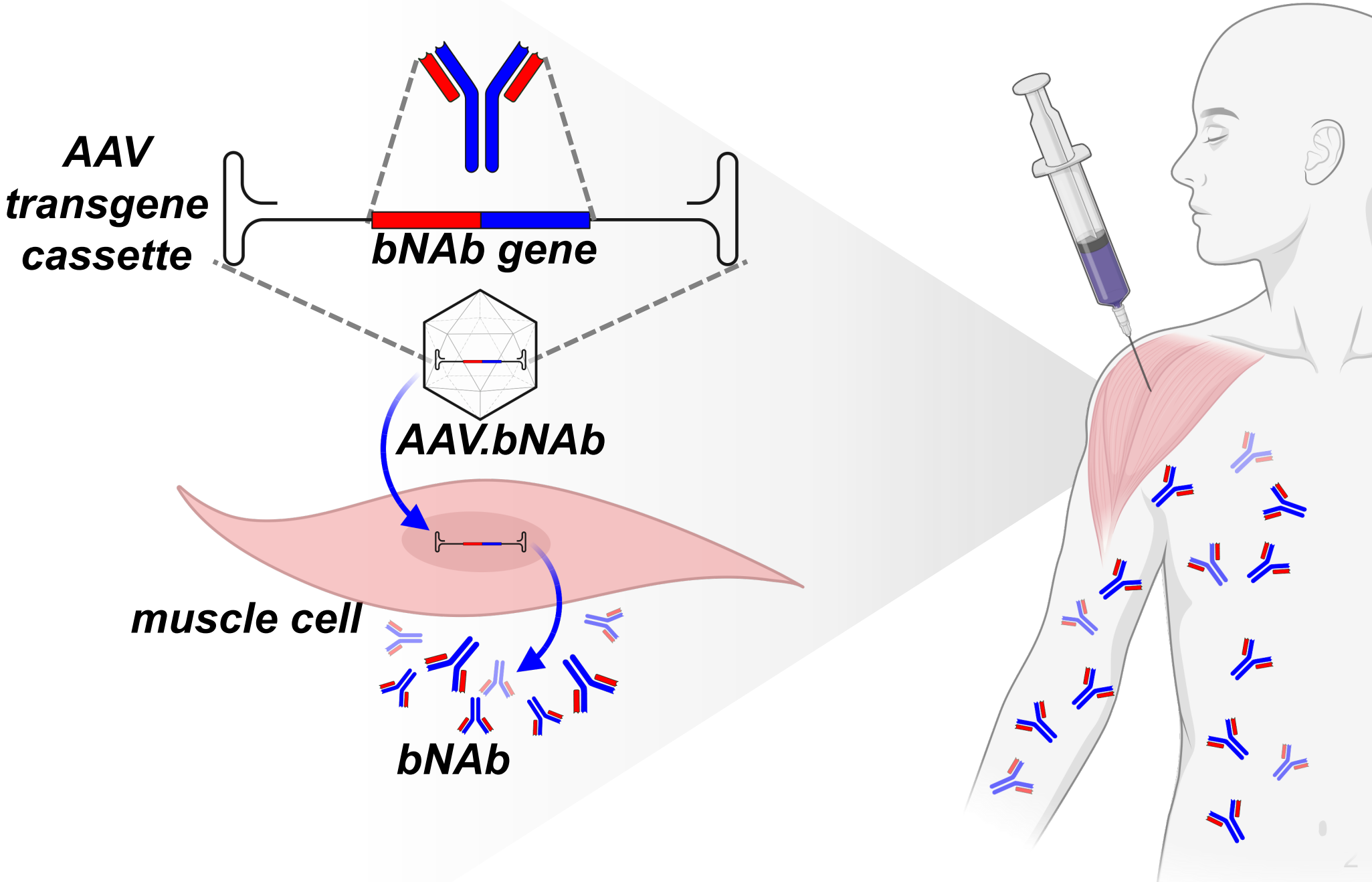
Overcoming immune responses to AAV-delivered bNAbs

Michael Kuipa, Peter Koroma, Isai Leguizamo, Priya Dhole & Matthew R. Gardner

Disclosure

M.K., P.K., I.L., and M.R.G. are inventors on a pending patent application for the use of PD-L1 and immune checkpoint pathway ligands for gene therapy applications.

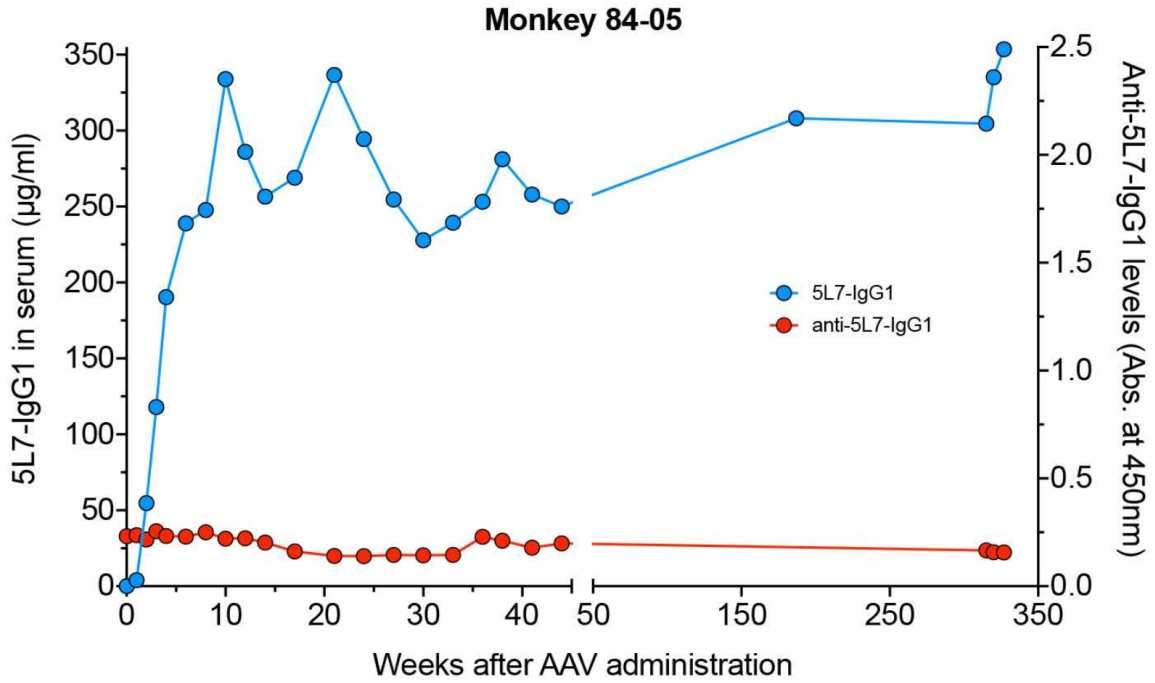
AAV-vectored bNAbs for HIV therapy and protection

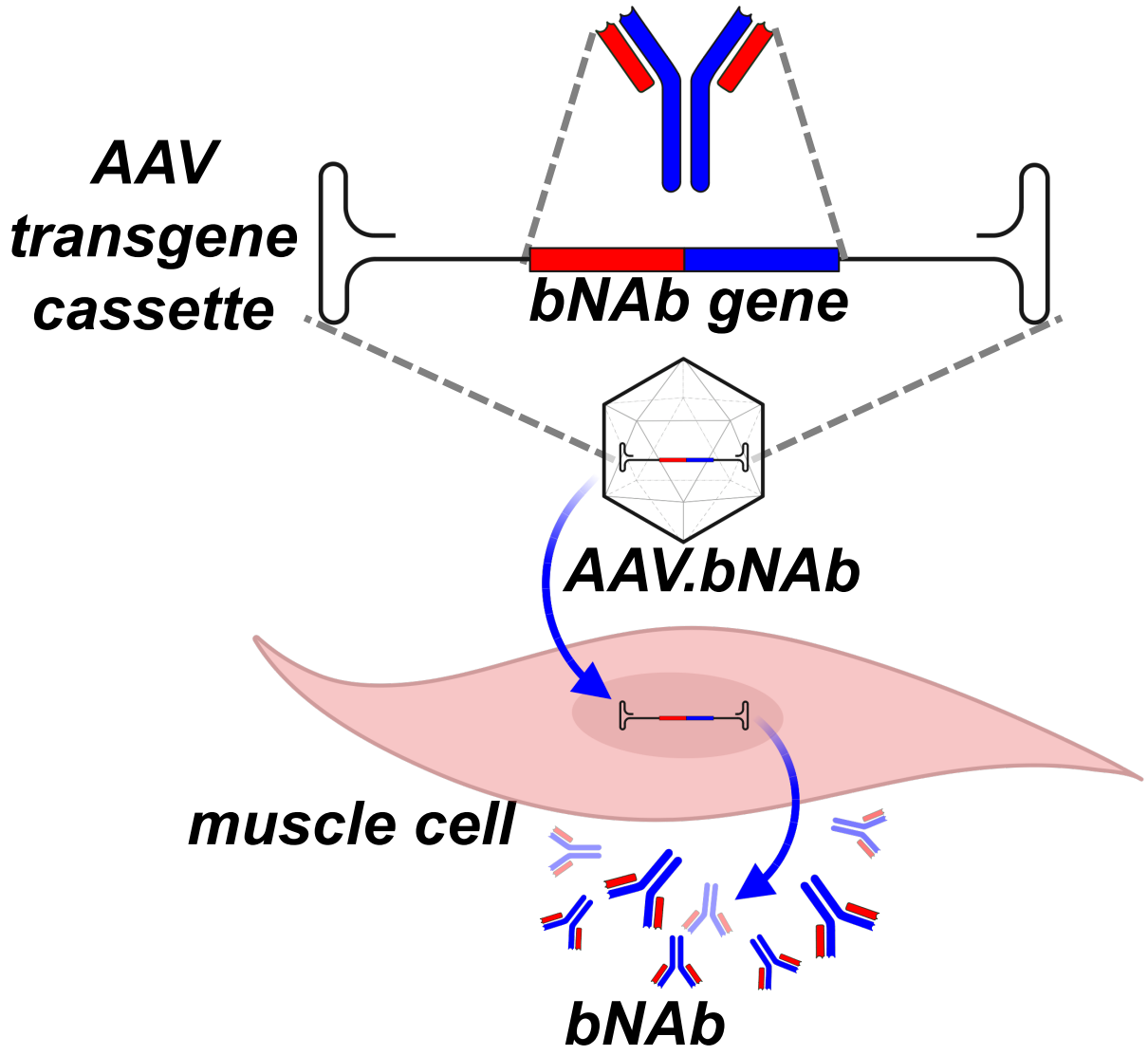


AAV-vectored bNAbs for HIV therapy and protection

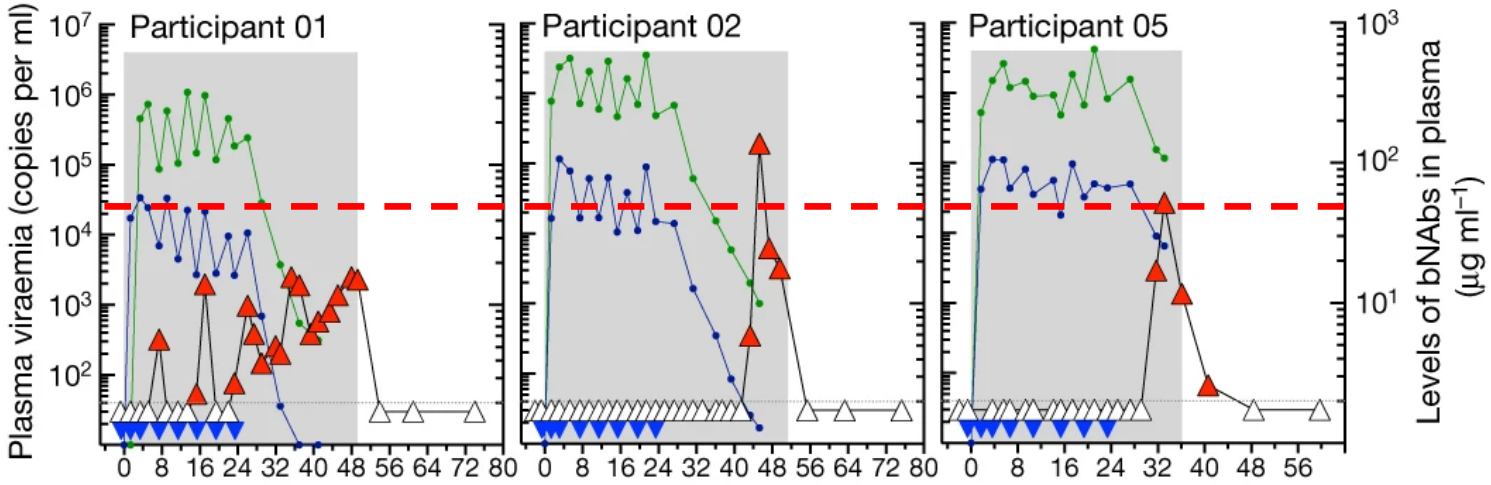
- **Expression of AAV-vectored Abs can be maintained for years**

Martinez-Navio et al., Front. Immunol., 2020





Our target: 50 µg/mL of each inhibitor



- **Clinical trials demonstrate 10-1074 + 3BNC117 suppression without ART on sensitive reservoirs**

Sneller et al., Nat., 2022;

Mendozza et al., Nat., 2018

- **When the conc. of one antibody drops (typically < 20-50 µg/mL), virus rebounds**

