Potential for AAV-SLB101–Mediated Gene Transfer Treatment in the Context of Natural Seropositivity and After an AAVrh74 Treatment

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FDA=US Food and Drug Administration

Disclosures

- I am a full-time employee at Solid Biosciences Inc. and hold equity in the company

Overcoming Anti-AAV Antibody Barriers Can Improve Gene Therapy Availability

- Pre-existing or treatment-induced anti-AAV antibodies can limit efficacy of AAV gene therapies
  - NAbs may prevent effective transduction, particularly with systemic delivery
- Anti-AAV antibodies result from environmental exposure or prior AAV treatment
  - A single dose may elicit a robust humoral response, precluding redosing with the same or related serotypes

Prevent Transduction

Decrease Patient Enrollment

Complement Activation

Prevent Redosing

Goal: Characterization of anti-AAV antibodies to therapeutic capsids can mitigate immune response barriers and optimize treatment efficacy

AAV=adeno-associated virus; NAb=neutralizing antibody.

Mendell JR, et al. *Mol Ther Methods Clin Dev*. 2022;25:74-83.

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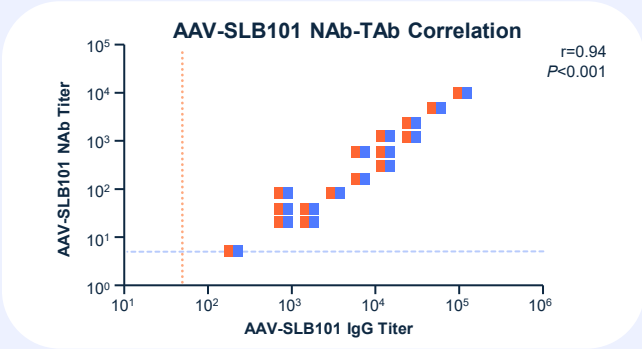
Assays for Anti-AAV Antibodies Inform Inclusion Criteria and Dosing Strategy

AAV Seropositivity

- Pre-existing anti-AAV antibodies in serum arise from natural exposure to wild-type AAV and vary by serotype, geography, and age[1]
- Anti-AAV antibodies include binding TAbs (recognize the AAV capsid) and NAbs (block vector transduction)[2]



NAbs[2,3]

In vitro cell-based transduction assay

Measures functional inhibition of AAV-mediated gene transfer by patient antibodies

More labor-intensive and variable than ELISA-based methods

Requires live cells, transduction reagents, and optimized conditions for each serotype

Enables determination of a transduction-inhibitory titer threshold

Titers can be correlated with vector potency reductions and used to guide clinical inclusion

ELISA=enzyme-linked immunosorbent assay; IgG=immunoglobulin G; TAb=total antibody.

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. 3. Cao L, et al. *Gene Ther*. 2023;30(1-2):150-159.

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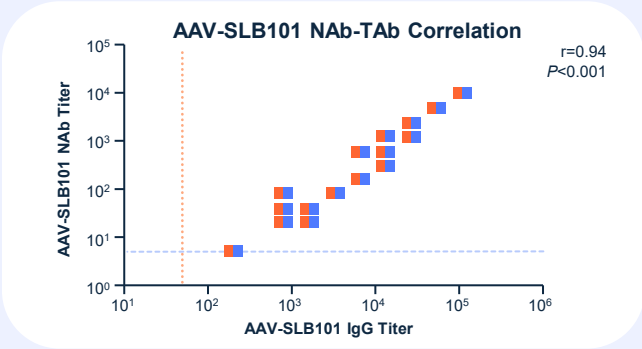


TAbs[2,3]

Capture-based ELISA format

Detects binding antibodies against AAV capsids without measuring functional neutralization

Interpretation depends on assay sensitivity and defined threshold

Thresholds are often empirically derived and may not directly correlate with impact on transduction

Operationally simpler for clinical trial integration

More amenable to standardization and high-throughput implementation than cell-based assays

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. 3. Cao L, et al. *Gene Ther*. 2023;30(1-2):150-159.

