



the
collaboration
for AIDS vaccine discovery

Adenovirus vectors induce expansion of memory CD4 T cells with a mucosal homing phenotype that are readily susceptible to HIV-1 infection.

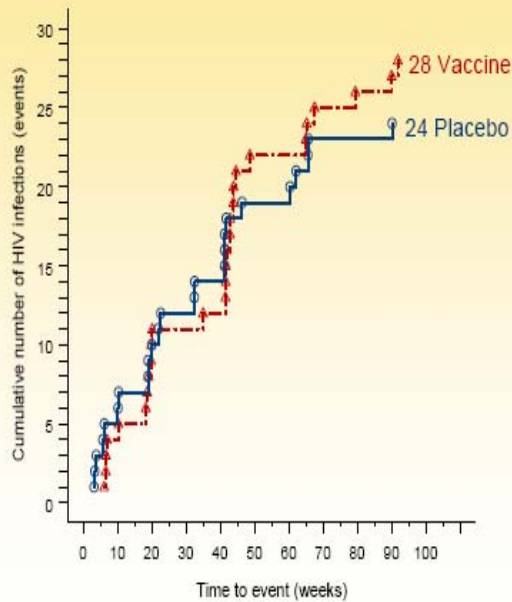
Adel Benlahrech
Imperial College London

Background

- Post hoc analysis of HIV STEP trial showed a possible increase in HIV-1 susceptibility in vaccinated individuals with pre-existing immunity to Ad5.

Background

Cumulative Number of HIV Infections:
MITT population (males), Ad5 \leq 200

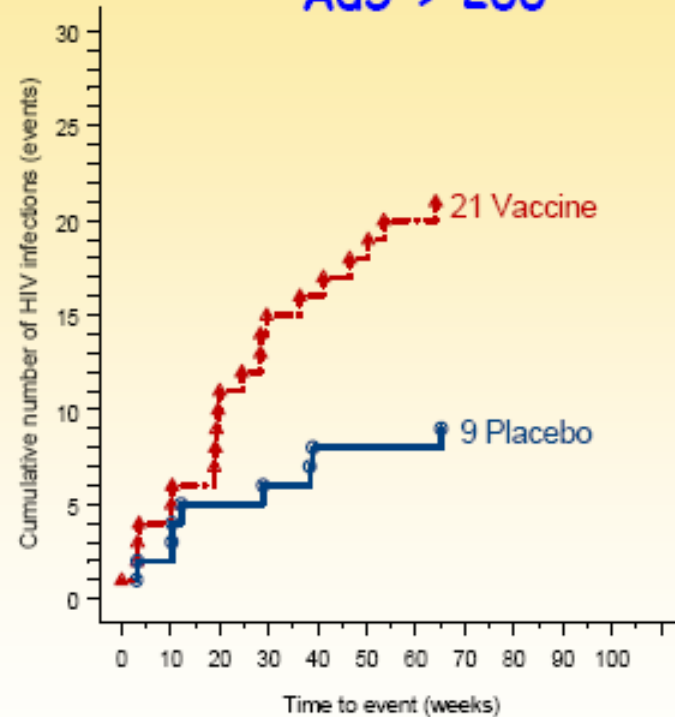


1-tailed p-value = 0.322 (for $VE_{INF} \neq 0$)
2-tailed p-value = 0.581 (for $VE_{INF} \neq 0$)

Cases accrued as of Oct 17, 2007

15
07-Nov-2007

Ad5 > 200



1-tailed p-value = 0.020 (for $VE_{INF} \neq 0$)
2-tailed p-value = 0.029 (for $VE_{INF} \neq 0$)