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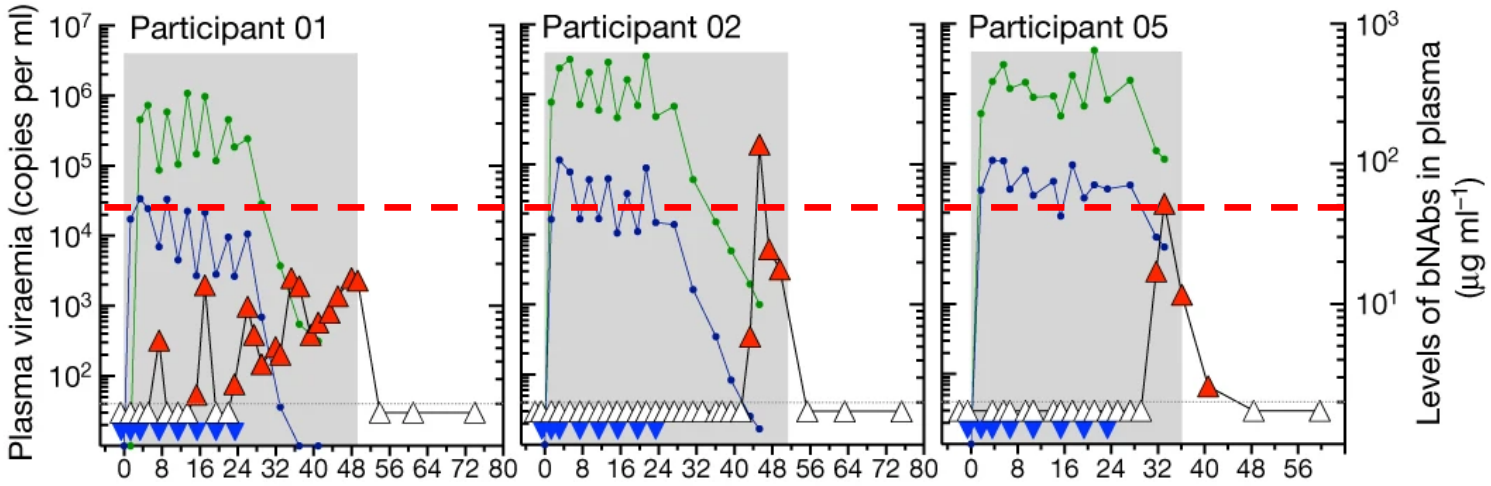

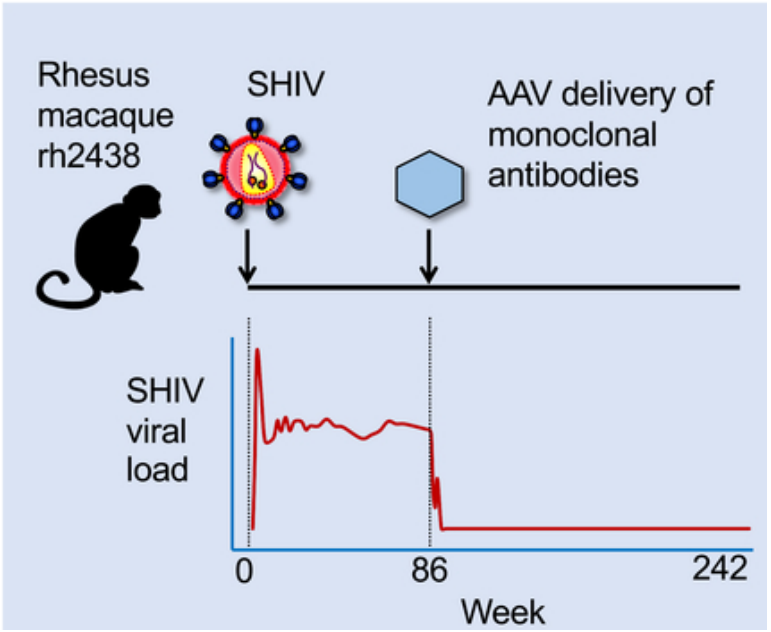

- **Clinical trials demonstrate 10-1074 + 3BNC117 suppression without ART on sensitive reservoirs**

  Sneller et al., Nat., 2022;

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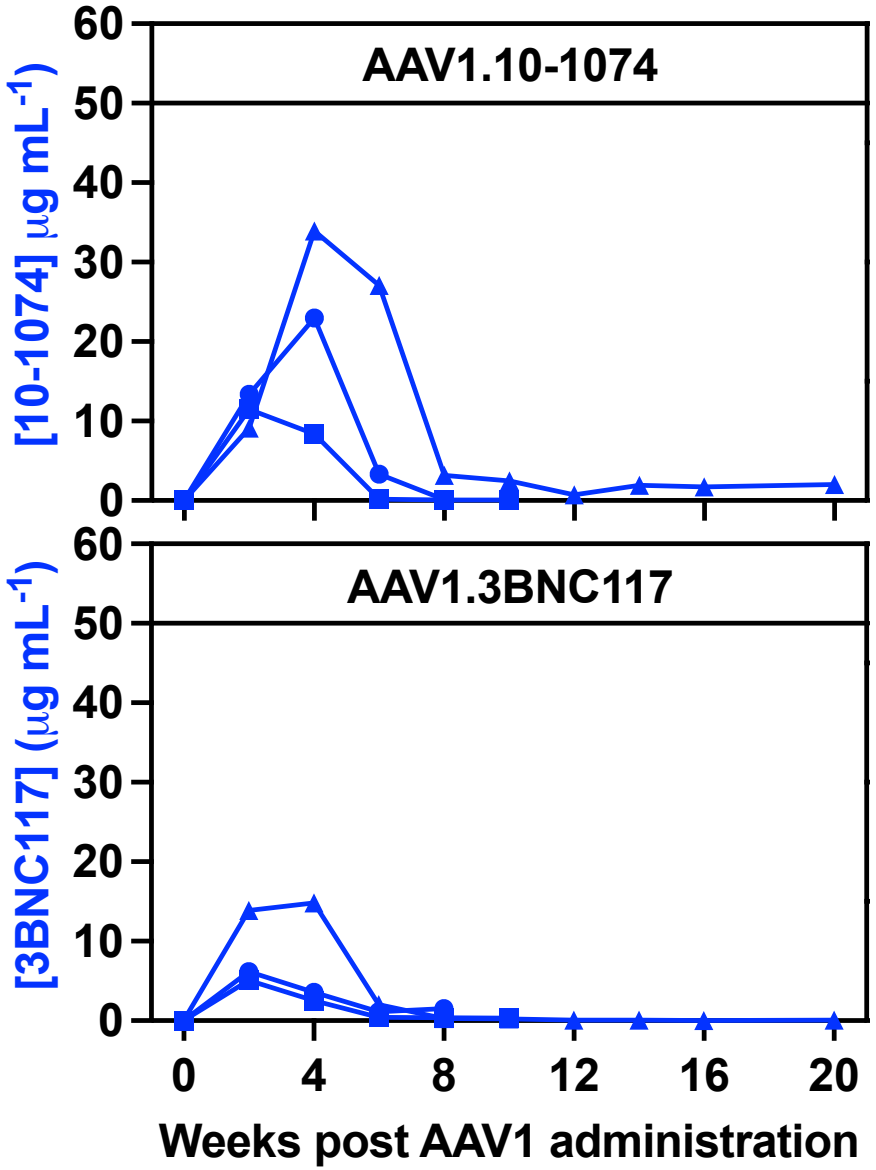
- **When the conc. of one antibody drops (typically < 20-50 µg/mL), virus rebounds**

- **The "Miami Monkey" sustained viral suppression after AAV-delivered bNAbs**

  Martinez-Navio et al,. Immuni., 2019

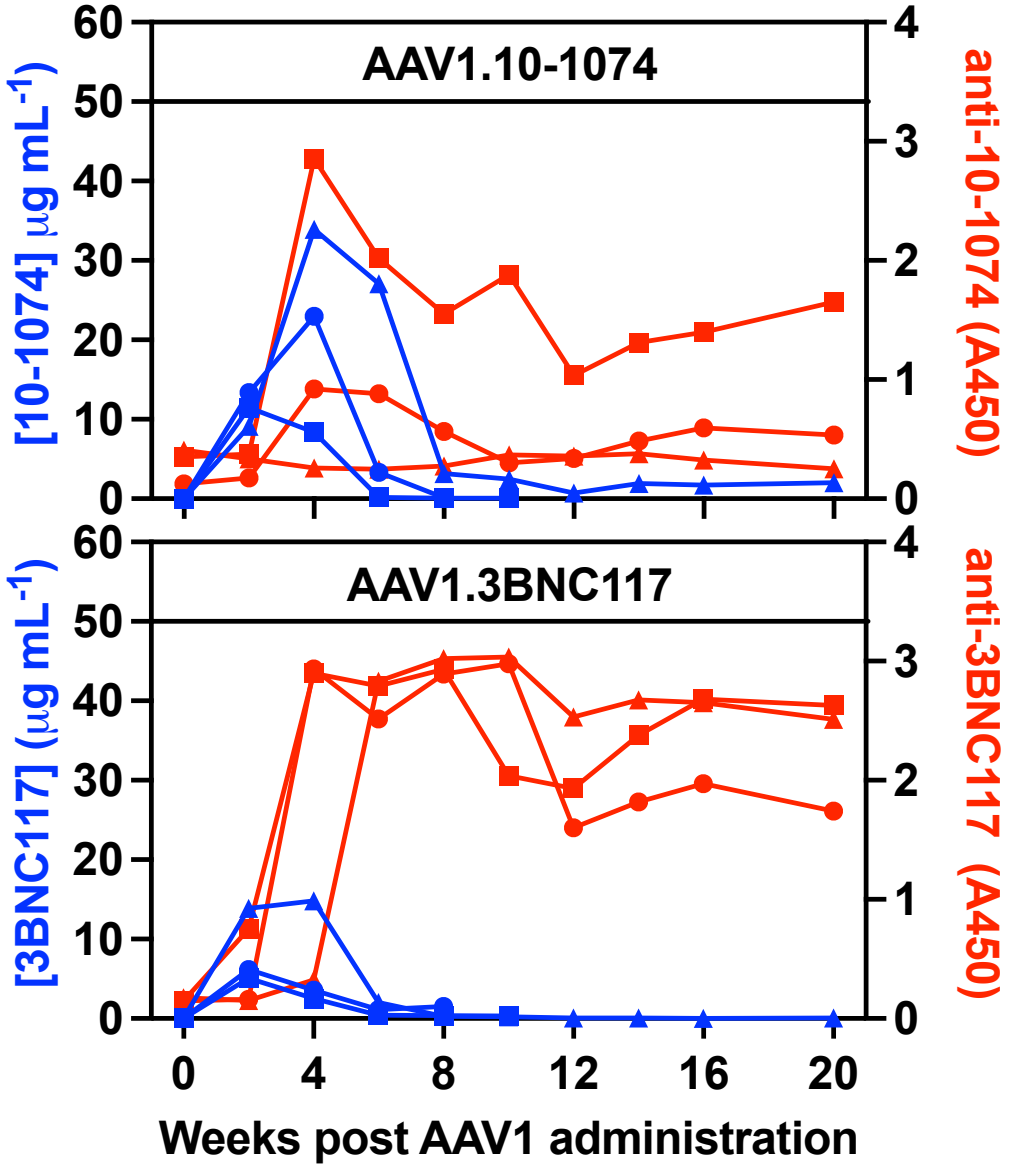
- **[10-1074] range 100-200 µg/mL**
- **[3BNC117] range 50-150 µg/mL**

AAV studies with HIV bNAbs limited by immune responses



Gardner et al., Mol. Ther., 2019

AAV studies with HIV bNAbs limited by immune responses



Gardner et al., Mol. Ther., 2019

AAV studies with HIV bNAbs limited by immune responses

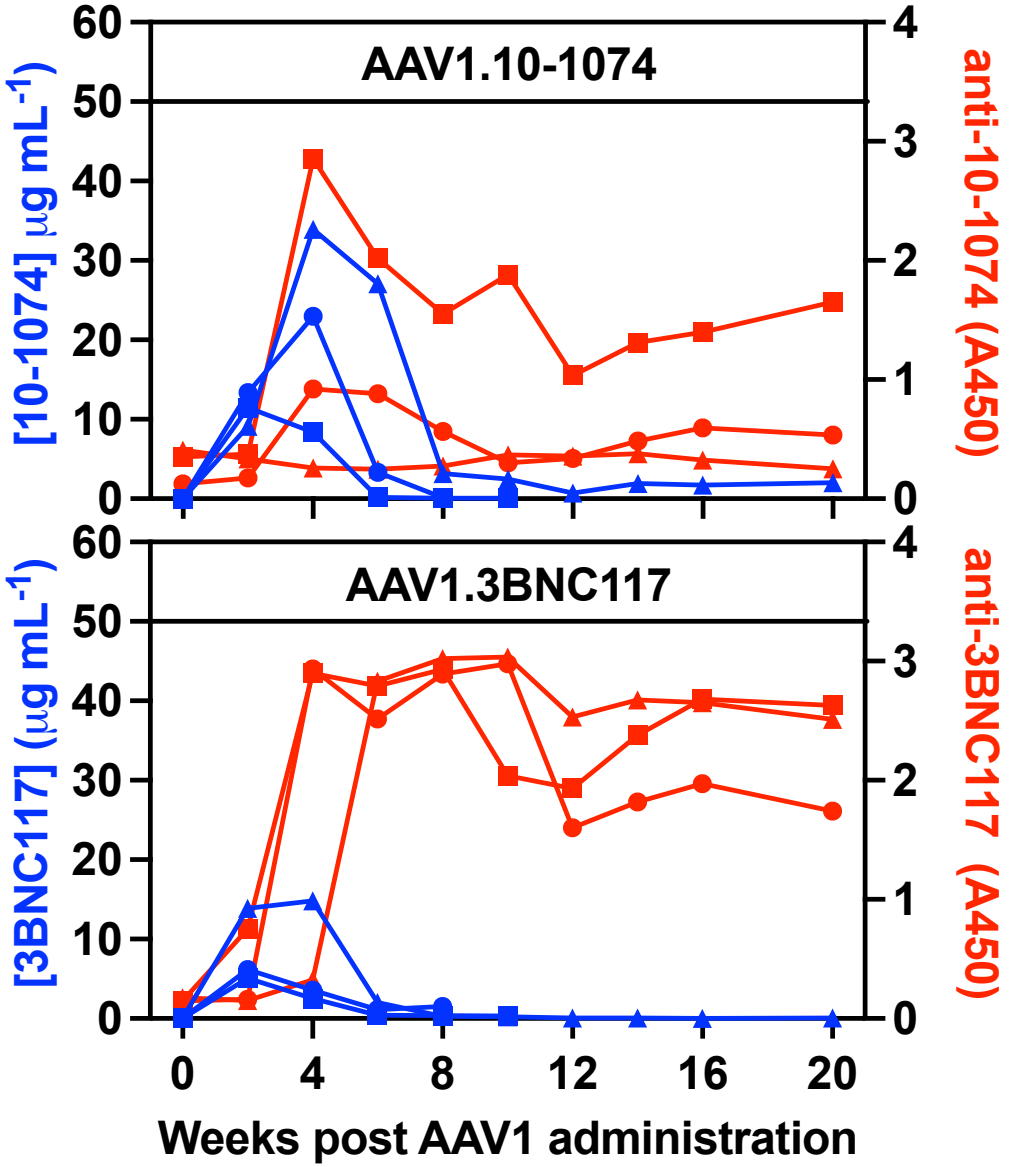
Nonhuman primate studies

- **Fuchs et al., PLoS Pathog., 2015**
- **Saunders et al., J. Vir., 2015**
- **Martinez-Navio et al., Mol. Ther., 2016**