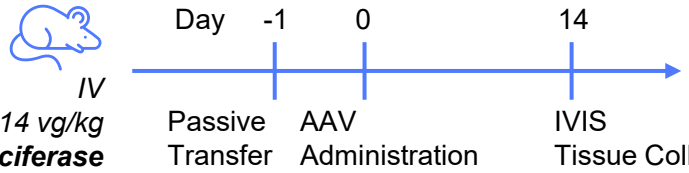
Understanding the Relationship Between TAb and Transduction Neutralization Is Important in Gene Therapy Trials

Why does this matter? Inform patient eligibility, Optimize dosing strategy, Estimate treatment success

Question:
Can we define a titer "threshold" that negatively impacts transduction based on a TAb titer?

- Passive transfer study of human sera characterized on an internal TAb assay into RAG2 KO mouse model
- RAG2 KO mouse model:
  - Lacks T and B cells
  - Clean system as endogenous antibodies will not interfere

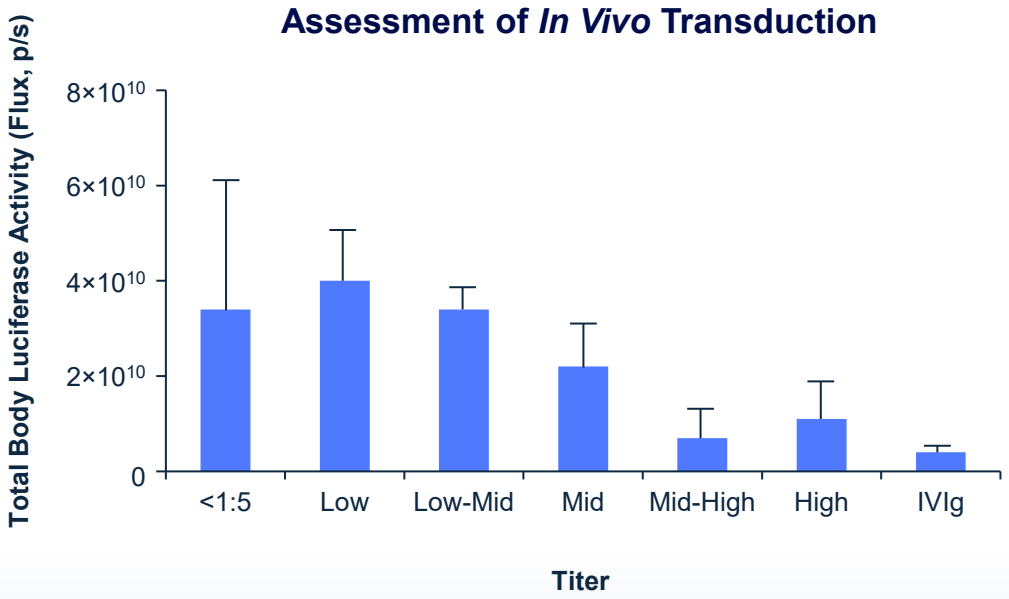
Study Design