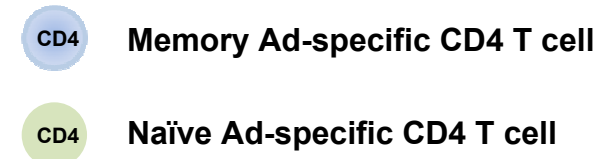
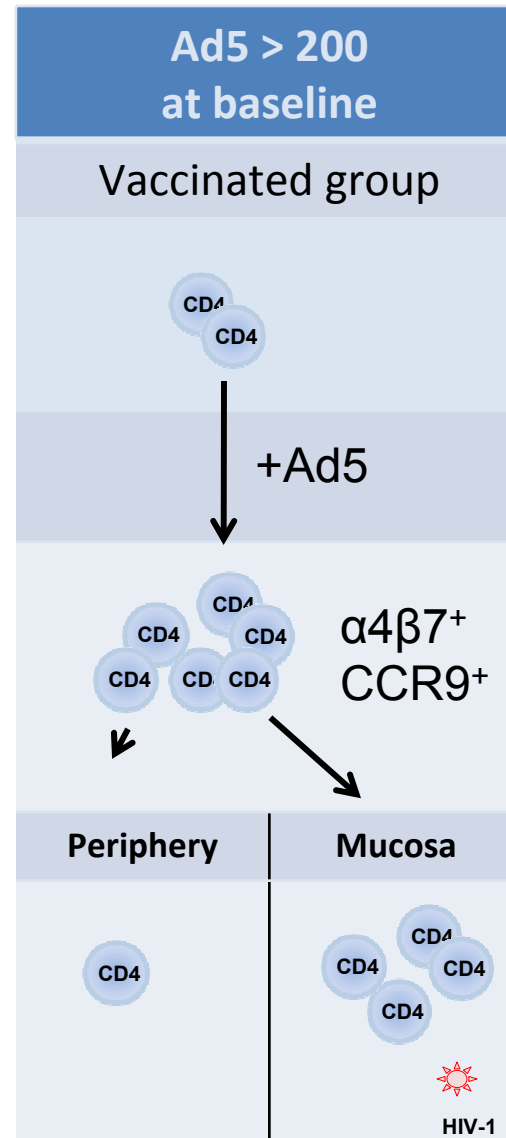
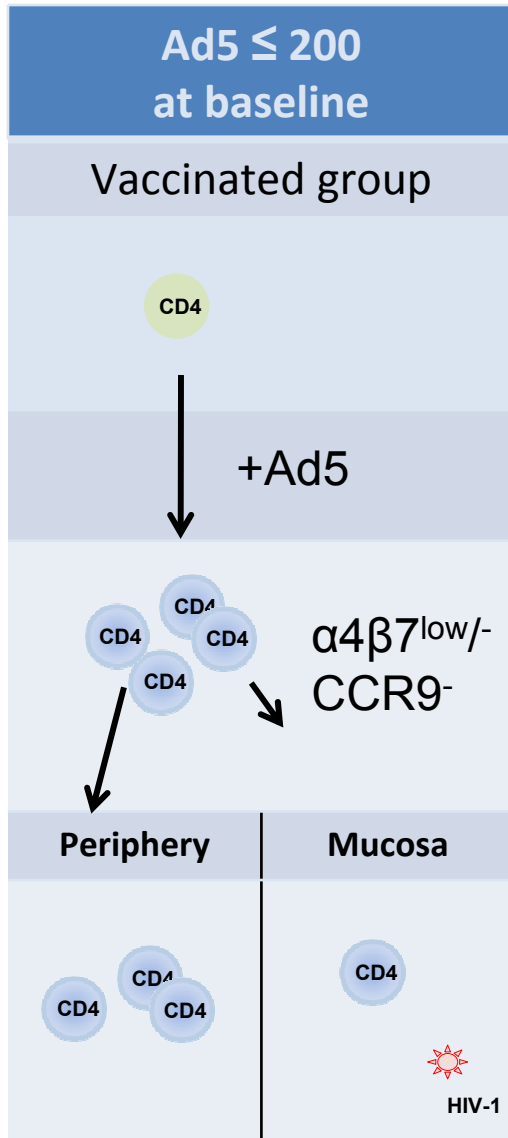
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Taken from <http://www.hvtn.org/fgm/1107slides/Robertsonfinal.pdf>

Background

- is T cell activation and migration to mucosal sites a possible cause?

Hypothesis



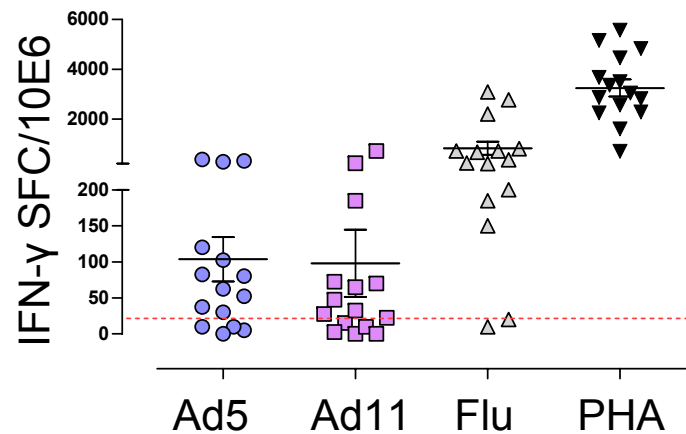
Aims

- investigate T cell responses against Ad5 and serologically distinct Ad11:
 - Cytokines (IFN- γ , IL-2, TNF- α)
 - Proliferation
 - Mucosal homing markers (α 4 β 7 and CCR9)
 - CCR5 expression and susceptibility to HIV-1 infection in vitro