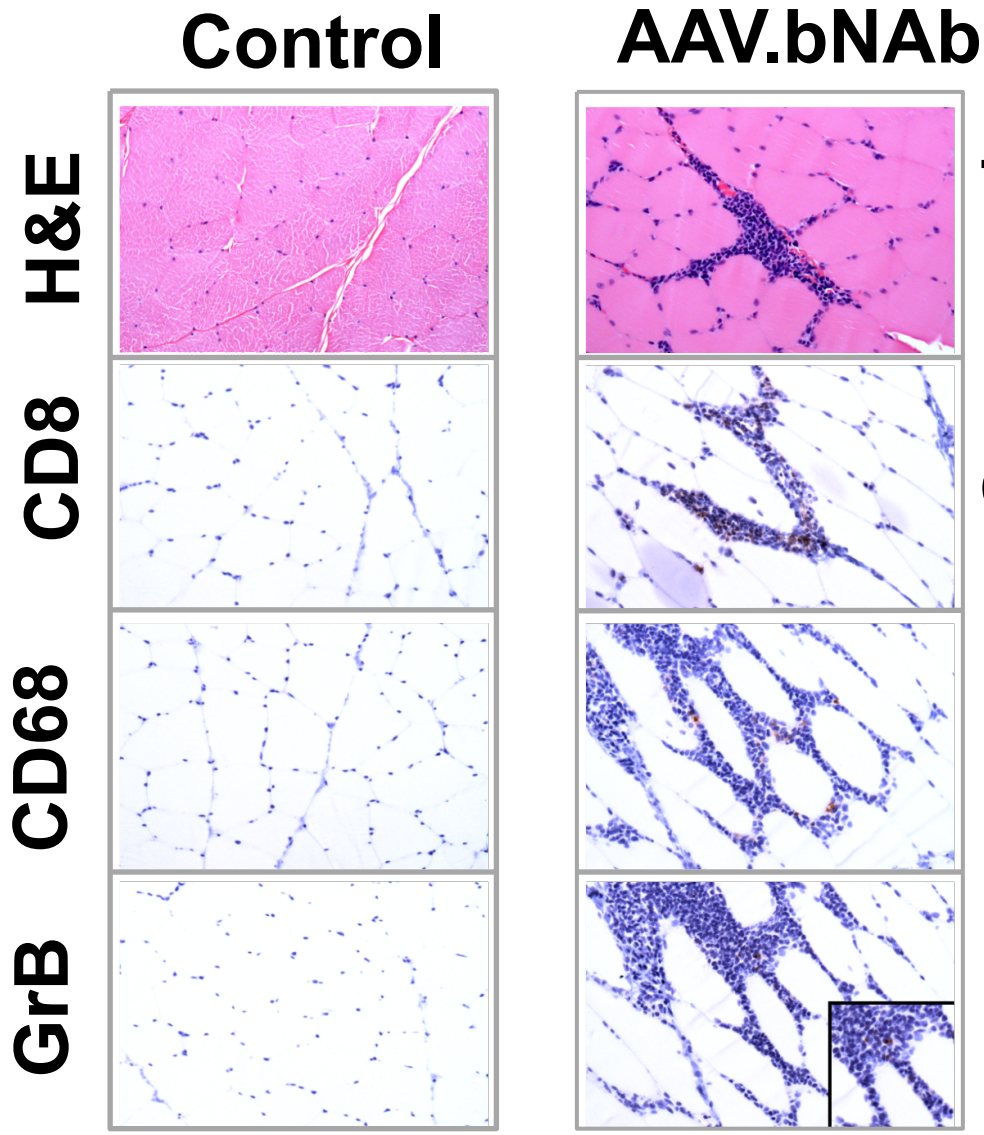
Human clinical studies

- **Priddy et al., Lancet, 2019**
- **Casazza et al., Nat. Med., 2022**

Gardner et al., Mol. Ther., 2019



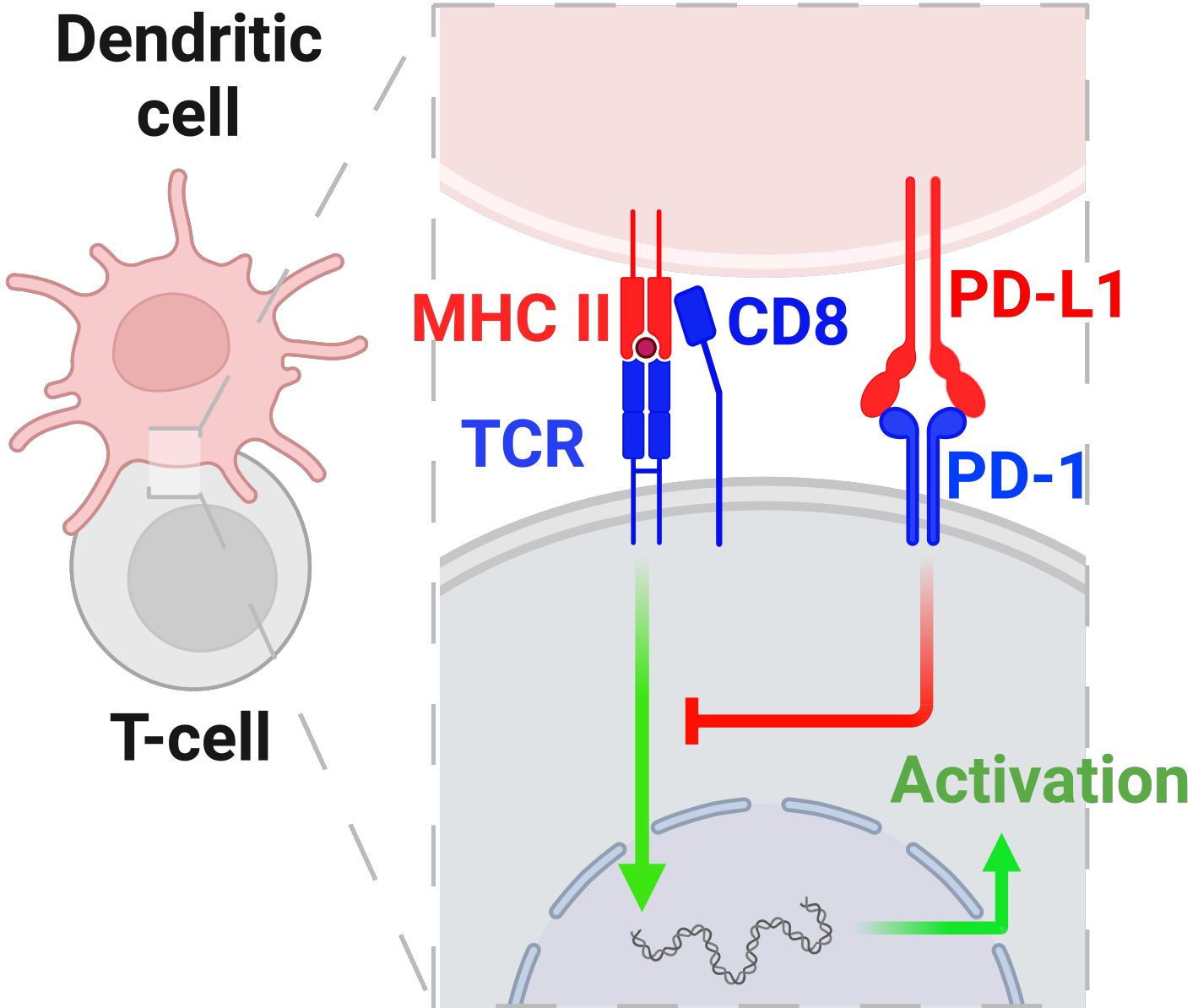
Host immune response targets AAV.bNAb transduced tissue