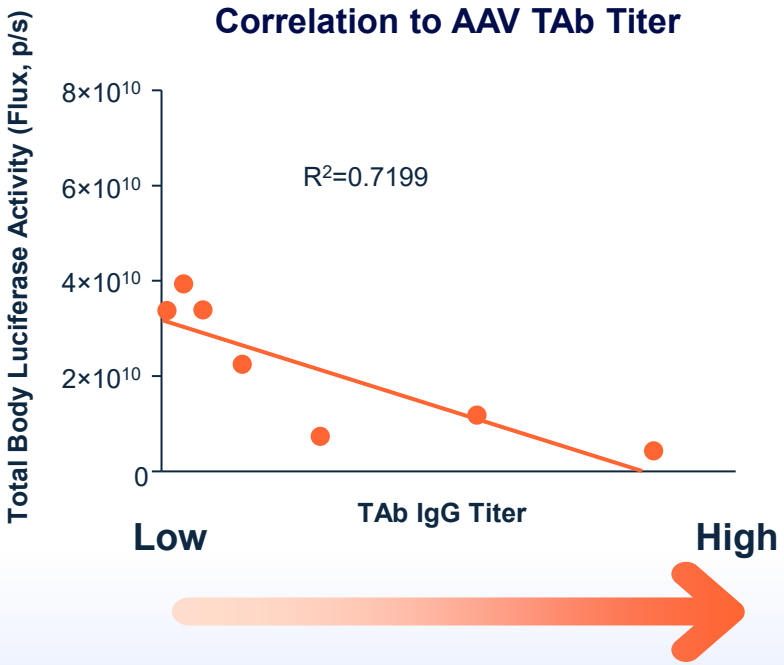


Group	Titer	Human ID	N
1	<1:5	Negative Control Human Donor	5
2	Low	Human Donor 1	5
3	Low-Mid	Human Donor 2	5
4	Mid	Human Donor 3	5
5	Mid-High	Human Donor 4	5
6	High	Human Donor 5	5
7	2 g/kg IVIg	Positive Control	5

IVIg=intravenous immunoglobulin; IVIS=in vivo imaging system; KO=knockout; RAG2=recombination activation gene 2.
Data on file. Solid Biosciences. 2025.

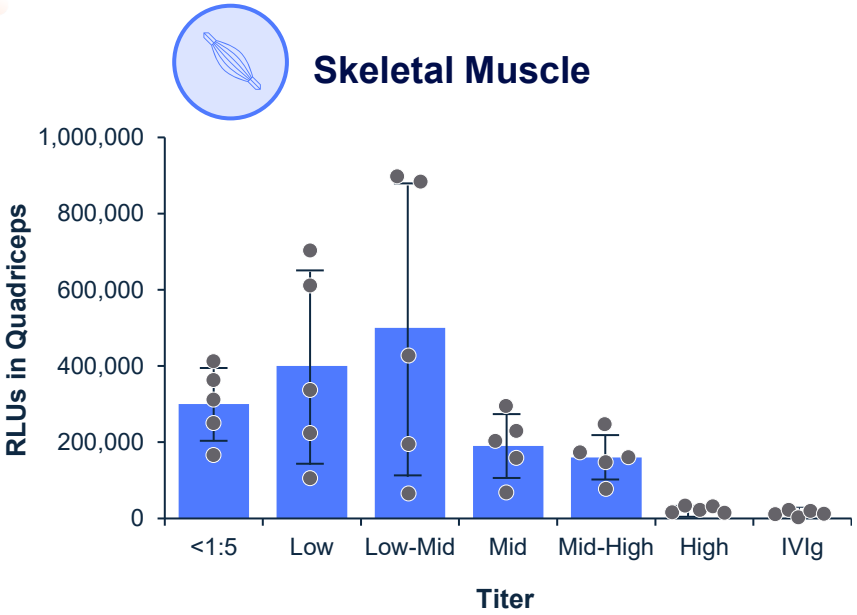
AAV TAb Titer Generally Correlated With *In Vivo* Transduction

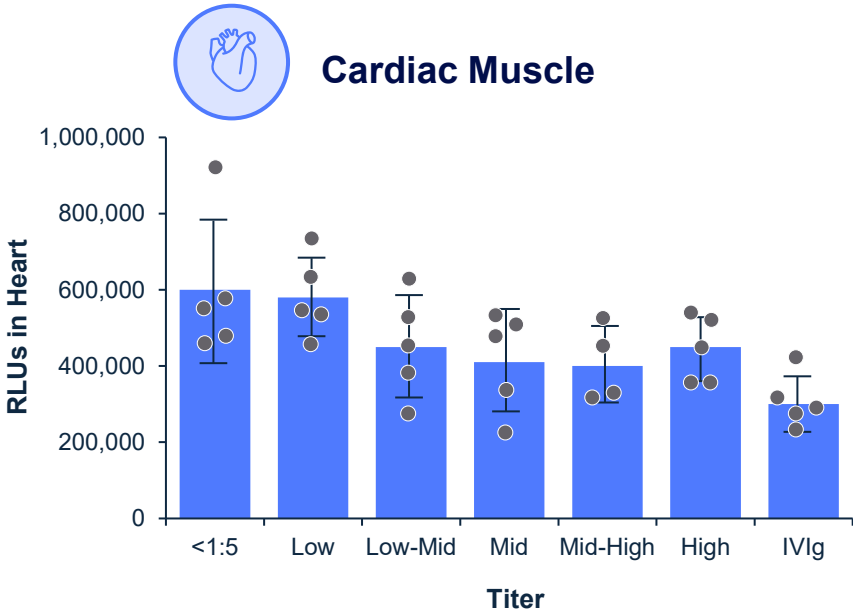




p/s=photons per second.
Data on file. Solid Biosciences. 2025.