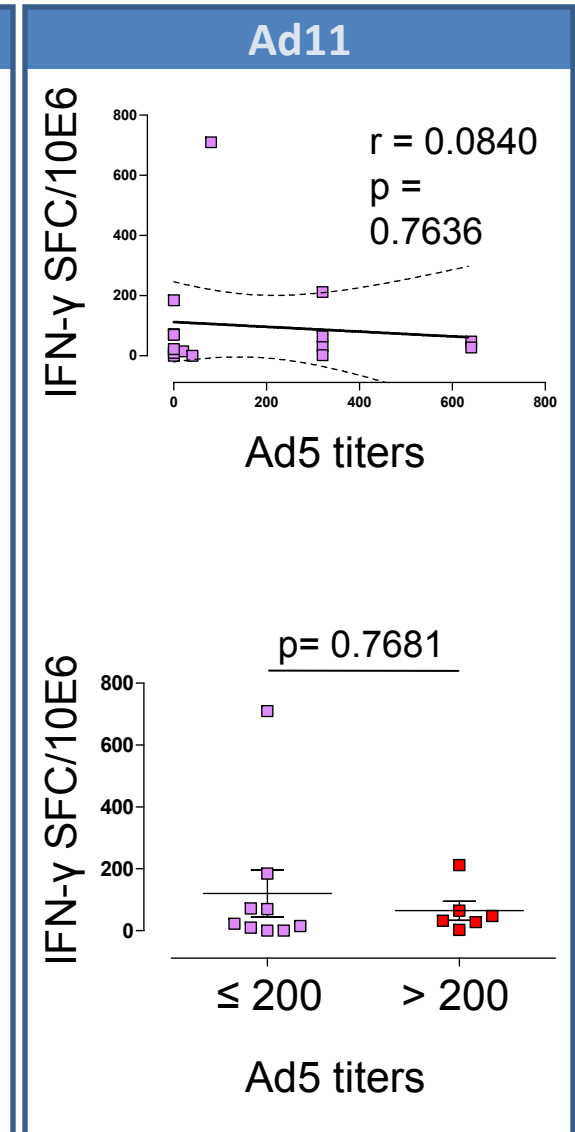
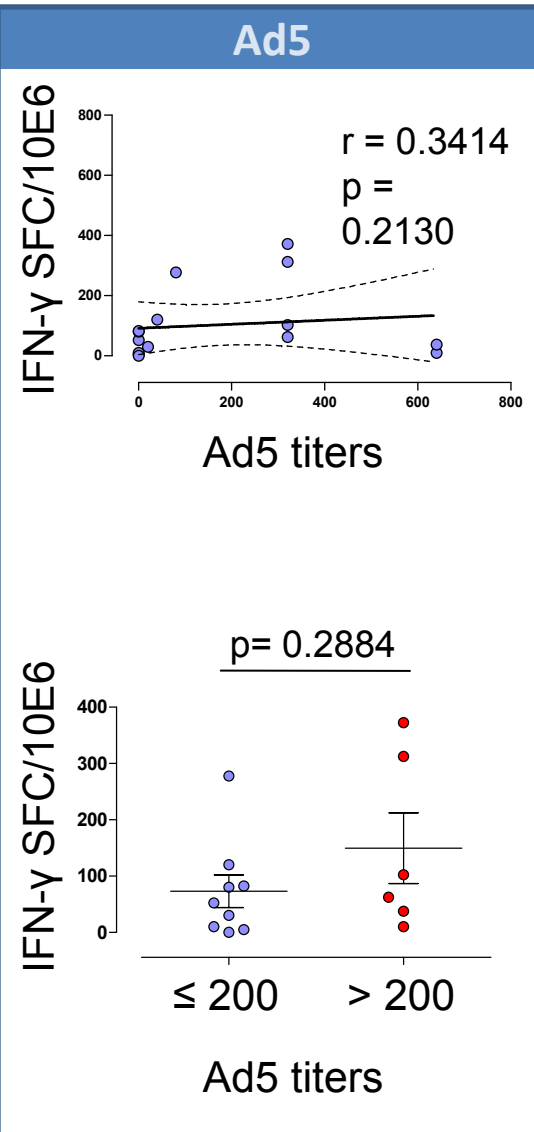
Study Design

- 20 healthy volunteers + 6 buffy coats
 - Ad5 Ab titers
 - Ad11 Ab titers
- Dendritic cells (DC) were generated from monocytes and pulsed with:
 - Ad5-CMV-eGFP (E1 and E3 deleted)
 - Ad11-CMV-eGFP (E1 and E3 deleted)
 - Tetanus toxoid (TT)
 - Heat-inactivated influenza (Flu)
 - Staphylococcus enterotoxin B (SEB)
 - Phytohaemagglutinin (PHA)
- DC were co-cultured with PBMC or lymphocytes
 - 24 hours (IFN- γ ELISPOT)
 - 24 hours (intracellular cytokine staining)
 - 5 days (CFSE proliferation)
 - 7-10 days (HIV-1 infection)