GrB: granzyme B
CTL: cytotoxic T lymphocyte

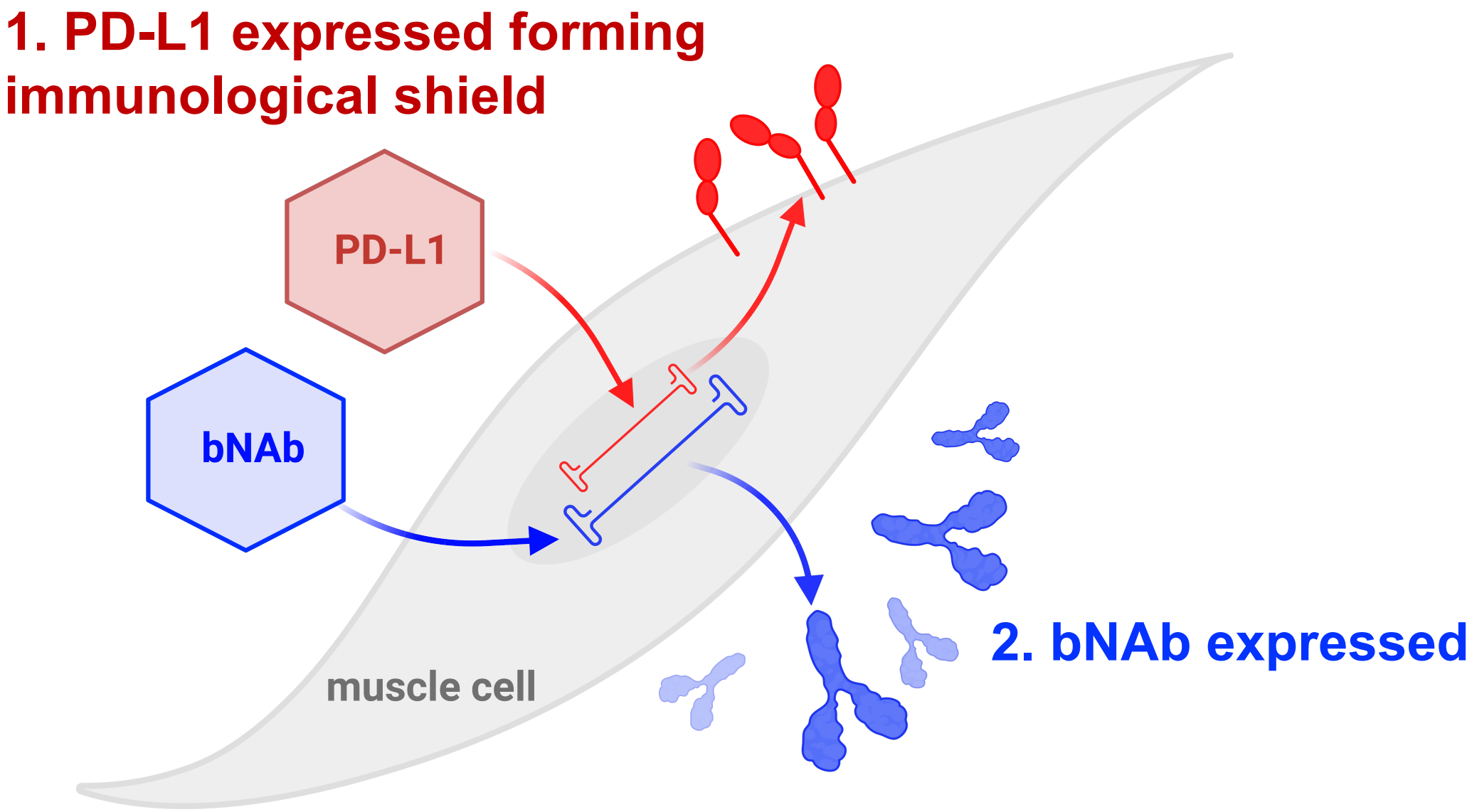
Charles Bailey

The PD-1/PD-L1 immune checkpoint pathway inhibits T cell activation



BioRender

Leveraging PD-1/PD-L1 to improve AAV.bNAb delivery



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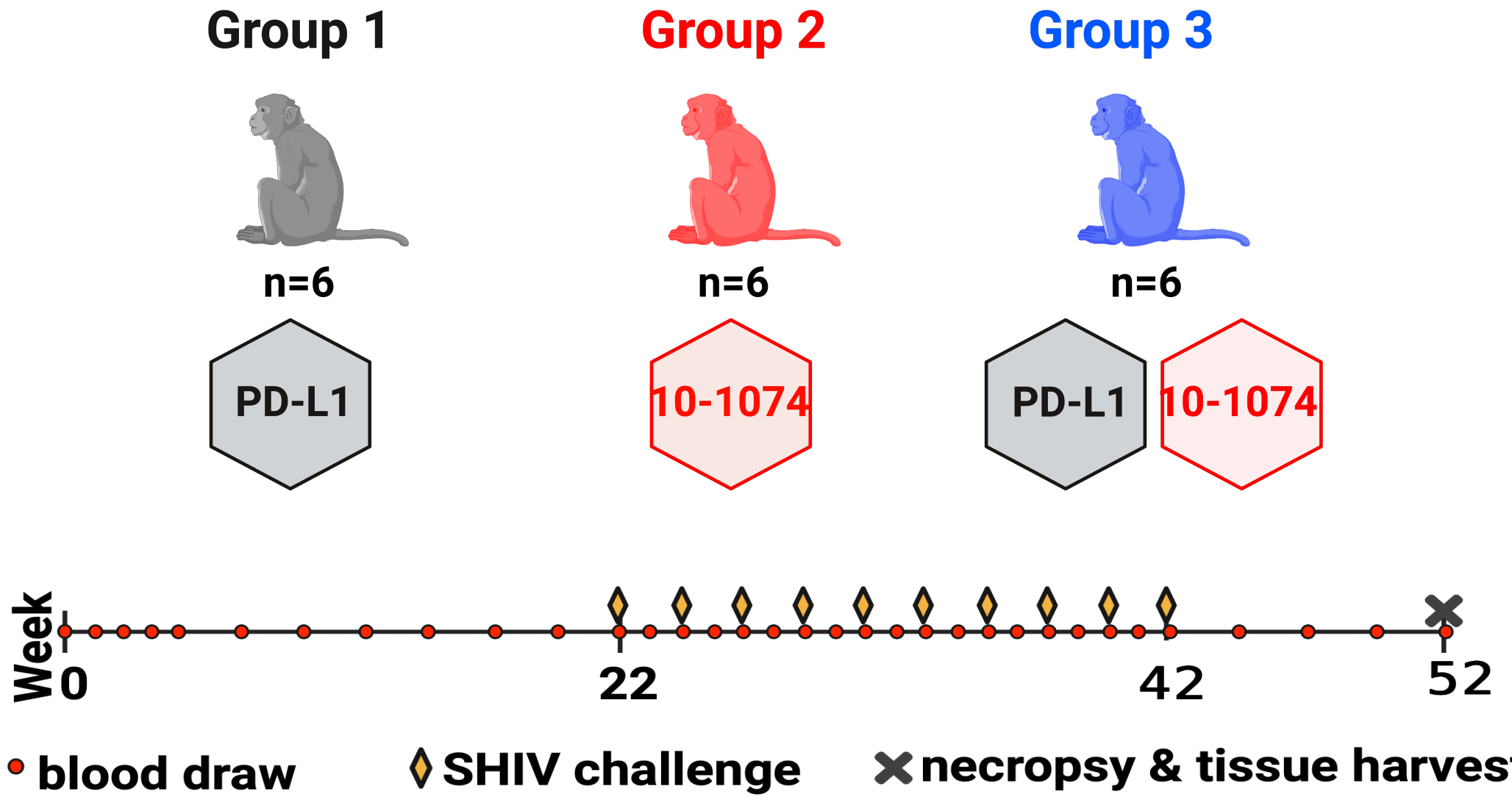
Study Design



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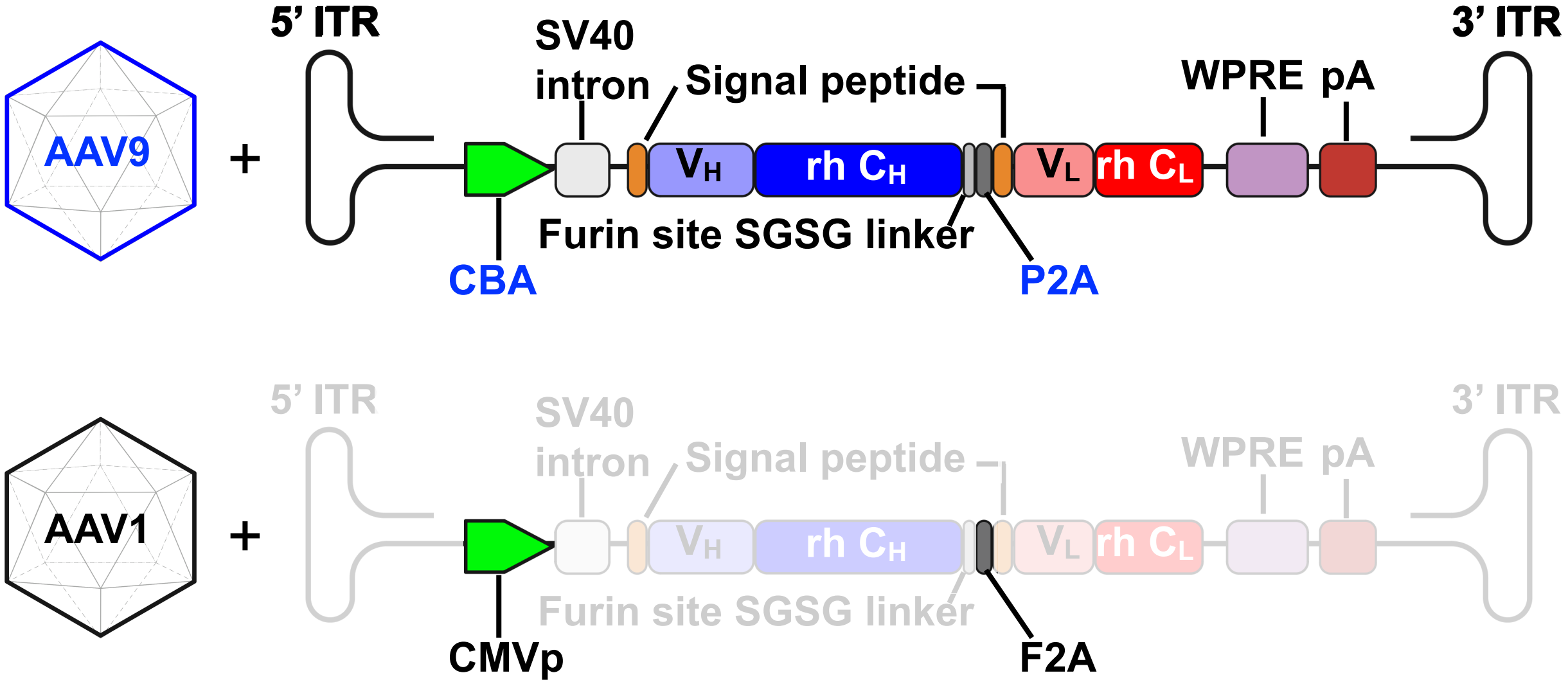
Optimized AAV-vectored antibody expression

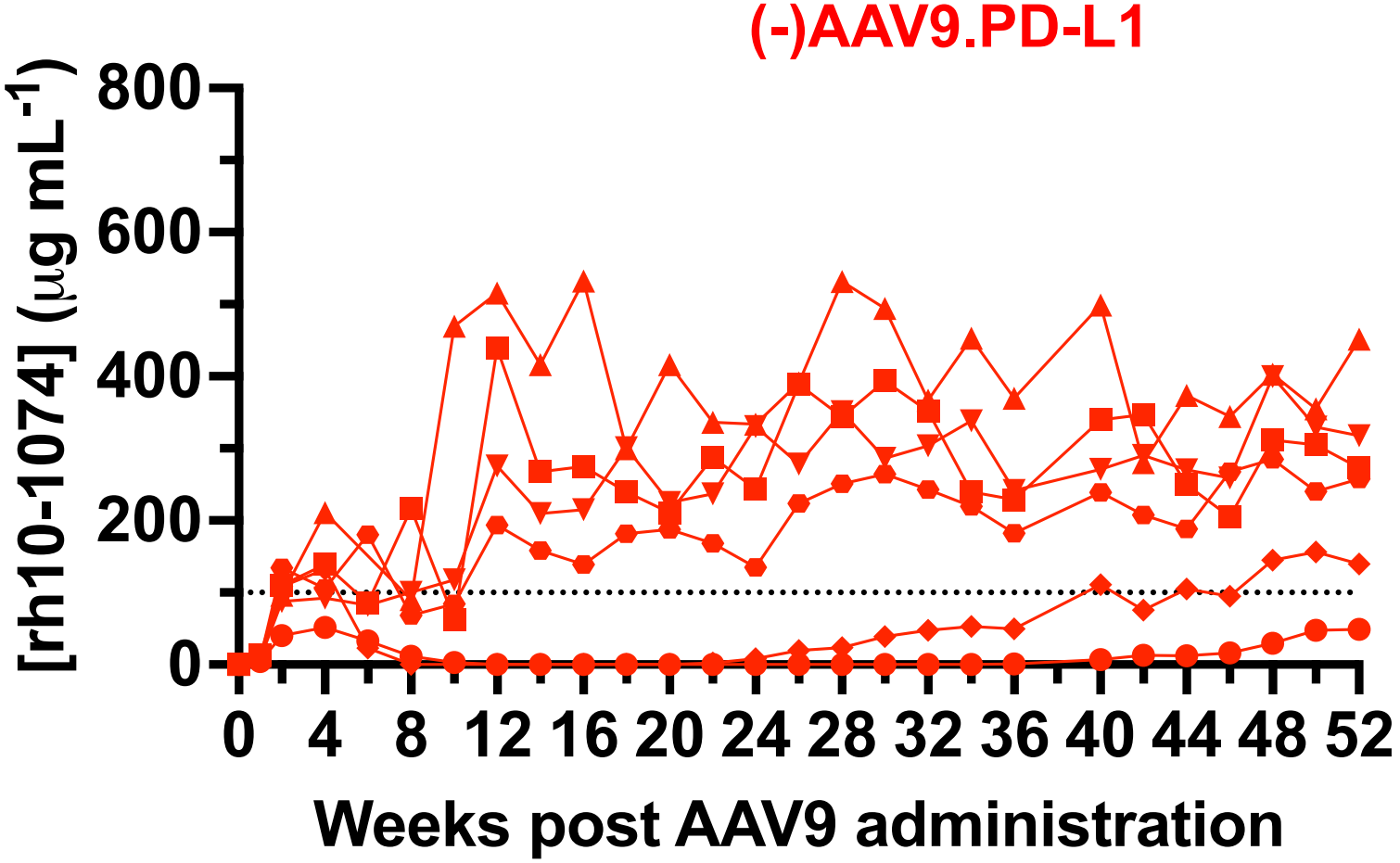
ITR: inverted terminal repeat



Davis-Gardner et al., Front Immunol., 2023

Co-administration of AAV9.PD-L1 & AAV9.10-1074 improves 10-1074 serum concentrations

