



**Reduced Immunogenicity but
Enhanced Control of SIV
Challenge by a DNA/MVA Vaccine
in the Presence of Preexisting
Immunity to Vaccinia**

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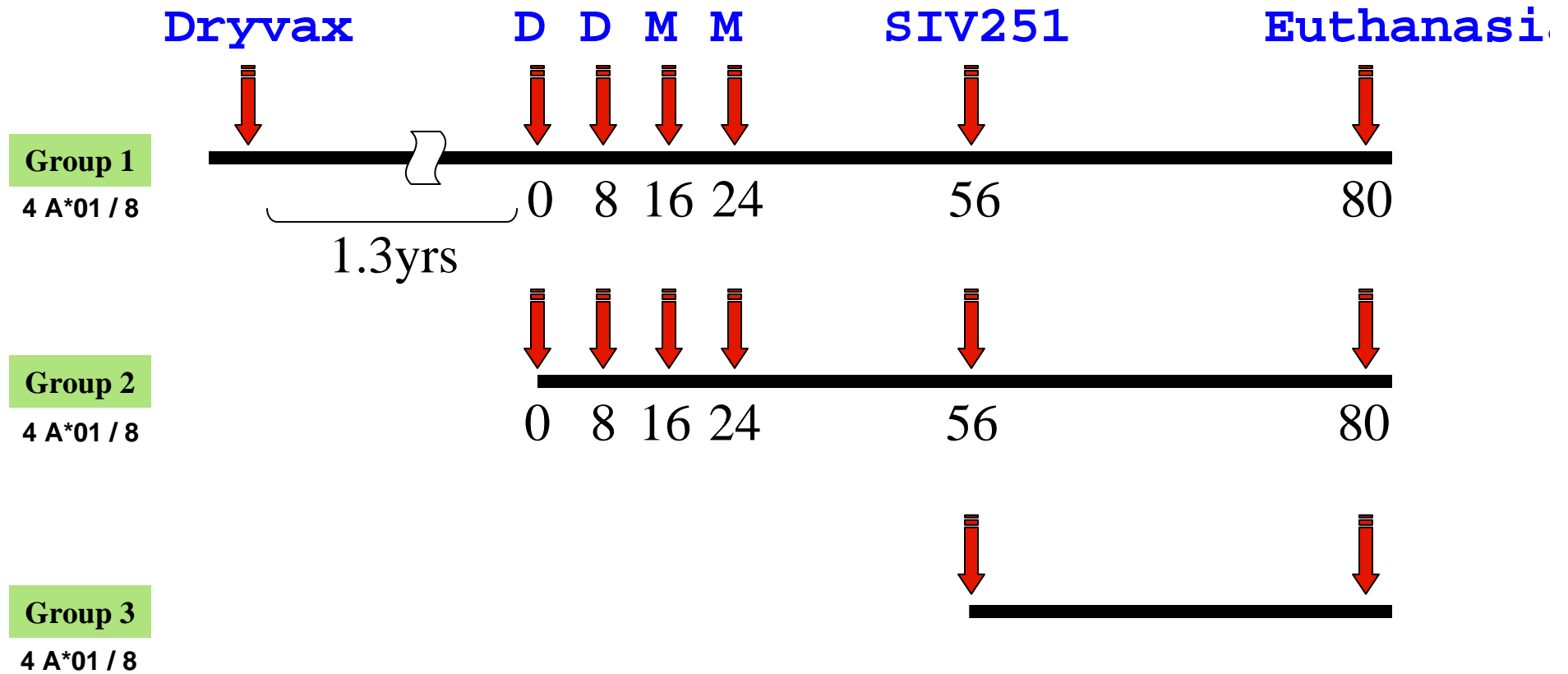
Background

- We demonstrated that a SHIV vaccine consisting of DNA prime and rMVA boost can control a pathogenic SHIV challenge in macaques
- Our DNA/MVA HIV vaccine is showing good immunogenicity in humans in HVTN 065
- Because of the similarities between vaccinia and MVA, preexisting immunity to vaccinia (vaccination for smallpox) may hinder the immunogenicity of DNA/MVA vaccines

Objective

How pre-existing immunity to vaccinia affects the immunogenicity and efficacy of DNA/MVA SIV vaccines in macaques?

