AAV-Delivered Antibody Reaches Mucosal Sites and Protects Against SHIV Infection in Rhesus Macaques

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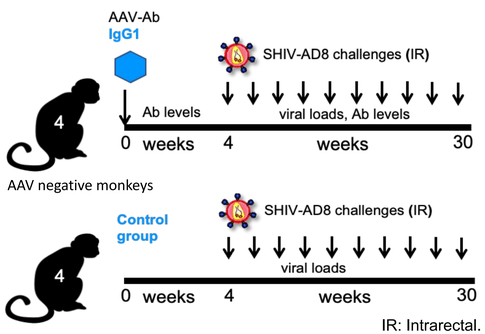
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BACKGROUND

- Recombinant adeno-associated virus (AAV) has been widely used as a vector for gene delivery applications because of its safety and cost-efficiency: one single injection can account for long term expression of the transgene.
- Broadly neutralizing antibodies (bNAbs) have emerged as promising tools for HIV prevention and therapy.
- Here, our goal was to assess mucosal protection with AAV-delivered anti-HIV PCIN63 antibody, which targets the CD4 binding site on the HIV envelope glycoprotein.

METHODS



IR: Intrarectal.

Table I. Challenges with PBMC-derived virus stock*.

#	p27 (pg)	$TCID_{50}$
1	100	10
2	100	10
3	200	20
4	400	40
5	400	40
6	400	40
7	400	40
8	400	40
9	800	80
10	4,000	385

$TCID_{50}$ = Tissue Culture Infectious Dose 50%.

SHIV (Simian/Human Immunodeficiency Virus) is a hybrid virus combining a Simian Immunodeficiency Virus (SIV) backbone with a HIV-1 envelope protein.

*Two prior IR challenges were performed using HEK293T cells: one at a dose of 100 pg of p27, and one at a dose of 200 pg. No infections were reported in these two initial challenges.

Antibody Detection: PCIN63 IgG was quantified in serum and mucosal samples (rectal and saliva) by Enzyme-Linked Immunosorbent Assay (ELISA).

SHIV-AD8 Viral Loads: Plasma viral RNA levels were measured by quantitative RT-PCR.

Standard protective efficacy calculation:

$$\text{Vaccine efficacy (VE)} = 1 - \frac{\text{risk in vaccinated}}{\text{risk in controls}}$$

Orenstein et al, 1985.

AAV-delivered anti-HIV bNAb PCIN63 reached mucosal sites and conferred 67% protection against SHIV infection in rhesus macaques following multiple mucosal challenges after a single vector administration.

RESULTS

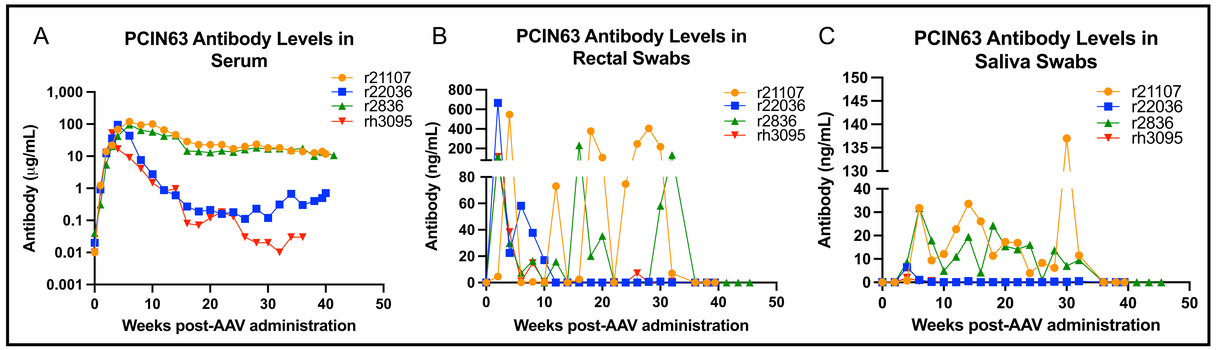


Figure 1. Levels of anti-HIV bNAb PCIN63 engineered as rhesus IgG and delivered by intramuscular AAV injection detected by ELISA in serum (A), rectal swabs (B) and saliva swabs (C).

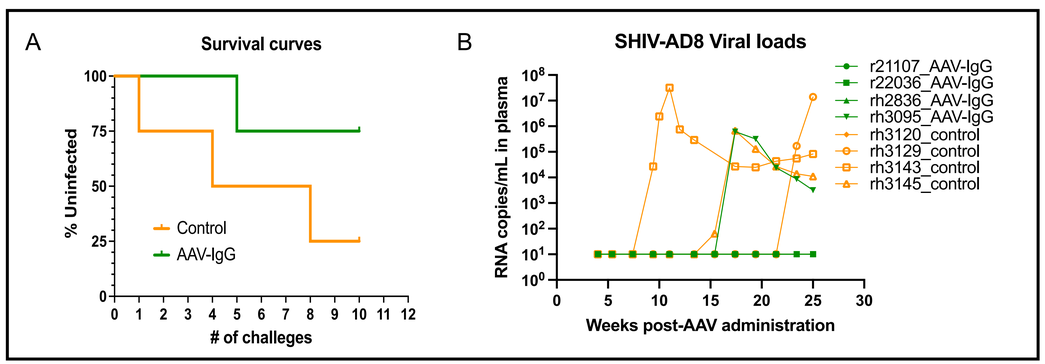


Figure 2. Survival curves (A) of the challenge phase (IR challenges with SHIV-AD8, PBMC-derived stock). SHIV-AD8 viral loads (B) in plasma. AAV-PCIN63 recipients in green and controls in yellow.

PLAIN LANGUAGE SUMMARY
A single injection of a viral vector succeeded in producing anti-HIV PCIN63 antibody, and this neutralizing antibody was able to reach mucosal tissues, resulting in a 67% level of protection against AIDS-virus infection in rhesus macaques.

- All four AAV-treated monkeys successfully expressed anti-HIV bNAb PCIN63 presenting serum levels that peaked at a range of 53 to 119 µg/ml between weeks 3-6 post-AAV (Figure 1A).
- Two of the four monkeys maintained persistently high antibody levels in serum (~20 µg/ml) for over 40 weeks (r21107, in yellow; rh2836, in green) (Figure 1A).
- AAV-expressed PCIN63 was successfully detected in all four monkeys and across all analyzed compartments (Figure 1), indicating that antibodies delivered via intramuscular AAV administration can reach mucosal tissues.
- Detectability was intermittent in rectal samples and antibody levels were substantially higher than those observed in saliva, but such levels were more sustained (Figures 1B and 1C).
- After ten challenges with the SHIV-AD8 (PBMC-derived stock) at the doses indicated (Table I), 75% (3/4) of the AAV recipient macaques remained uninfected while 75% (3/4) of the untreated controls were infected (Figure 2).
- Using the standard protective efficacy calculation based on attack-rates, AAV-delivered PCIN63 conferred 67% protection.

CONCLUSIONS

- Our study shows that intramuscularly administered and AAV-expressed PCIN63-IgG is able to reach mucosal sites and provides meaningful protection against repeated mucosal SHIV challenges.
- These results highlight the potential of the AAV-delivered antibody approach to confer long-term protection against HIV infection after a single administration of vector.

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