4/6 in (-)AAV9.PD-L1 group sustained expression >100 µg/mL



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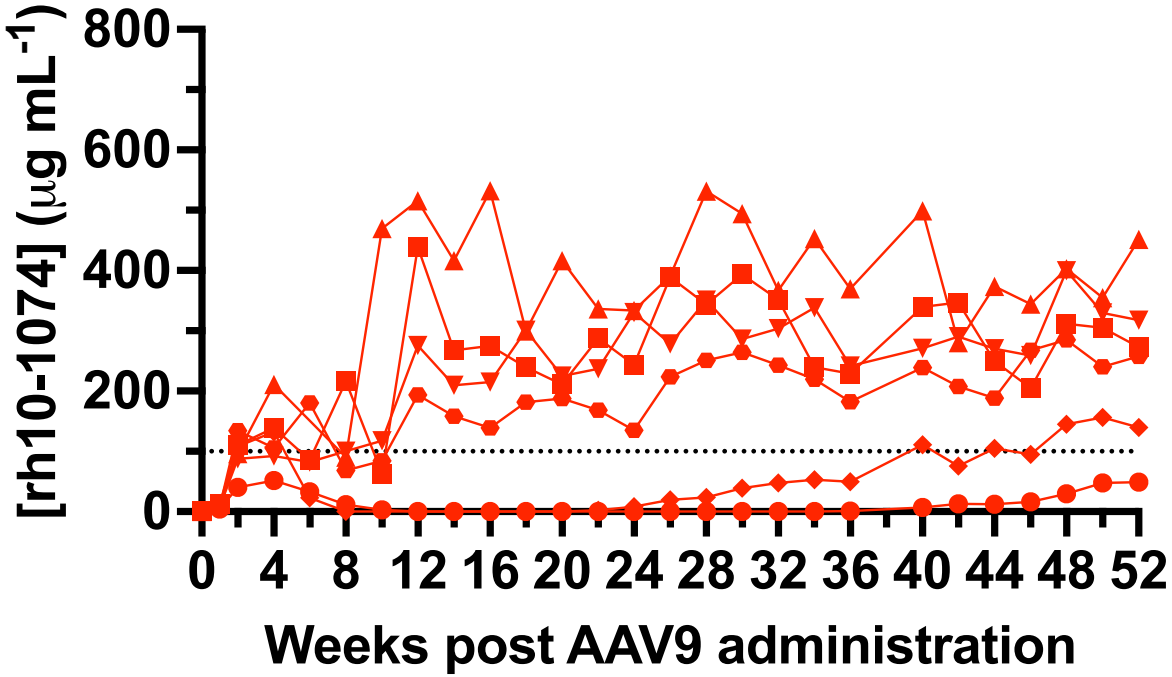
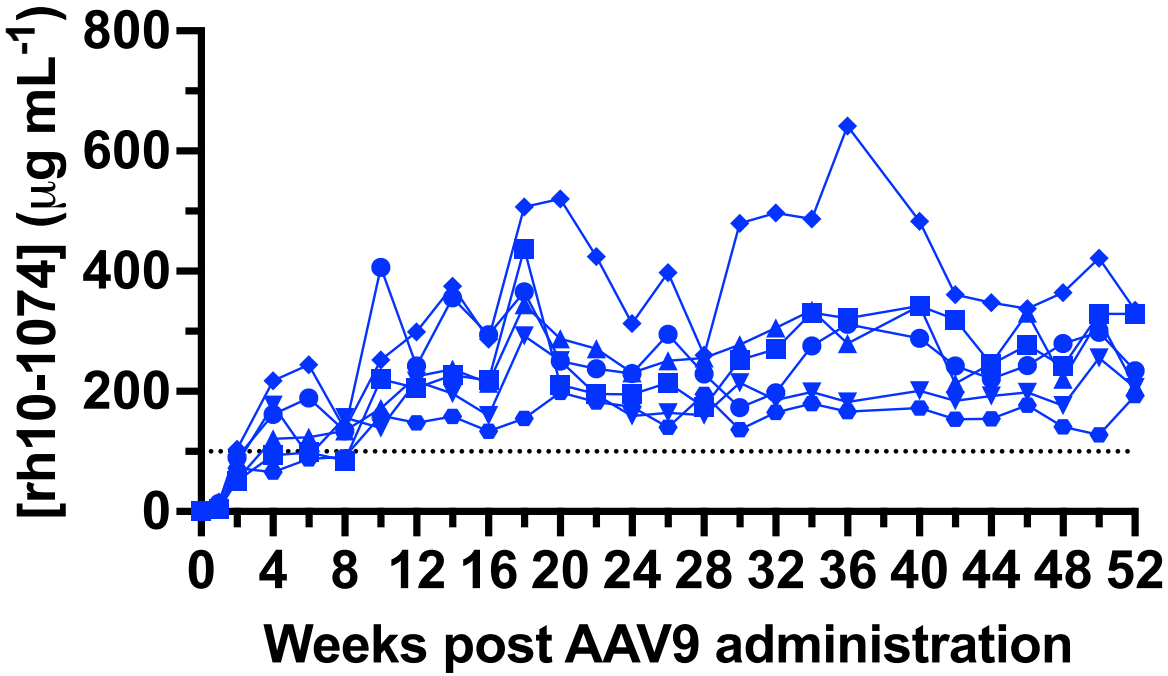
(-)AAV9.PD-L1

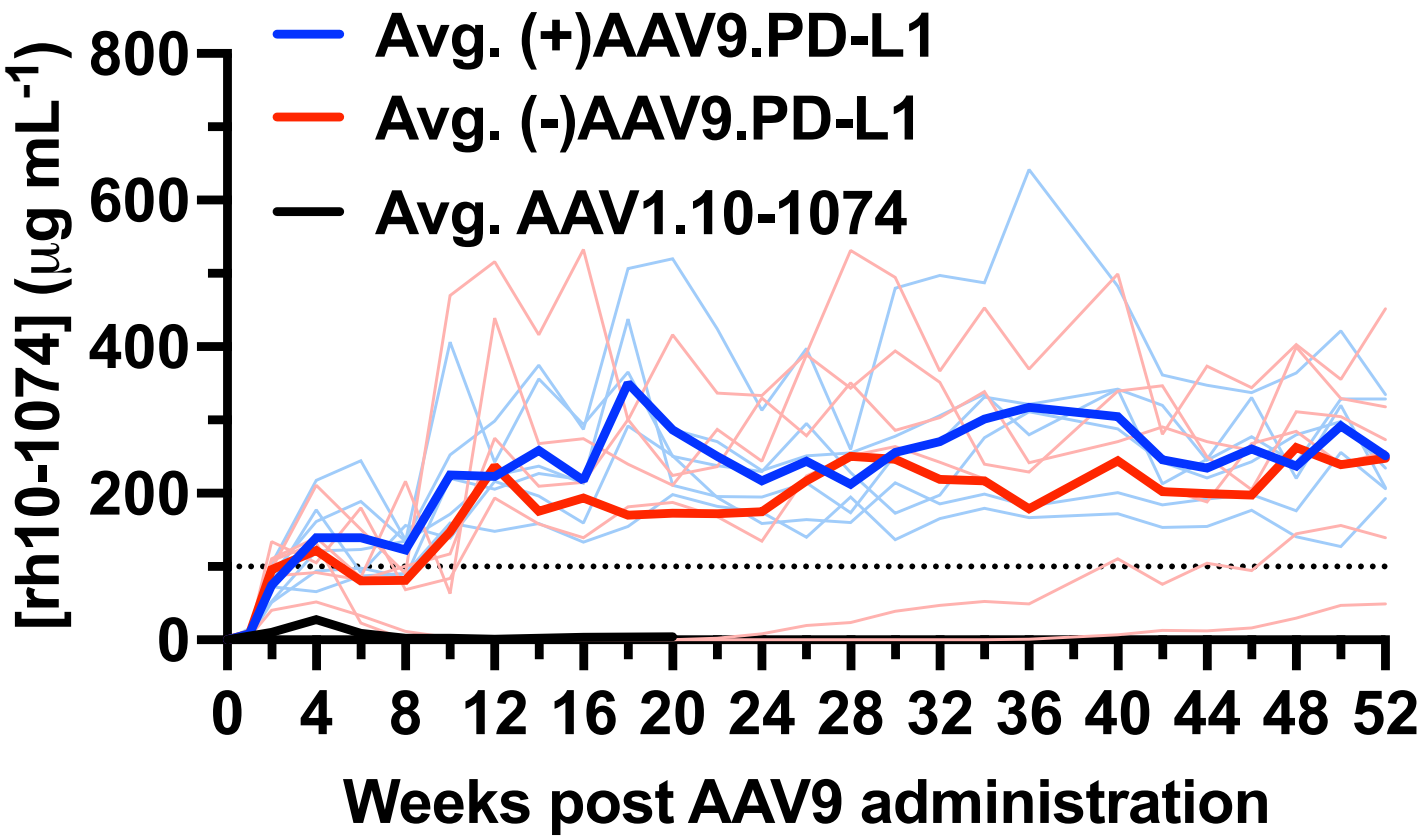


(+)AAV9.PD-L1

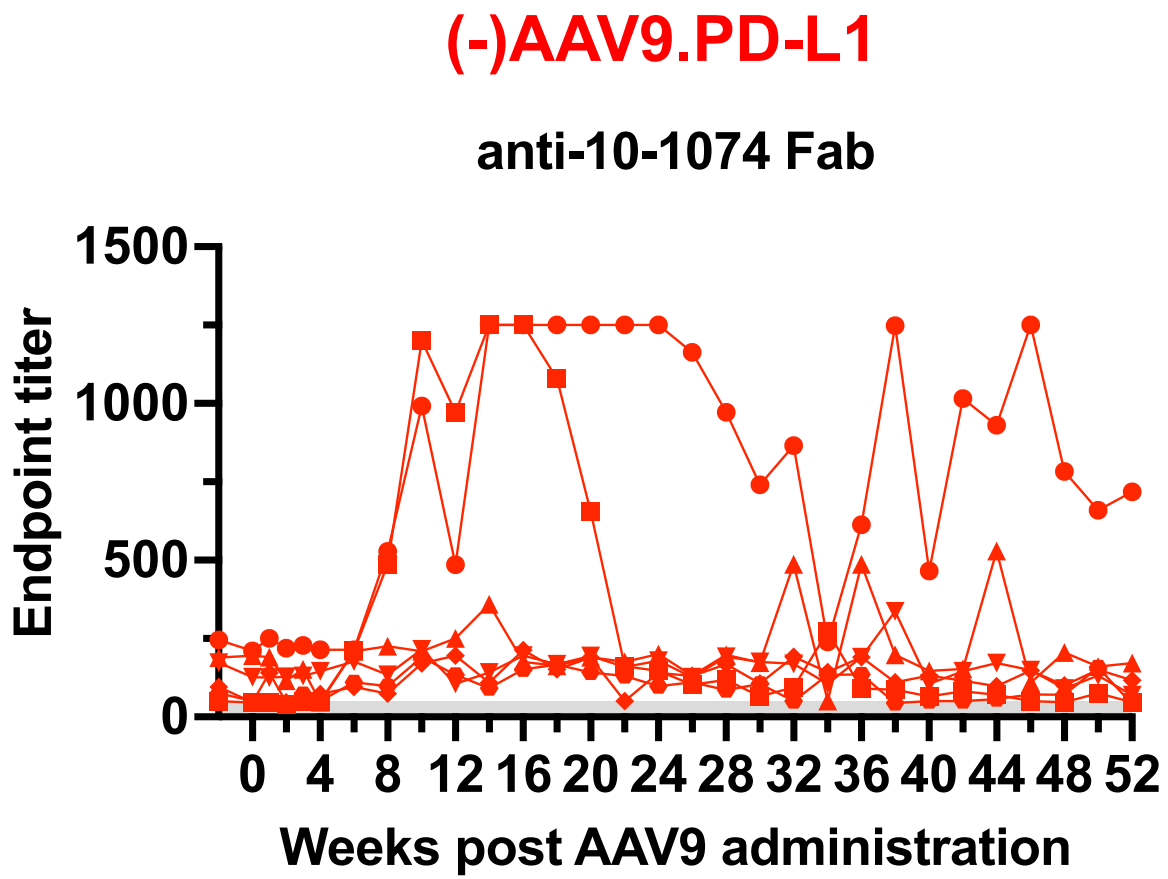


6/6 in (+)AAV9.PD-L1 group sustained expression >100 μg/mL

Co-administration of AAV9.PD-L1 & AAV9.10-1074 improves 10-1074 serum concentrations