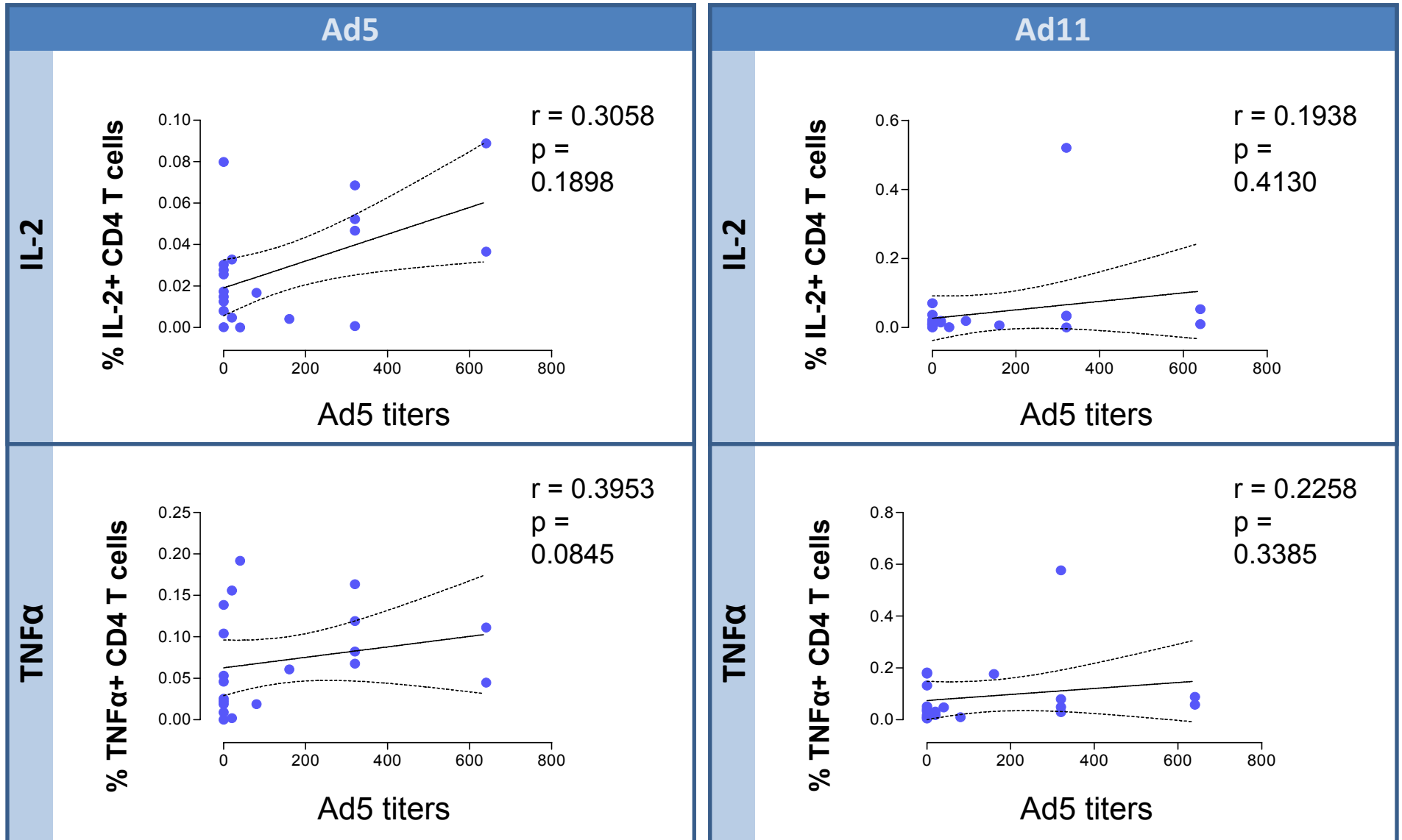
IFN- γ production in response to Ad5 or Ad11 does not correlate with Ad5 titers



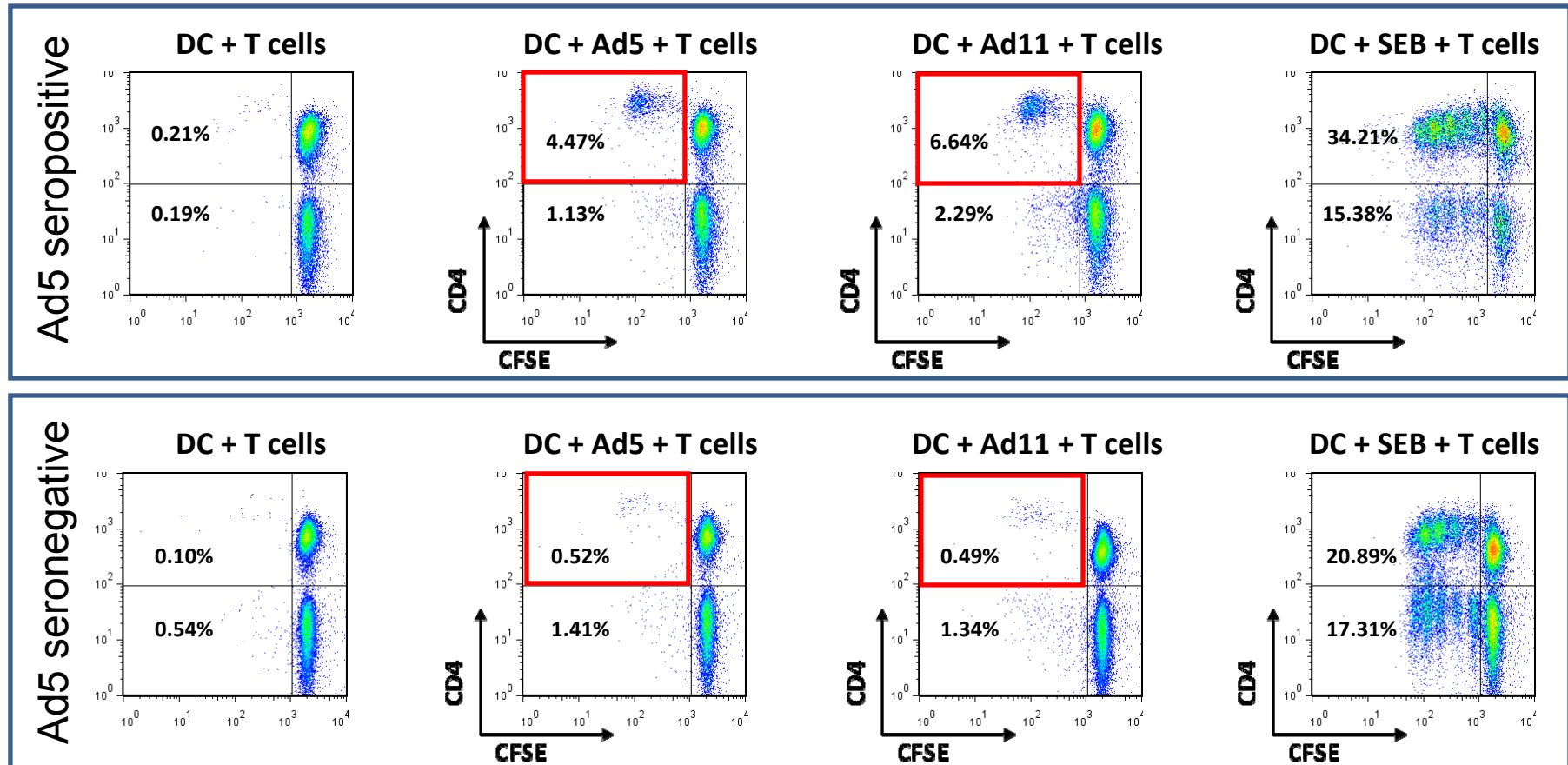
- 60% of individuals were Ad5 seropositive.
- 5% of individuals were Ad11 seropositive.
- 75 % of individuals responded to Ad5 or Ad11.