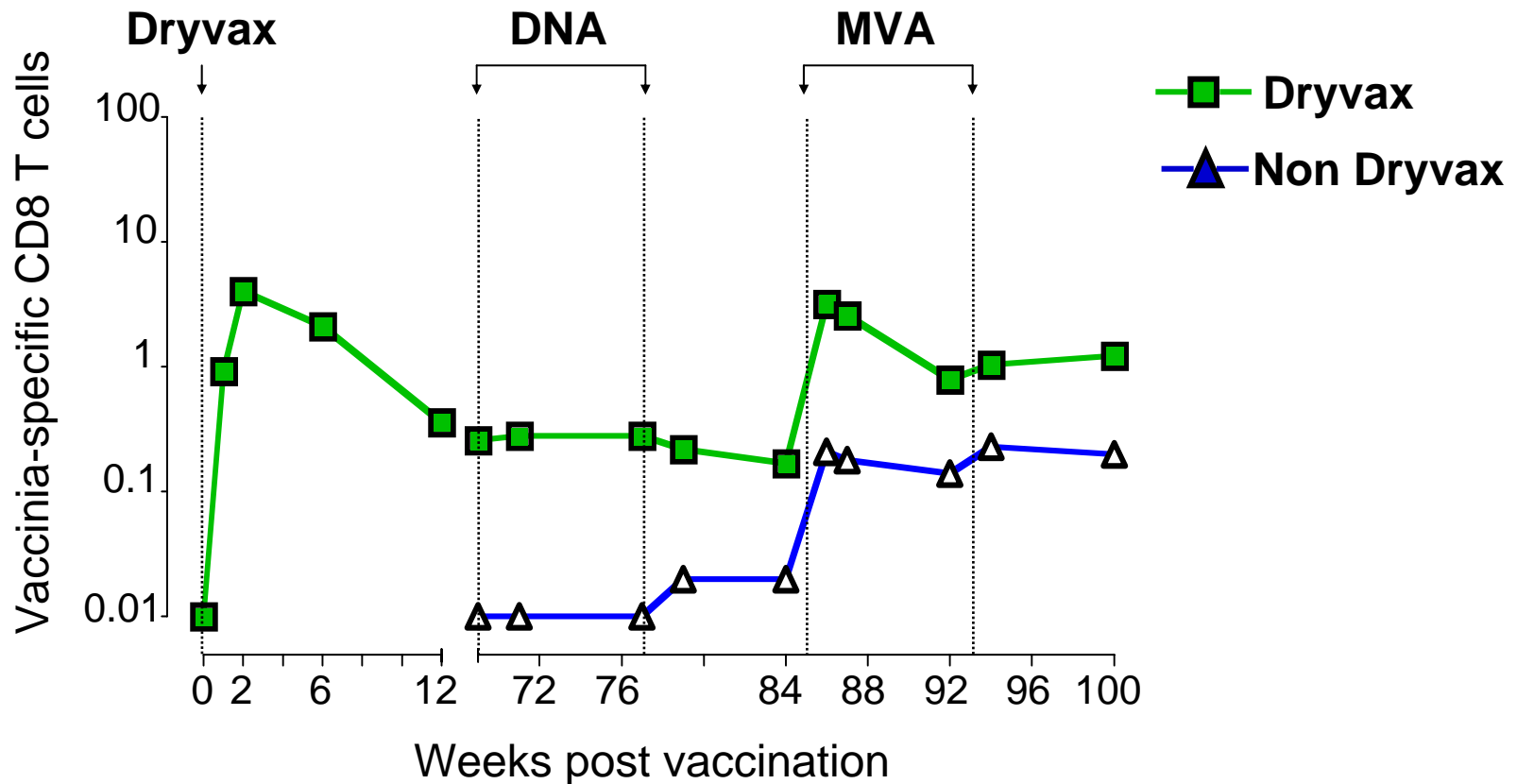
Study Design



Dryvax : about 10^5 pfu given percutaneously
DNA : SIV Gag-Pol-Tat-Rev-Env (1.2mg); I.M
rMVA : SIV Gag-Pol-Env (10^8 pfu); I.M
SIV mac251 : I.R challenge