Co-administration of AAV9.PD-L1 & AAV9.10-1074 decreases ADA



ADA- antidrug antibody

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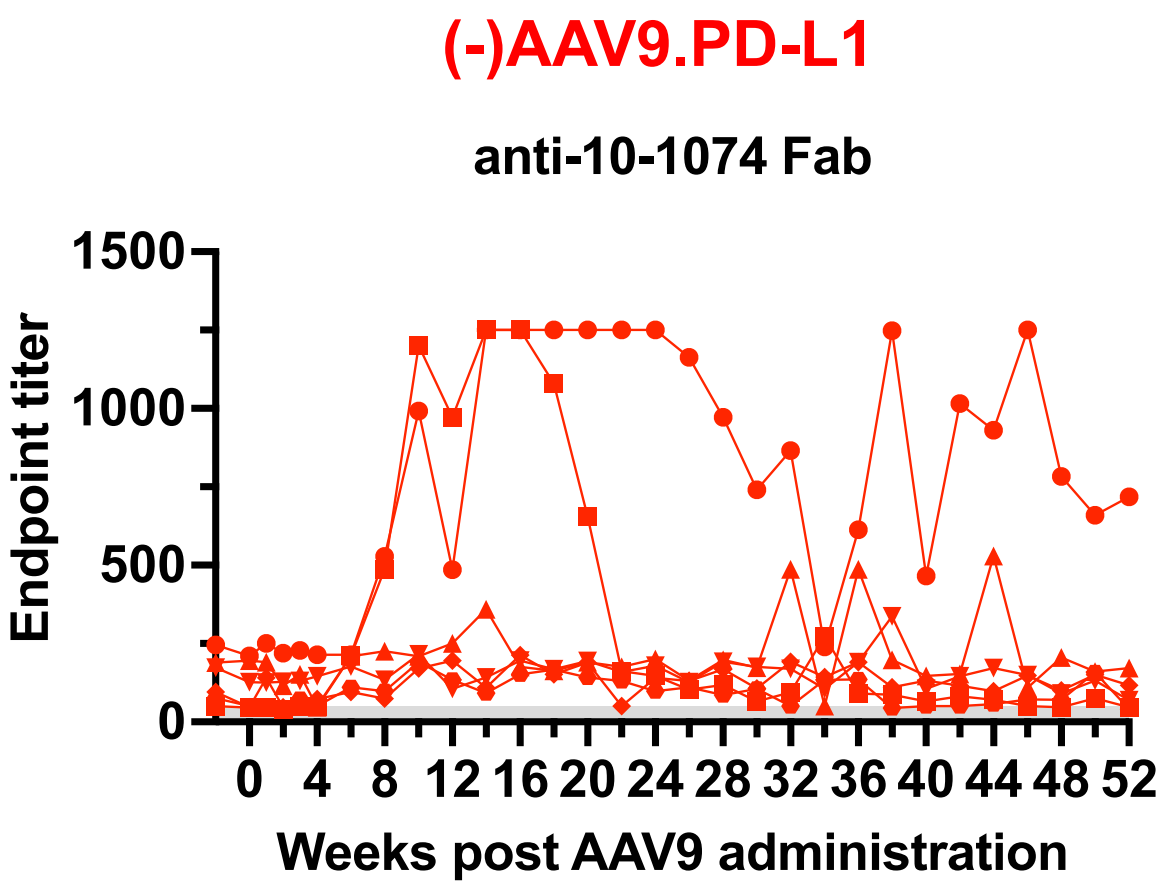
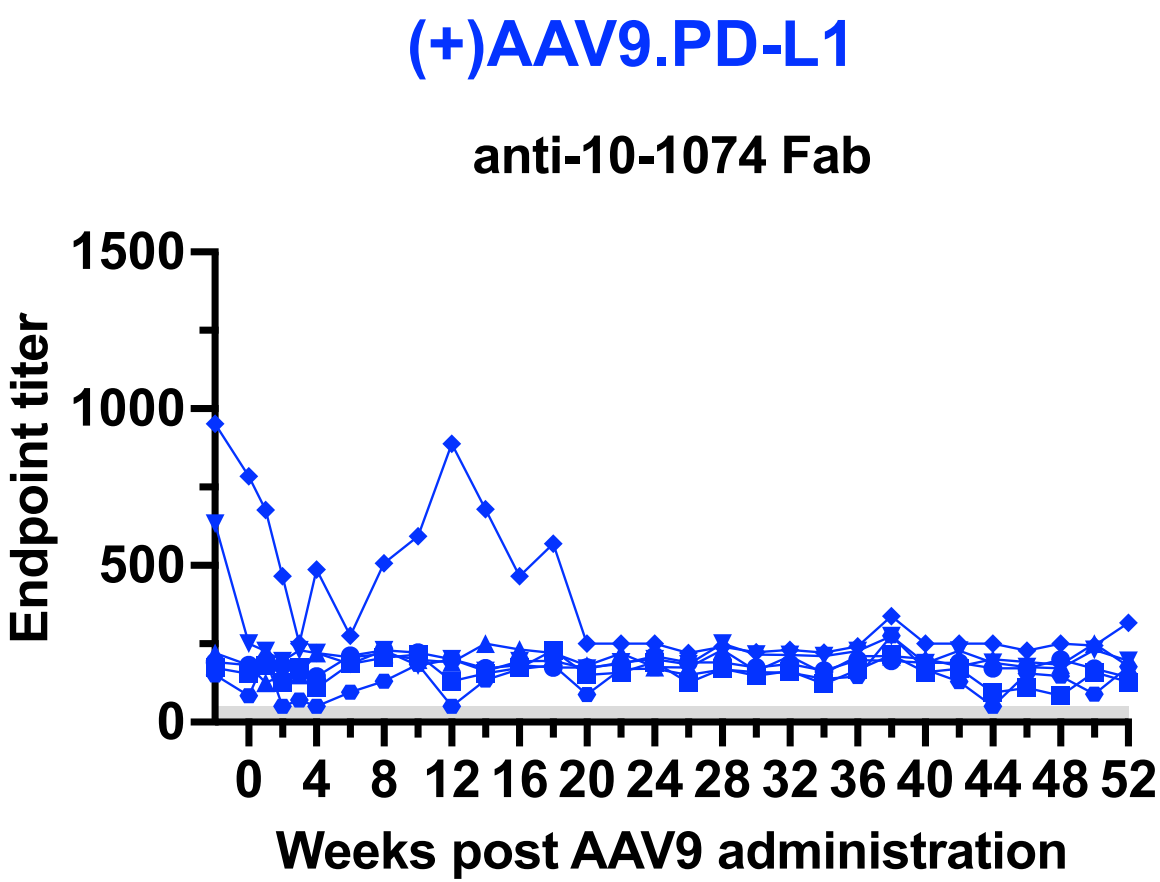
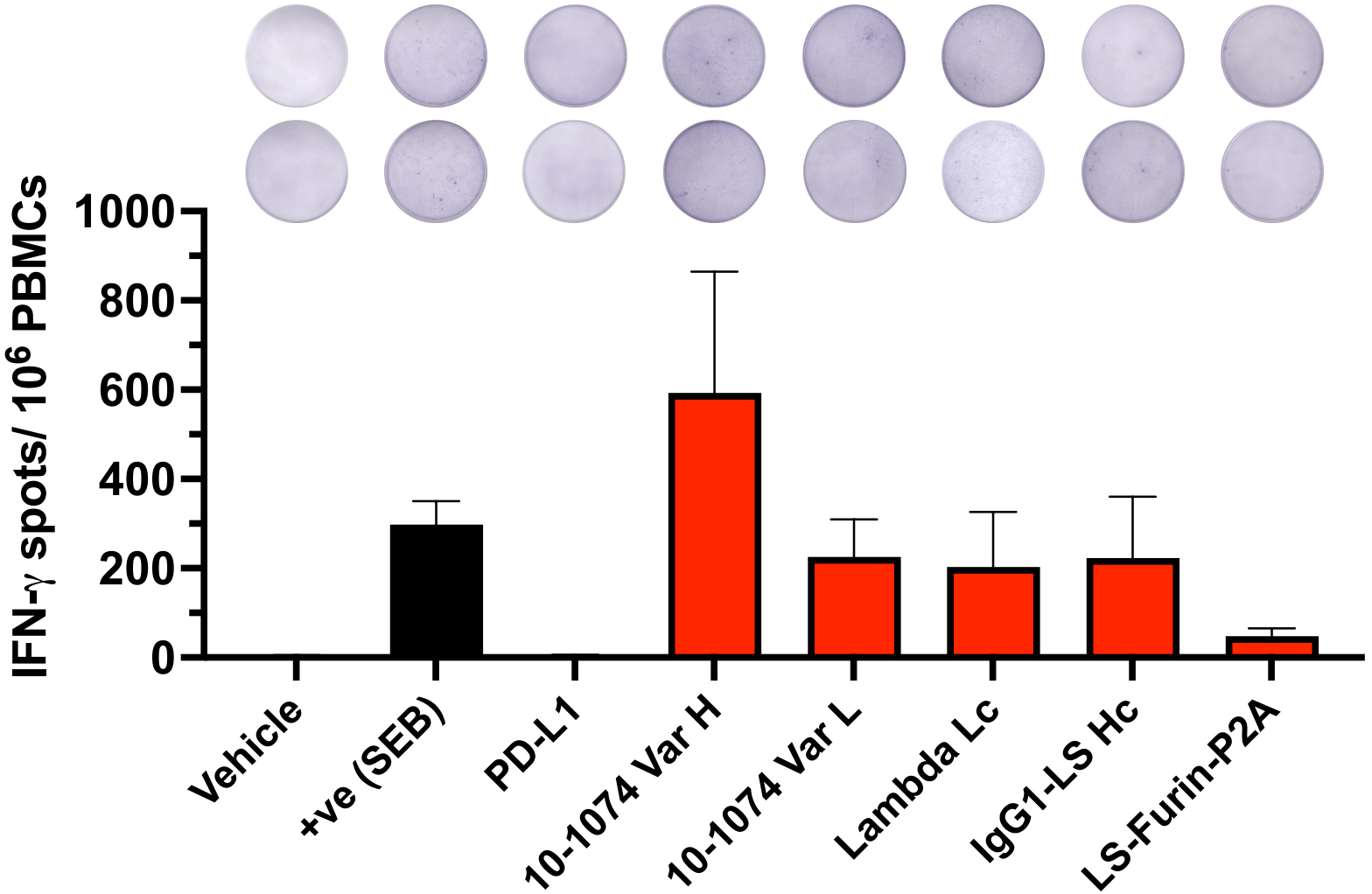