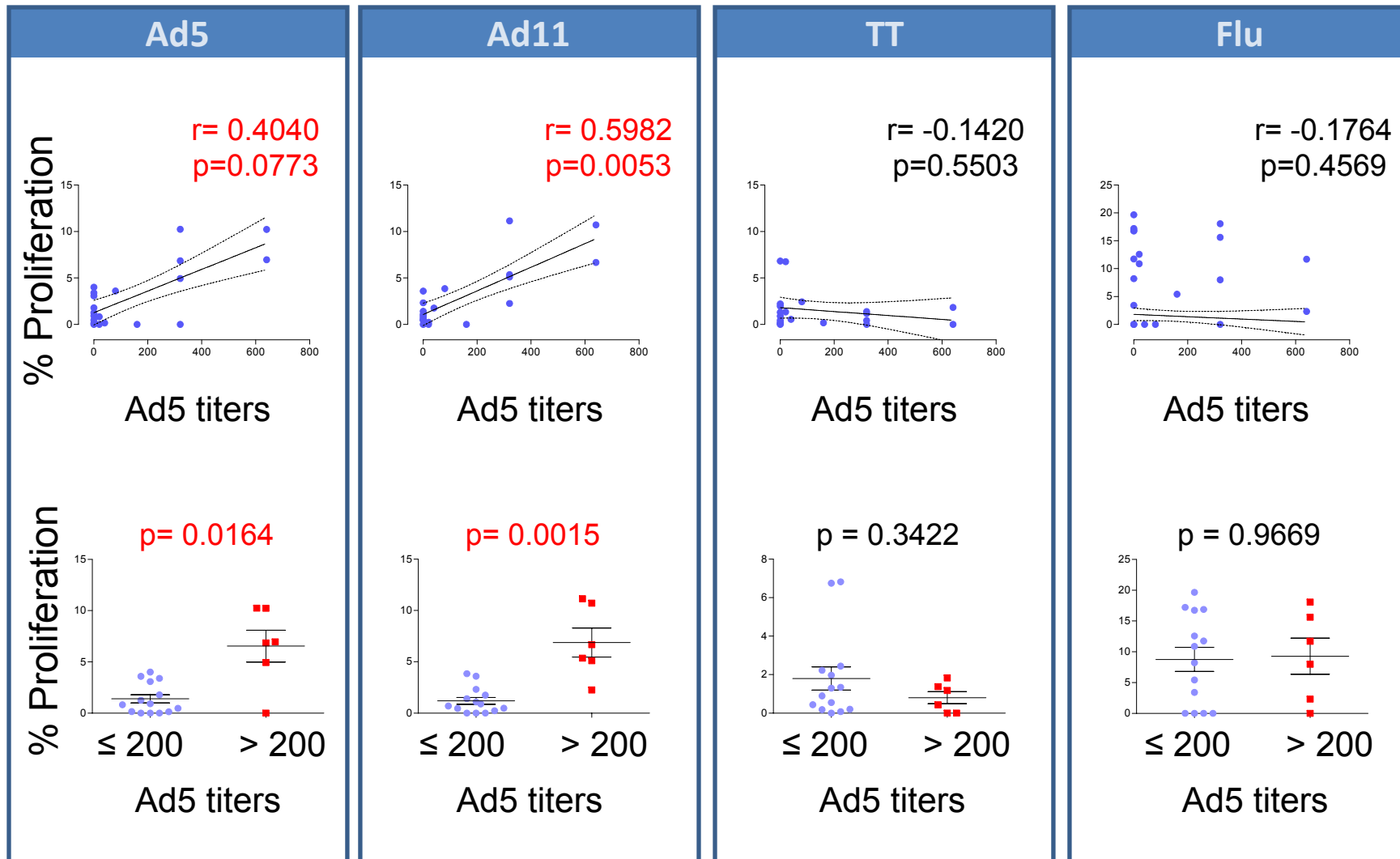
IL-2 and TNF α production in response to Ad5 or Ad11 does not correlate with Ad5 titers