**Vector (vaccinia)-specific
response**

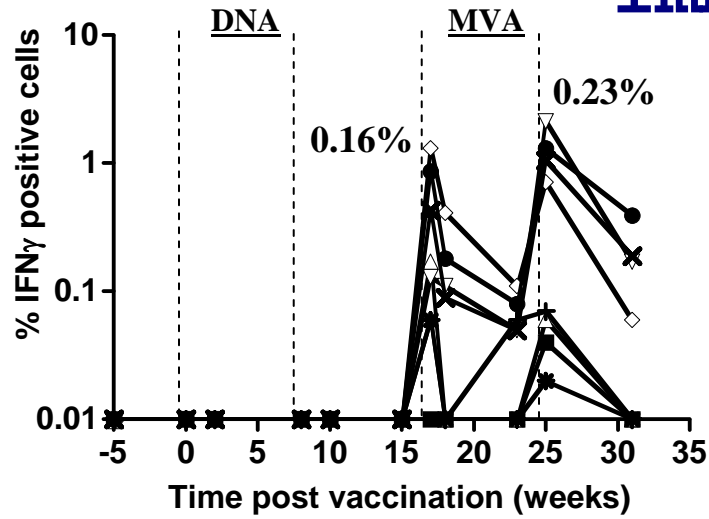
Higher magnitude of vaccinia-specific CD8 cells in the presence of pre-existing immunity - Geomean



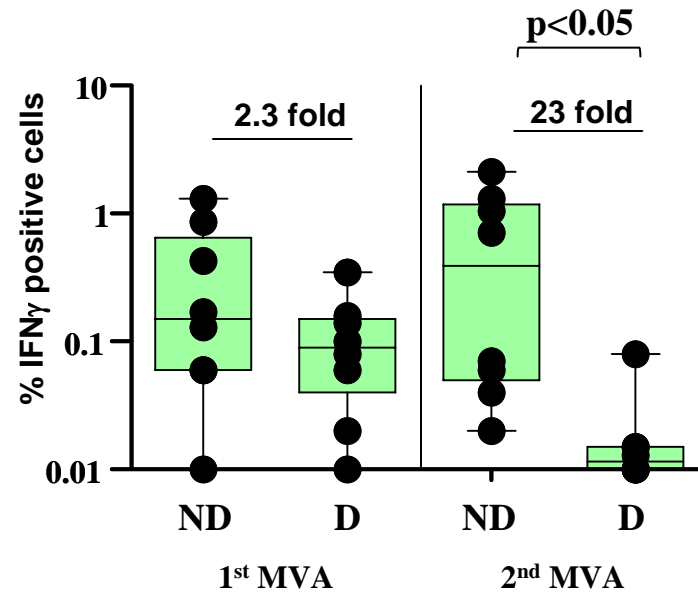
**Insert (SIV)-specific response
following DNA/MVA vaccination**

LOWER TIBETAN SPECIFIC CD8 RESPONSE
(SIV)
in the presence of pre-existing
immunity

