A strategy for durable AAV-vectored bNAb expression in adult rhesus macaques

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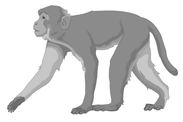
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BACKGROUND

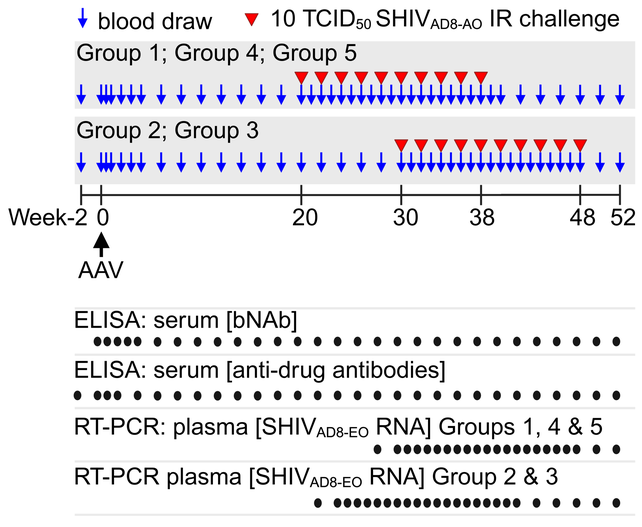
- Sustained expression of adeno-associated virus (AAV)-vectored anti-HIV-1 broadly neutralizing antibodies (bNAbs) could prevent and treat HIV-1 infection.
- **Problem:** Durable expression of AAV-vectored bNAbs *in vivo* is limited by host immune responses.
- PD-1 is an immune checkpoint protein on T cells that inhibits T-cell activity upon binding to **PD-L1**.
- **Hypothesis:** PD-L1 co-expression on AAV.bNAb-transduced cells maintains bNAb expression by suppressing host anti-drug antibodies (ADA) and T-cell responses.
- **Overall goal:** develop a model for prolonged AAV-vectored bNAb production in NHPs and possibly advance AAV-delivery of bNAbs for human clinical trials.

METHODS

Group 1: AAV9.PD-L1
Group 2: AAV9.10-1074
Group 3: AAV9.10-1074 + AAV9.PD-L1
Group 4: AAV9.3BNC117 + AAV9.PD-L1
Group 5: AAV9.3BNC117



n=6 per group



Co-expressed AAV-vectored PD-L1 *improves the expression and protective efficacy* of AAV-vectored bNAbs by *reducing host anti-bNAb immune responses* in rhesus macaques

RESULTS

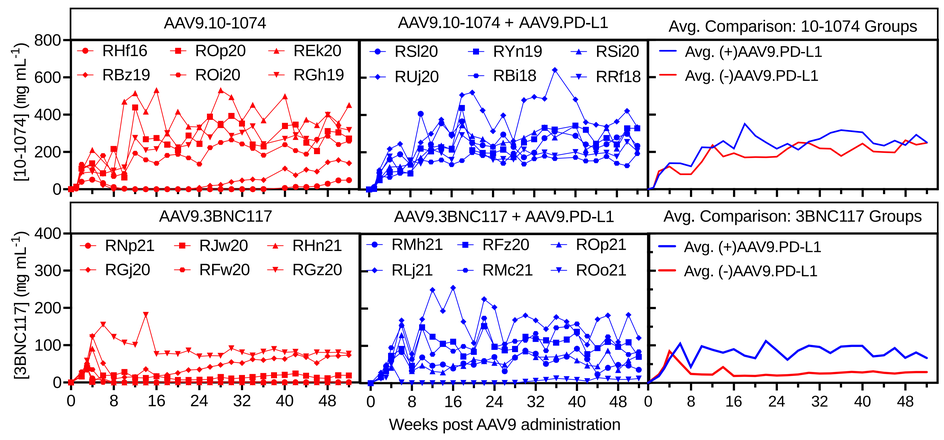


***Figure 1**: Serum bNAb levels determined by gp120 ELISA.*

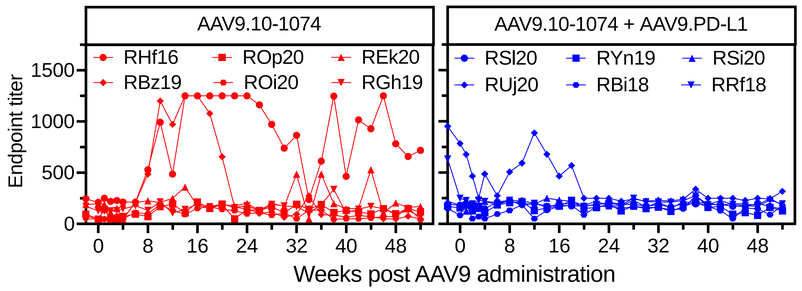


***Figure 2**: Serum ADA endpoint titers determined by 10-1074 Fab ELISA.*

RESULTS

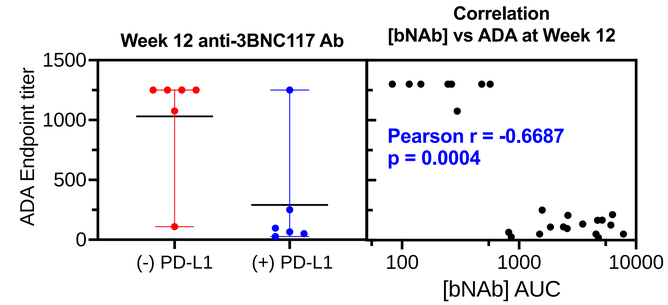


***Figure 3**: Serum ADA endpoint titers determined by 3BNC117 ELISA (left) and correlation between bNAb serum level area under the curve and ADA endpoint titers at Week 12 across all groups (right).*

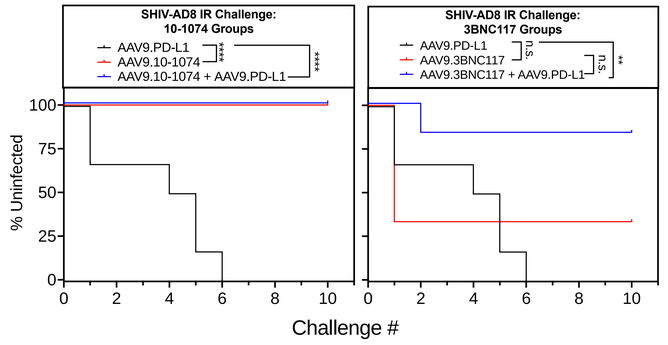


***Figure 4**: Kaplan-Meier analysis showing percent uninfected macaques after repeated low dose intrarectal SHIV challenge.*

CONCLUSIONS

- We have developed a strategy for sustained bNAb expression in NHPs.
- This will allow the prophylactic and therapeutic efficacy of AAV-delivered bNAbs to be studied in preclinical NHP models.

FUNDING

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