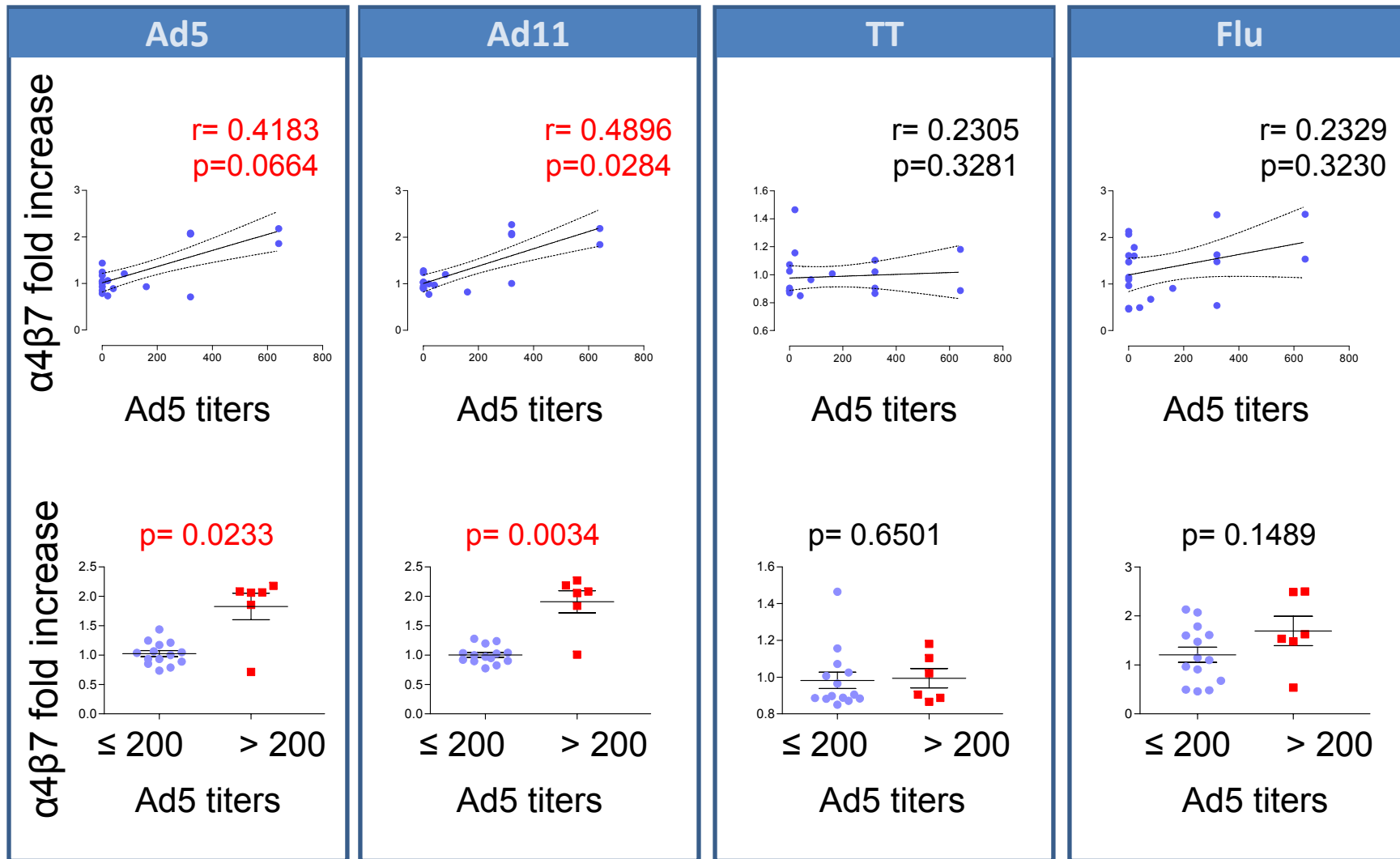
Ad5 and Ad11 induce proliferation of CD4 T cells