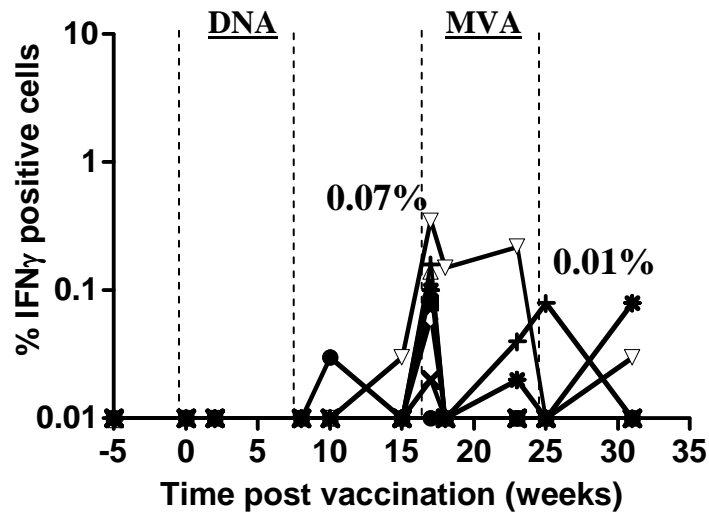
Non Dryvax



CD8 T cells

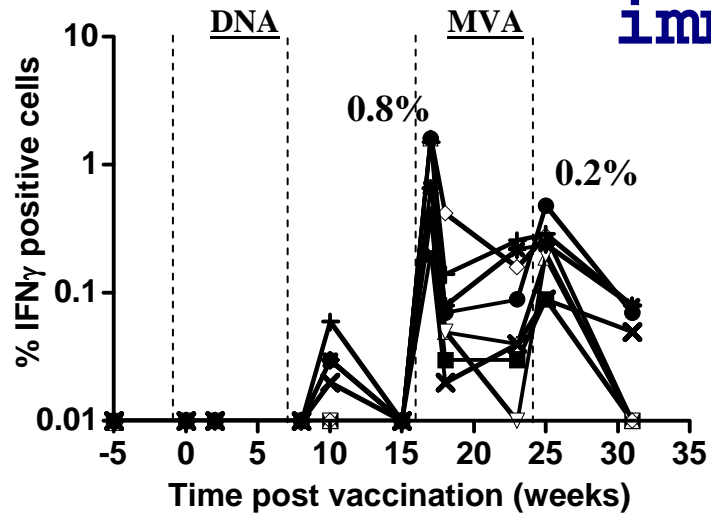


Dryvax

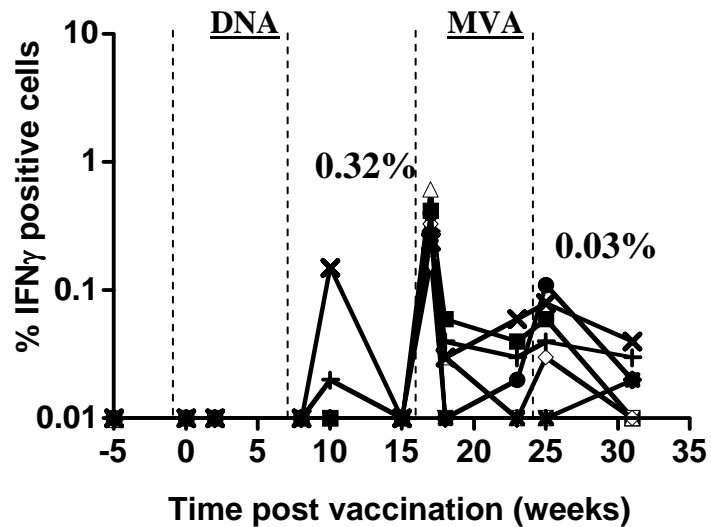


LOWER magnitude of HIV SPECIFIC CD4
response
in the presence of pre-existing
immunity

