction kinetics, sustained transgene expression, and resistance to neutralizing antibody inhibition in cardiac tissue
- These differentiated properties may broaden the clinical applicability of AAV-SLB101 by enabling effective treatment of seropositive patients otherwise excluded from gene therapy

REFERENCES

1. Mendell JR, et al. *Mol Ther Methods Clin Dev*. 2022;25:74-83. 2. Pan Y, et al. *Mol Ther Methods Clin Dev*. 2023;31:101126.

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DISCLOSURES

KP: Employee and shareholder of Solid Biosciences Inc.

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