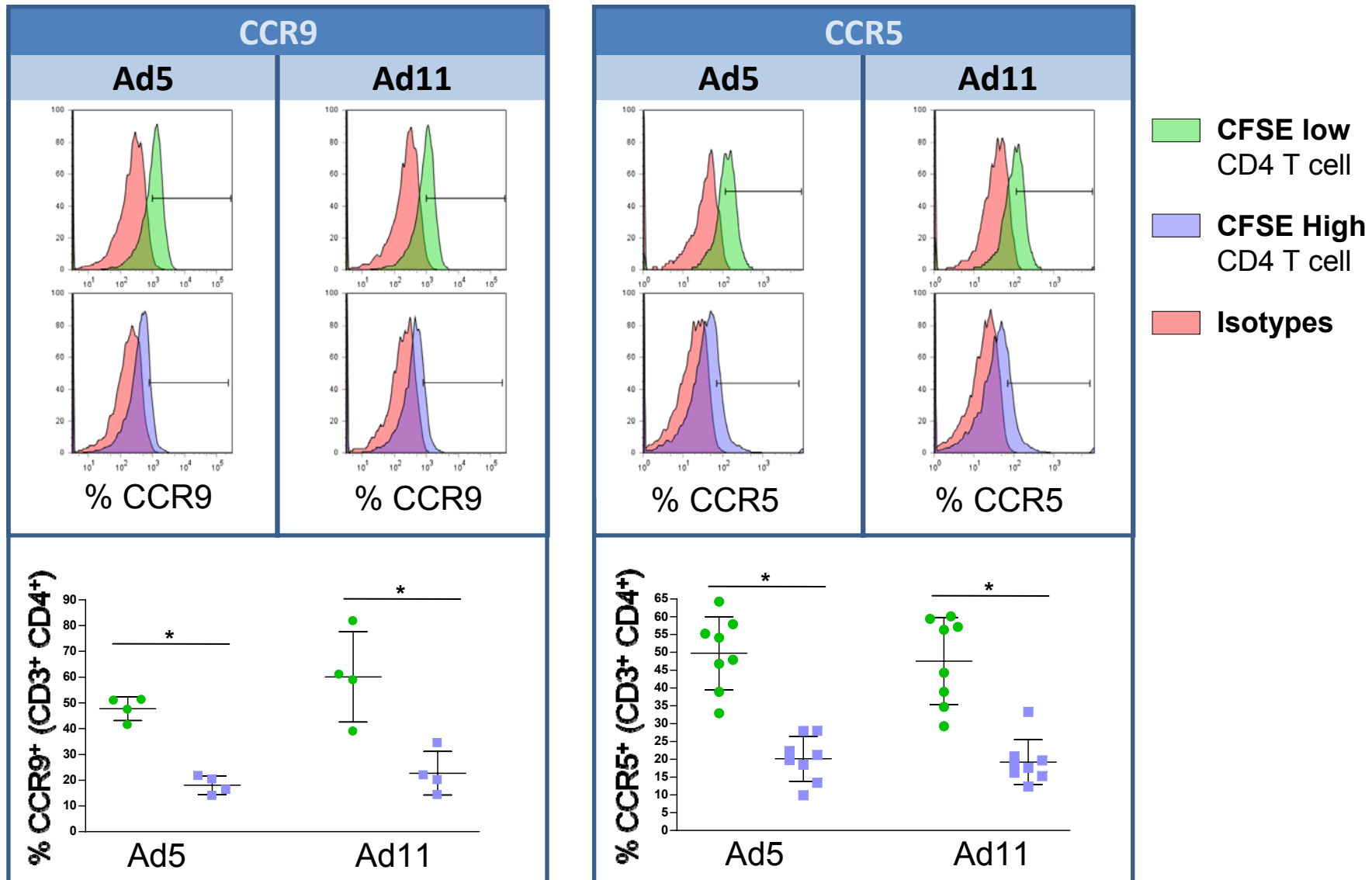
Adenoviruses induce proliferation of CD4 T cells in individuals with Ad5 titers >200