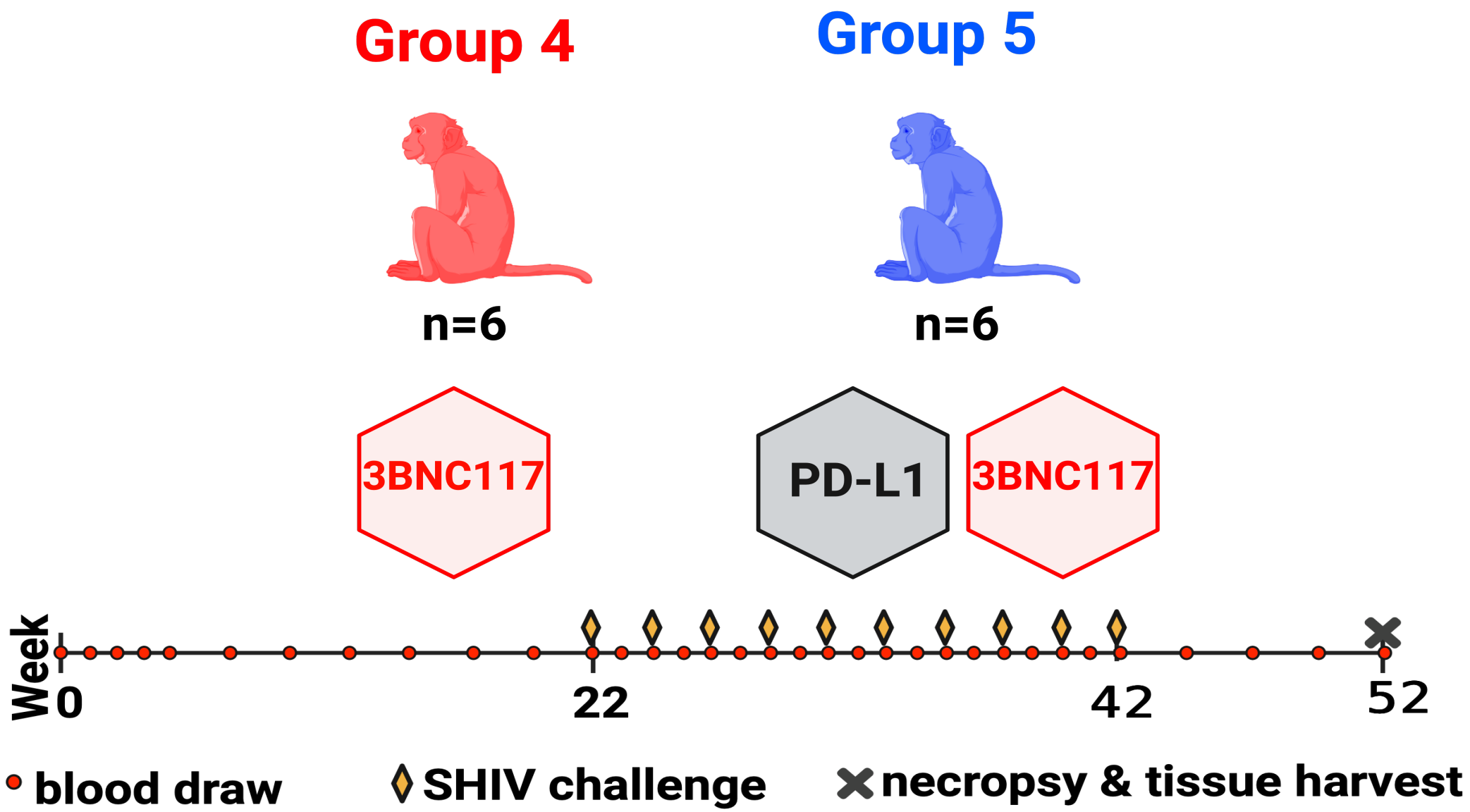


ADA- antidrug antibody

Animals with high ADA have anti-bNAb T cell responses



Study Design



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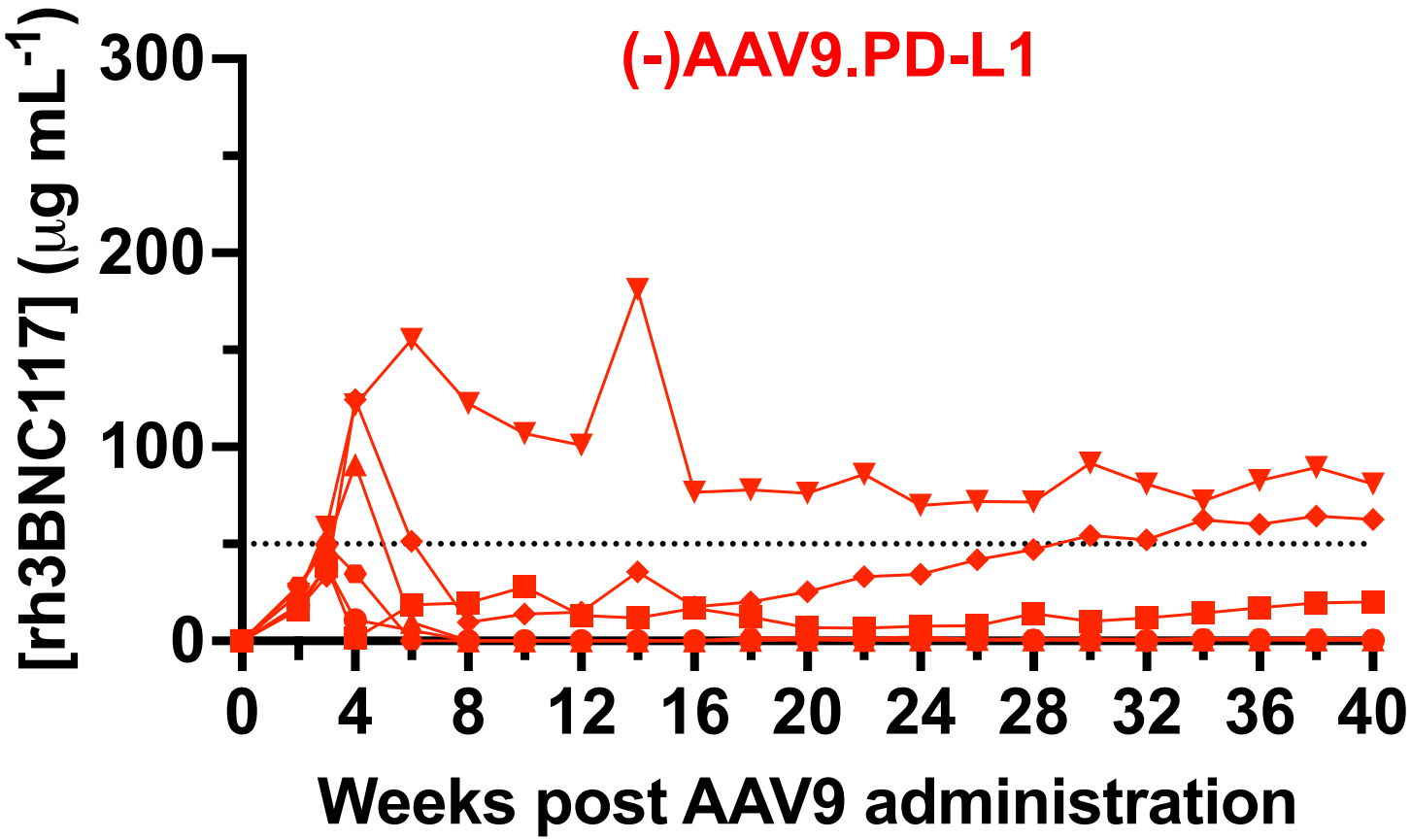
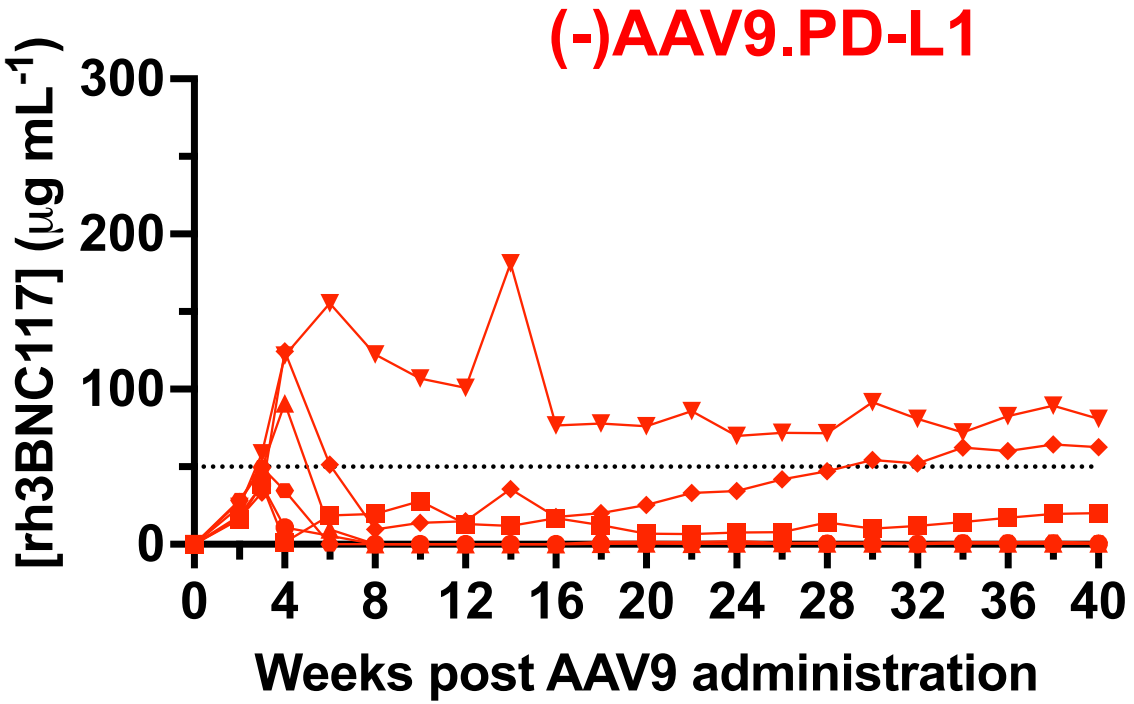
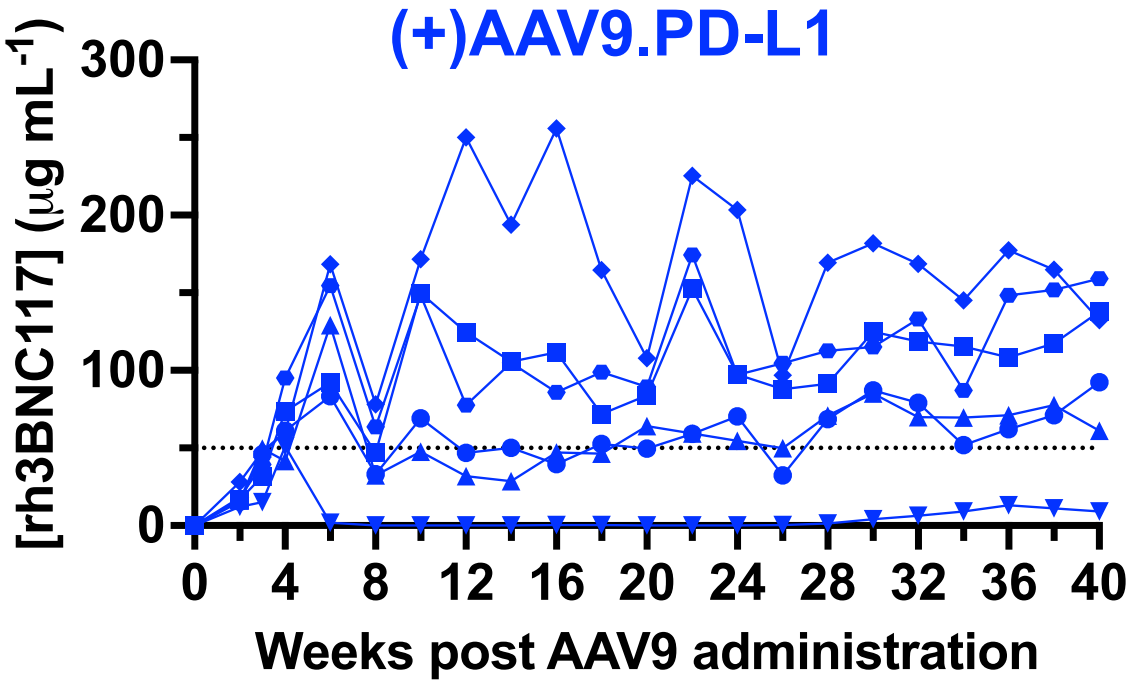
Co-administration of AAV9.PD-L1 & AAV9.3BNC117 improves 3BNC117 serum concentrations



1/6 in (-)AAV9.PD-L1 group sustained expression >50 μg/mL

Co-administration of AAV9.PD-L1 & AAV9.3BNC117 improves 3BNC117 serum concentrations

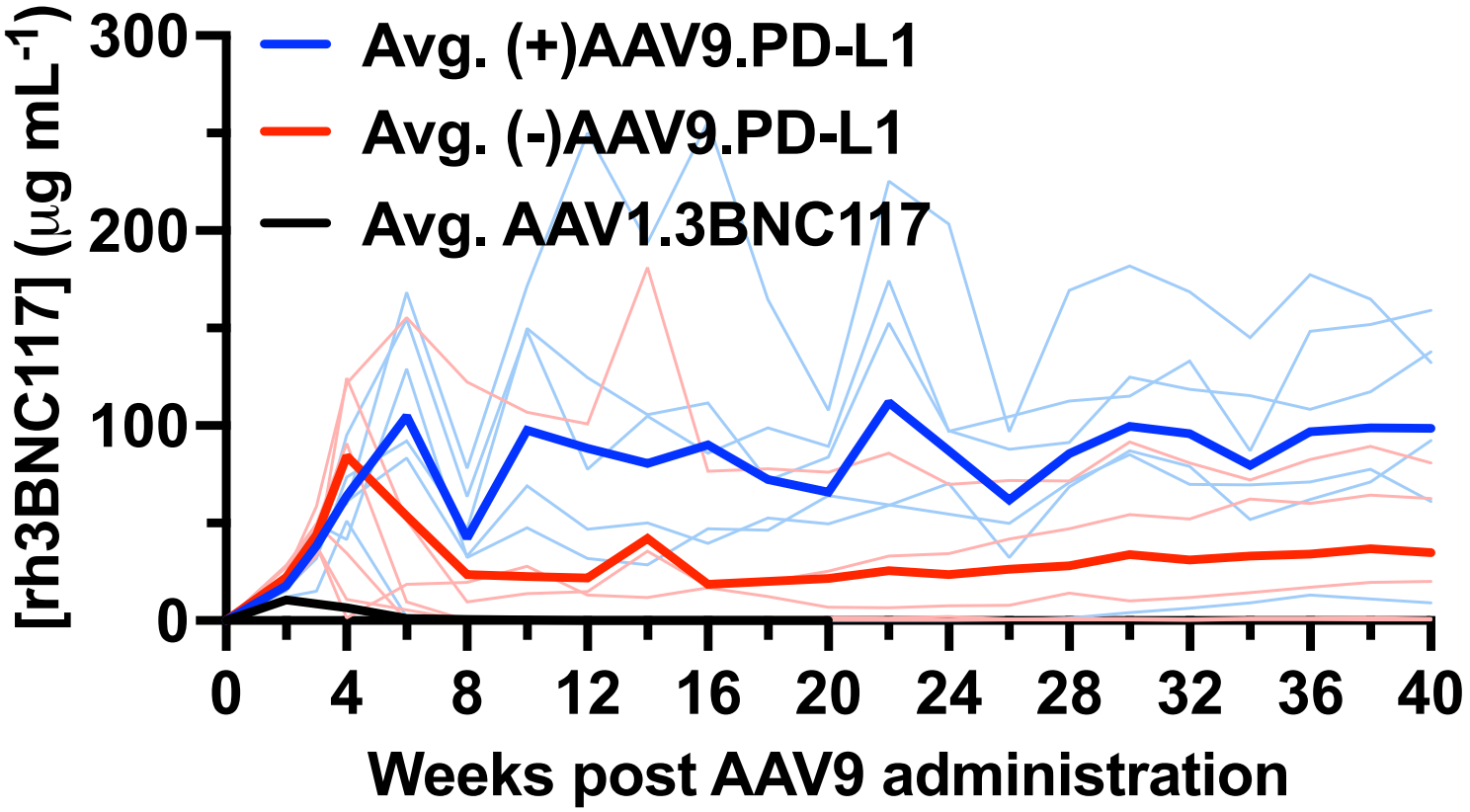




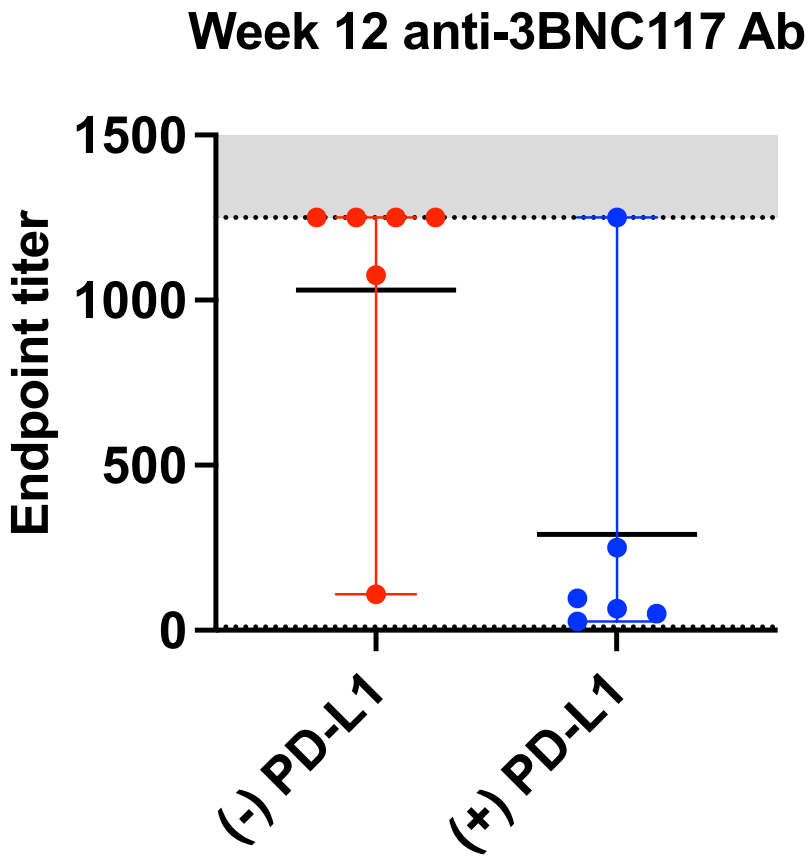
5/6 in (+)AAV9.PD-L1 group sustained expression >50 µg/mL

1/6 in (-)AAV9.PD-L1 group sustained expression >50 µg/mL

Co-administration of AAV9.PD-L1 & AAV9.3BNC117 improves 3BNC117 serum concentrations