Tissue Dependent Impact of AAV TAb Titer on Transduction





- Established TAb titer cutoff for skeletal muscle; low levels did not neutralize the capsid
- Observed less neutralization in the heart with high titer antibodies when compared to skeletal muscle
  - What is the impact of preexisting antibodies present from a prior vector administration?

RLU=relative light unit.
Data on file. Solid Biosciences. 2025.

Opportunity for Dosing With AAV-SLB101 Following Treatment With AAVrh74

Redosing remains a major barrier to broader use of AAV-based therapies[1]:

- High systemic AAV doses induce robust and persistent NAb responses
- Current immunomodulatory strategies have not successfully mitigated NAb levels to enable efficient redosing
- Seroprevalence data suggest limited opportunities for redosing with existing AAV capsids

The immune response to natural AAV infection may differ significantly from that elicited by therapeutic dosing

- C57 mice were immunized with $1x10^{10}$ particles of AAV/luc vectors via muscular injection[1]
- Thirty days later, sera from 3 mice was collected for NAb analysis[1]

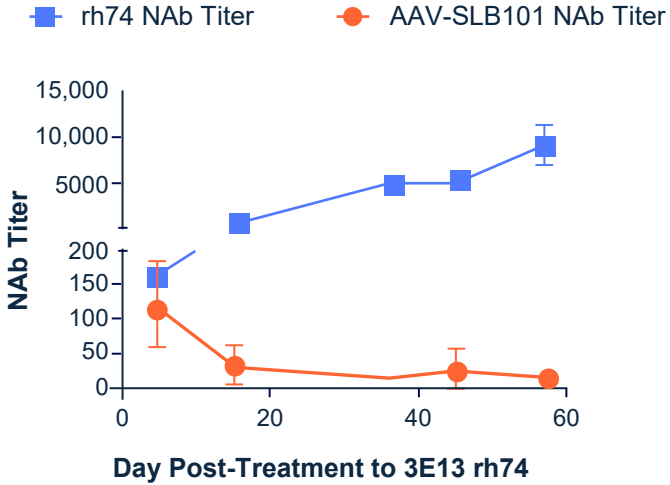
Capsid	AAV8 NAb[2]	AAV6 NAb[2]
AAV8	>1:1000	1:31.6

- NHPs were administered AAV8 and Nab antibodies levels were measured[2]

1. Bowles DE, et al. *Mol Ther*. 2012;20(2):443-455. 2. Mingozzi F, et al. *Mol Ther.* 2012;20(7):1410-1416.

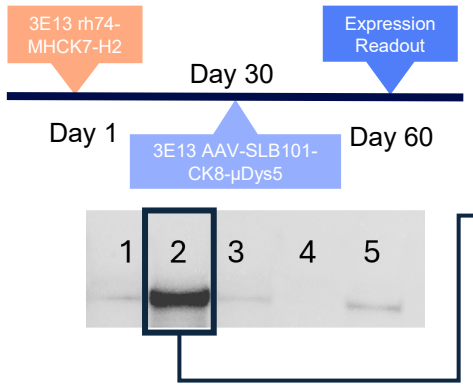
Low AAV-SLB101 NAb Titers Detected in AAVrh74-Dosed Mice, Enabling Potential for Redosing With AAV-SLB101

Longitudinal Assessment of AAV-SLB101 NAbs



Low AAV-SLB101 NAb in AAVrh74-dosed mice; NAb levels remain low up to 60 days

Low Anti-AAV-SLB101 Titers in AAVrh74 Dosed Mice Support the Opportunity For Redosing With AAV-SLB101