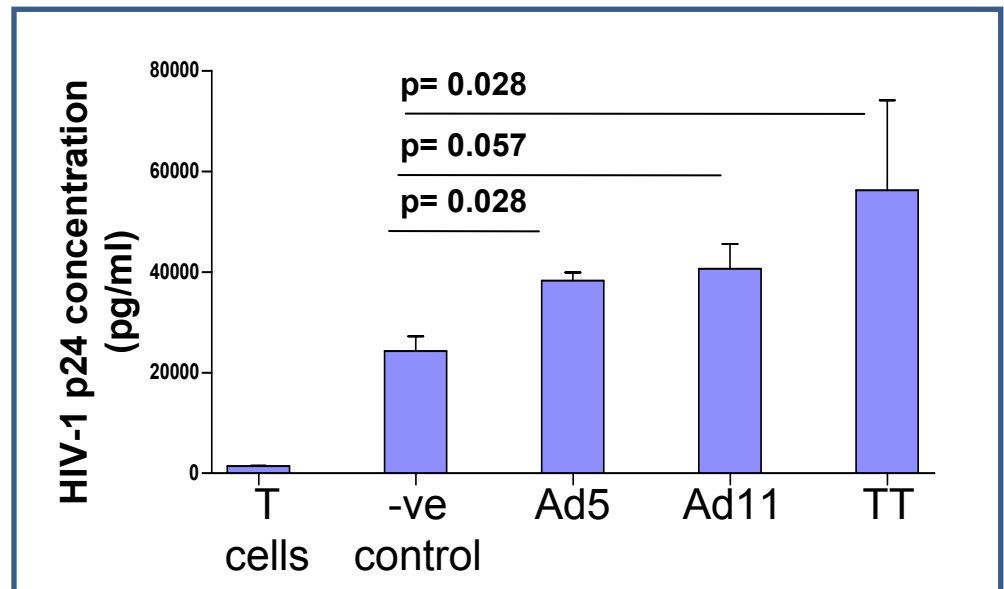
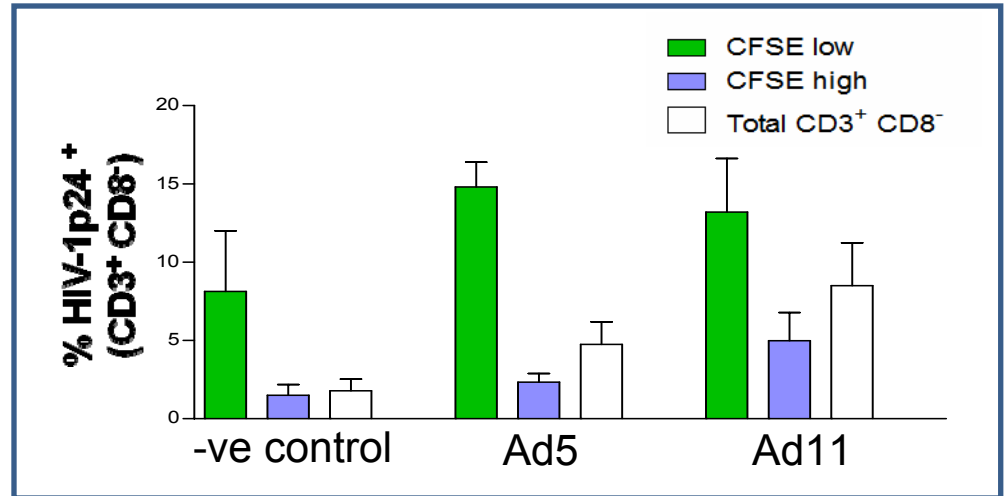
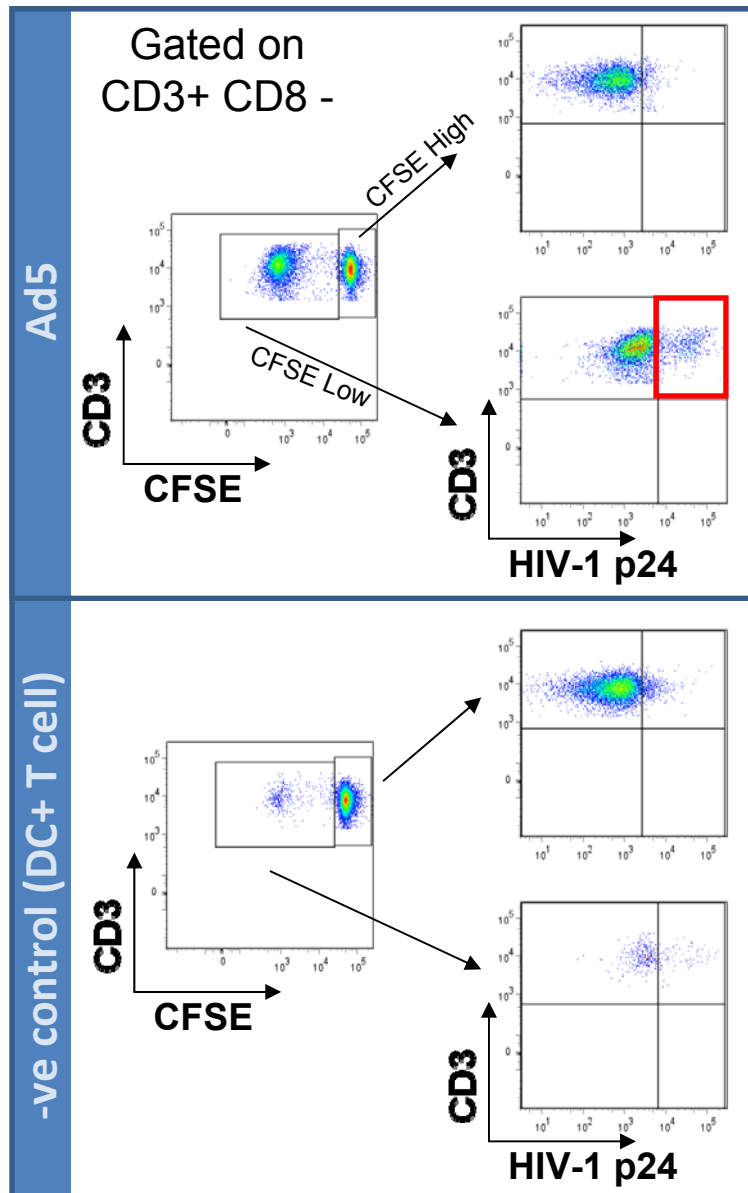
Adenoviruses induce proliferation of $\alpha 4\beta 7^+$ CD4 T cells in individuals with Ad5 titers >200



Activated Ad5 and Ad11 specific CD4 T cells express high levels of CCR9 and CCR5



HIV-1bal infects activated Ad-specific CD4 T cells



Conclusions

- Total IFN- γ , IL-2, or TNF α production in response to Ad5 or Ad11 does not correlate with Ad5 titers.
- Ad5 and Ad11 induce CD4 T cell proliferation in individuals with pre-existing Ad5 immunity.
- Ad5 and Ad11-specific CD4 T cells express high levels of α 4 β 7 and CCR9, indicating a mucosal homing potential.
- Activated Ad5 and Ad11 CD4 T cells express elevated levels of CCR5 and are susceptible to HIV-1 infection in vitro.



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Imperial College London

Steve Patterson
Andrea Meiser
Timos Papagatsias
Karen Logan
Romina Barbagallo
Frances Gotch



Linda Klavinskis
Veronique Bachy
Shan Herath



George Dickson
Julian Harris
Takis Athanasopoulos

BILL & MELINDA
GATES foundation