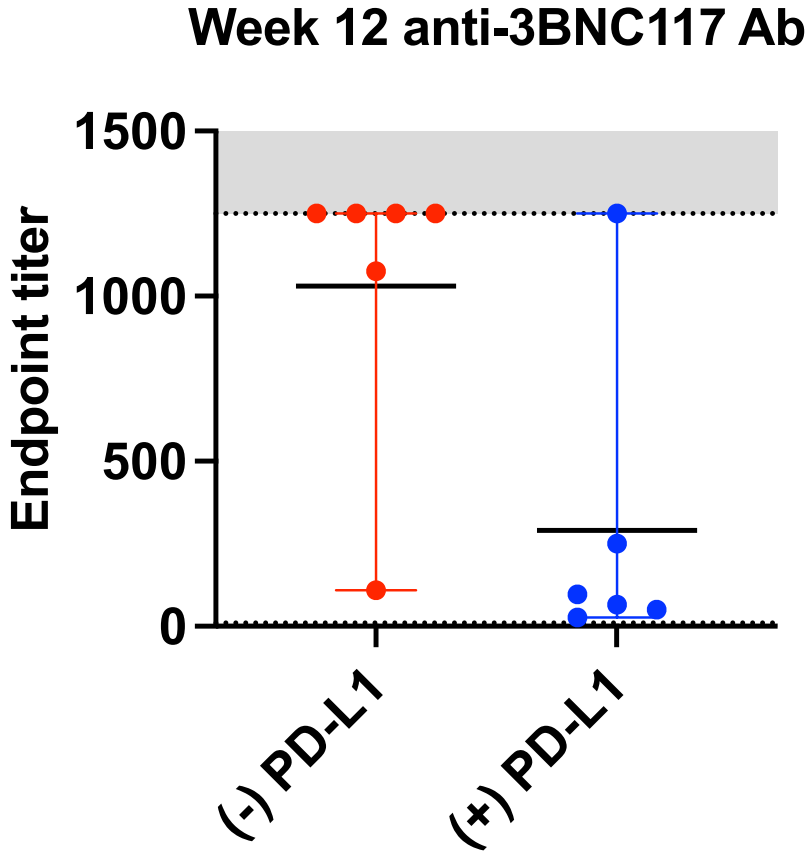


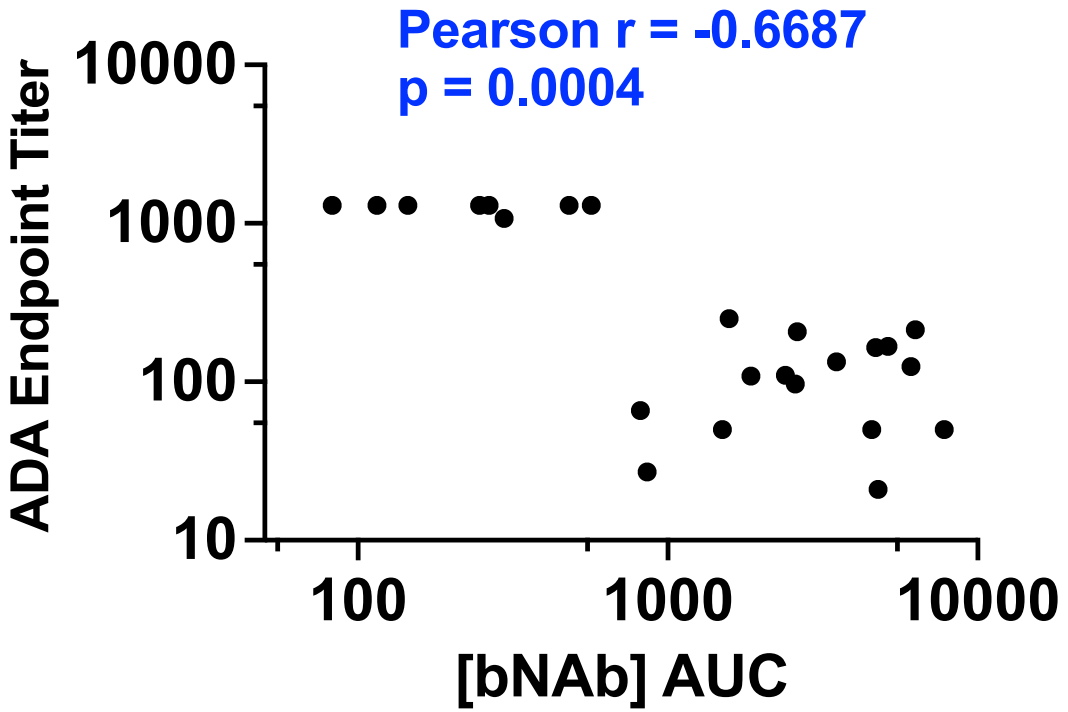
Co-administration of AAV9.PD-L1 & AAV9.3BNC117 decreases ADA at Week 12



sustained bNAb expression correlated with low/no ADA

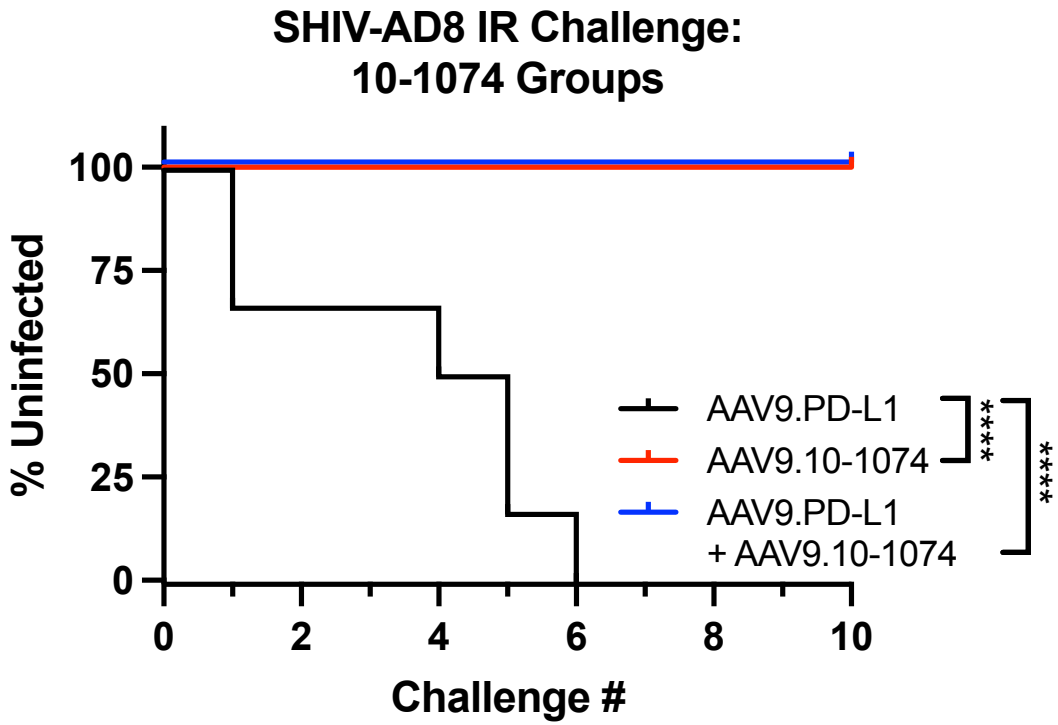
Co-administration of AAV9.PD-L1 & AAV9.3BNC117 decreases ADA at Week 12





sustained bNAb expression correlated with low/no ADA

AAV9.10-1074 and AAV9.3BNC117 protect against repeated SHIV-AD8 challenges



IR: intrarectal

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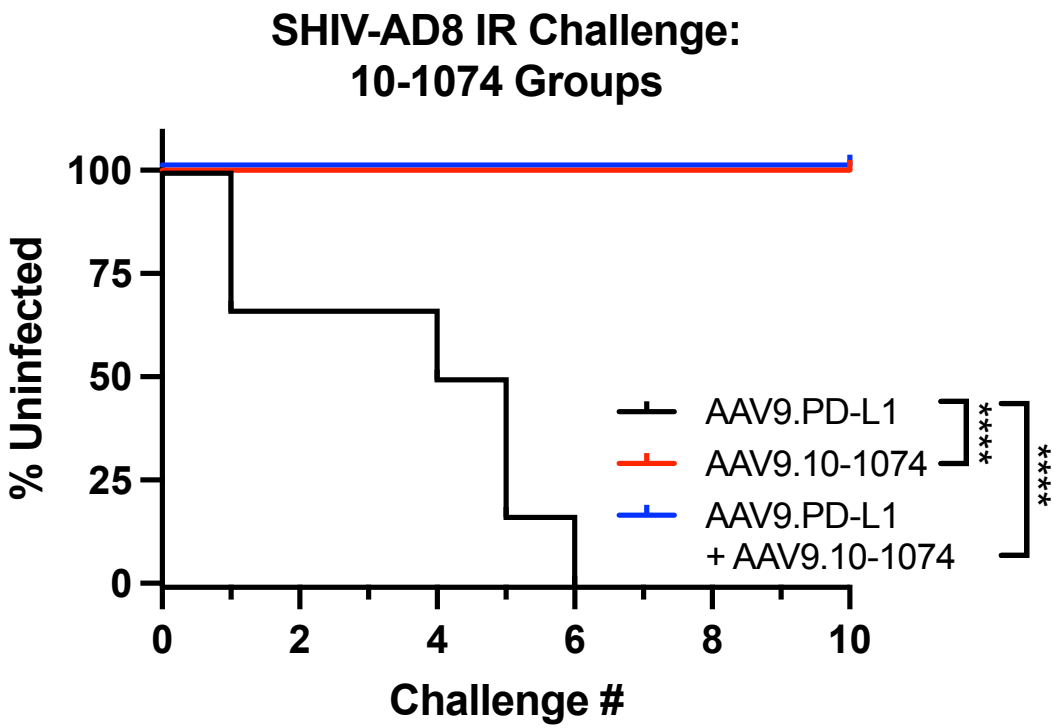
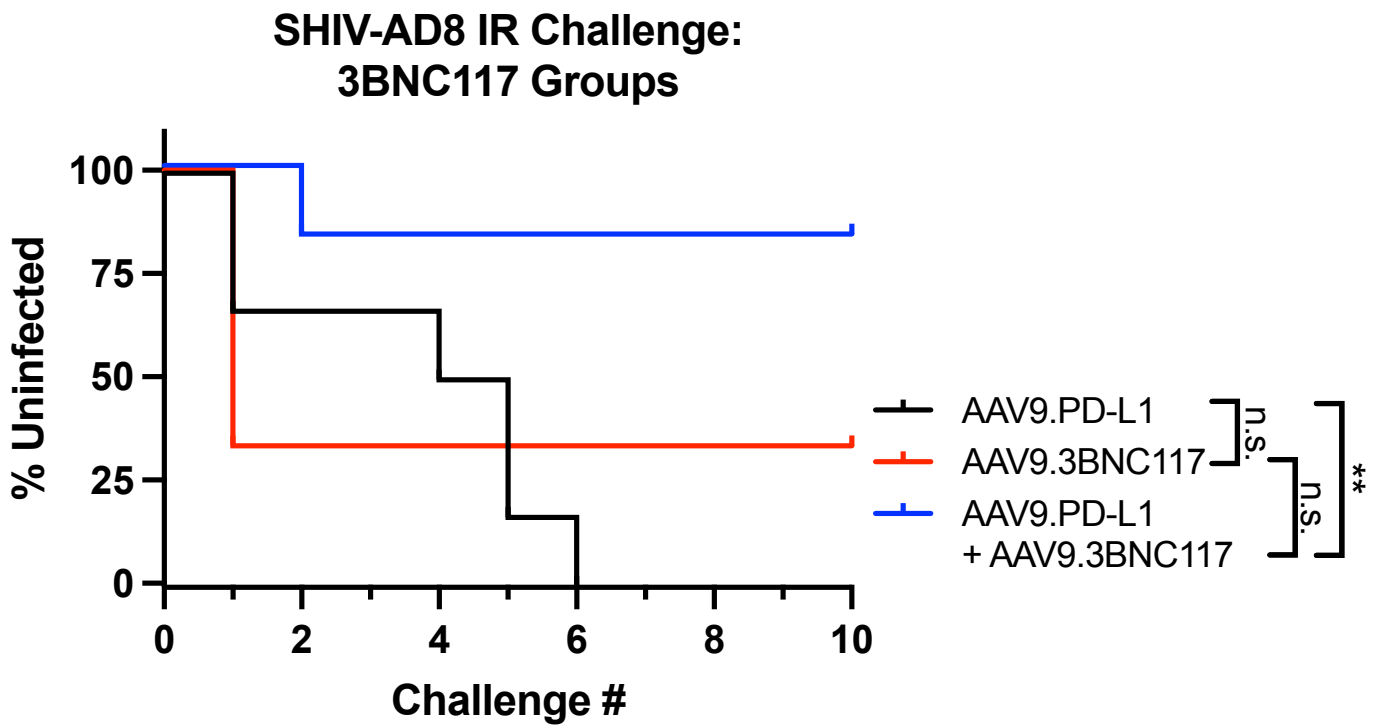




IR: intrarectal

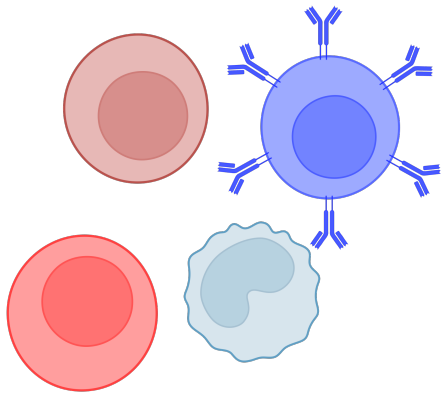
Conclusions

AAV9.PD-L1 improves the consistency of AAV9.10-1074 and AAV9.3BNC117 expression in macaques

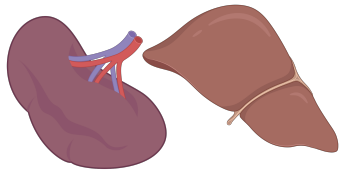
We have developed a strategy to evaluate new AAV vectors in nonhuman primates without the interference of the host immune response

Future Directions

ELISpot
T cell reactivity

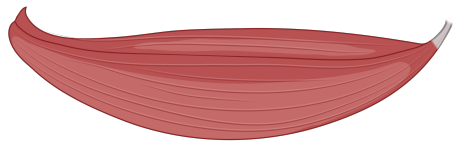


ddPCR
AAV transgene cassette biodistribution



RNA-seq
immunomodulatory genes

immunohistochemistry, spatial transcriptomics
PD-L1 expression



BioRender

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NIAID

Yoshi Nishimura

Overcoming immune responses to AAV-delivered bNAbs

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