AAV-SLB101 NAbs at Day 30

Animal	rh74 Titer	AAV-SLB101 Titer
1	5120	40
2	2560	<5
3	2560	10
4	2560	40
5	10,240	20

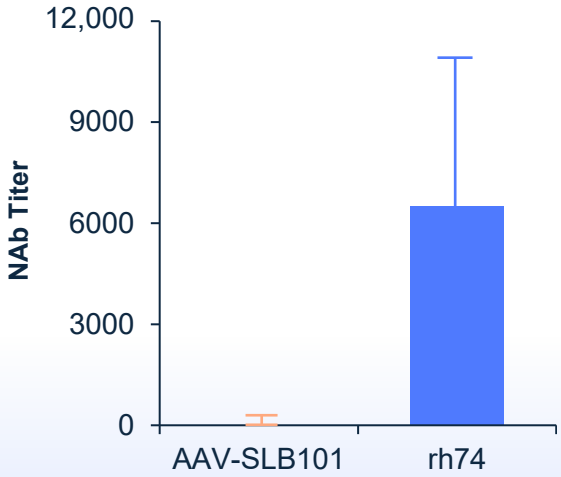
In mice dosed with AAVrh74 (Day 1) and subsequently with AAV-SLB101 (Day 30), transgene expression correlated with anti-AAV-SLB101 titers (Day 30)

µDys5=5-repeat microdystrophin.
Data on file. Solid Biosciences. 2025.

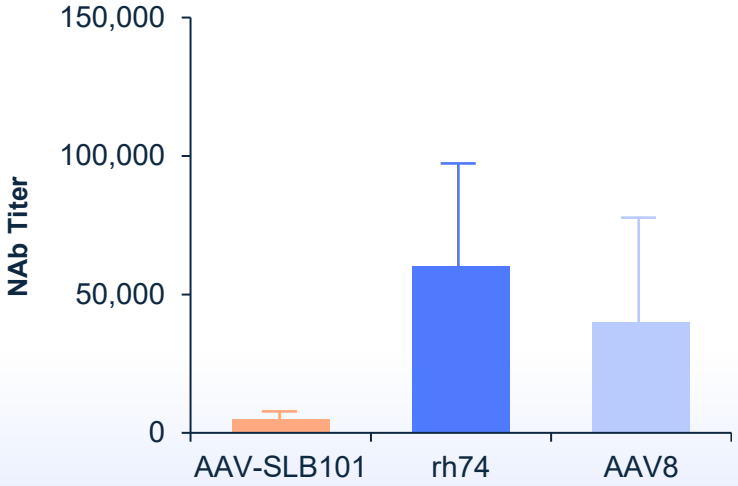
Low Anti-AAV-SLB101 Titers Detected in NHPs and Patients With Duchenne Dosed With AAVrh74

Exploring if current immunomodulation strategies support redosing with AAV-SLB101

Day 30 Assessment of AAV-SLB101 NAbs
n=6



Humans Dosed With AAVrh74 (Sera Samples)
n=3



NHP=nonhuman primate.
Data on file. Solid Biosciences. 2025.

Conclusions

TAb and NAb assays for anti-AAV antibodies can be useful for defining patient eligibility and optimizing dosing strategies[1]

Understanding the strengths and limitations of anti-AAV antibody assays is critical for informing clinical trial patient selection, redosing feasibility, and interpretation of transduction[1]

Holistic approaches that integrate assay type and titer threshold help select for patients likely to benefit from therapy while excluding those with truly inhibitory seropositivity[1]

Redosing with different AAV serotypes is being actively pursued and may circumvent pre-existing immunity and enable transduction in previously treated patients[2]

1. Mendell JR, et al. *Mol Ther Methods Clin Dev*. 2022;25:74-83. 2. Baatartsogt N, et al. *J Gene Med*. 2023;25(8):e3505.

Acknowledgements

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Cure Duchenne LINK

Individuals with DMD and their families & caregivers

If you would like to discuss opportunities to use AAV-SLB101, please contact Solid's BD team at businessdevelopment@solidbio.com

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