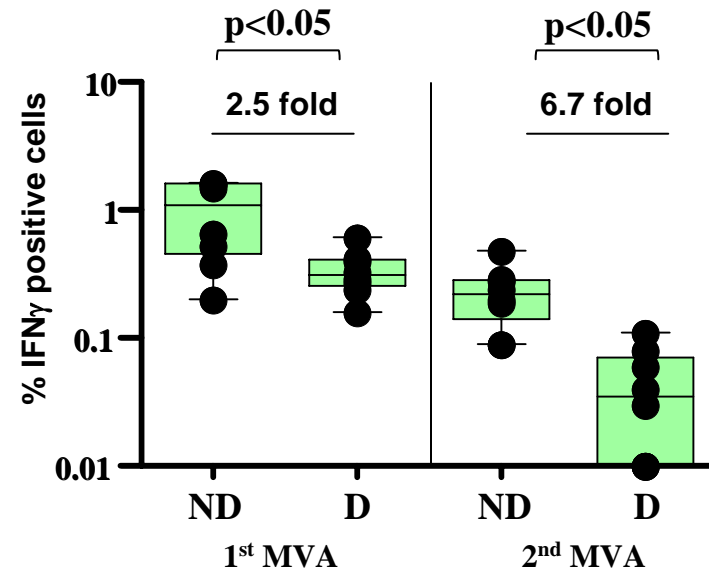
Non Dryvax



Dryvax



CD4 T cells

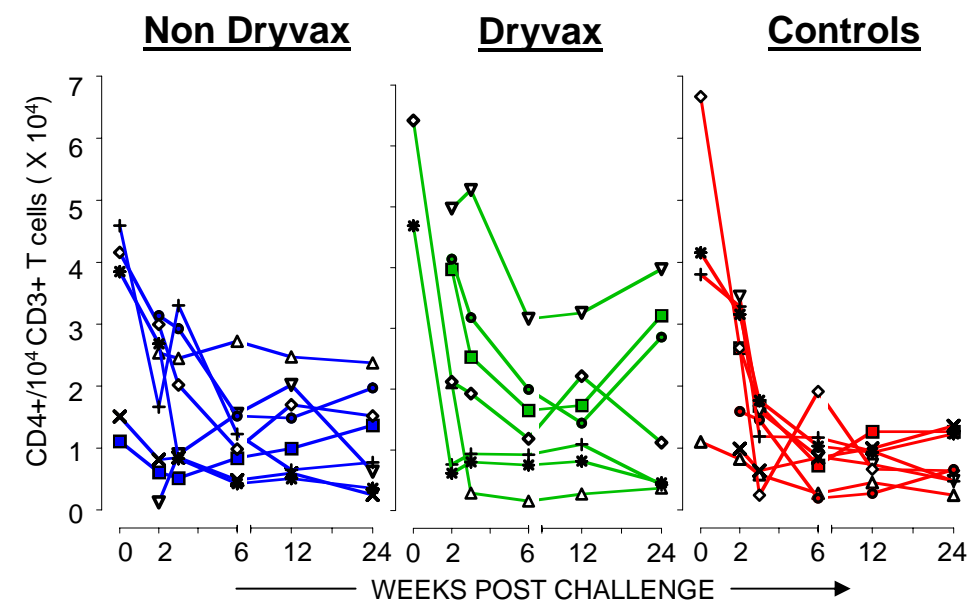
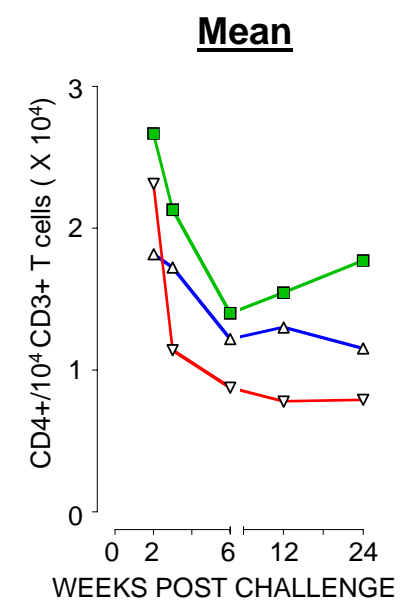
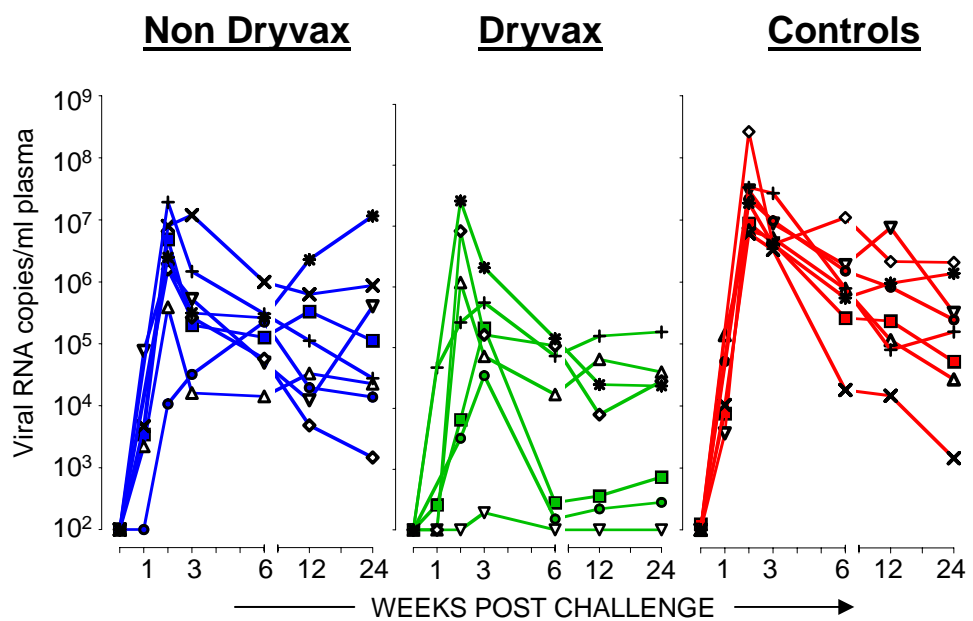
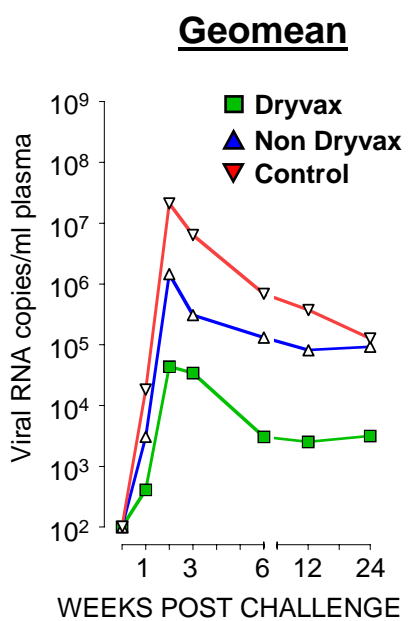


Conclusions for post vaccine immunity

- **Dryvax compared to non-Dryvax**
 - 10 fold higher levels of vaccinia (vector)-specific immunity
 - 6-20 fold lower levels of SIV (insert)-specific immunity

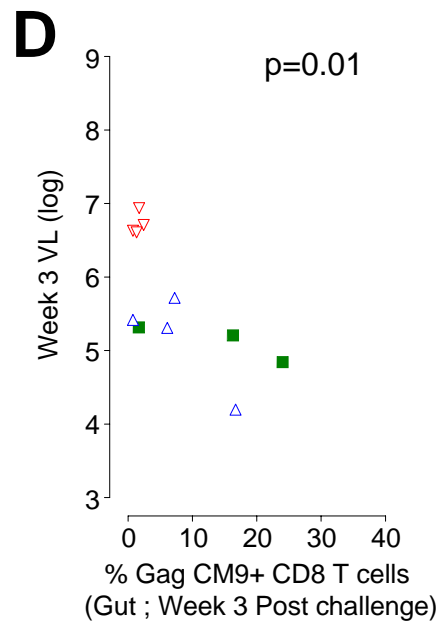
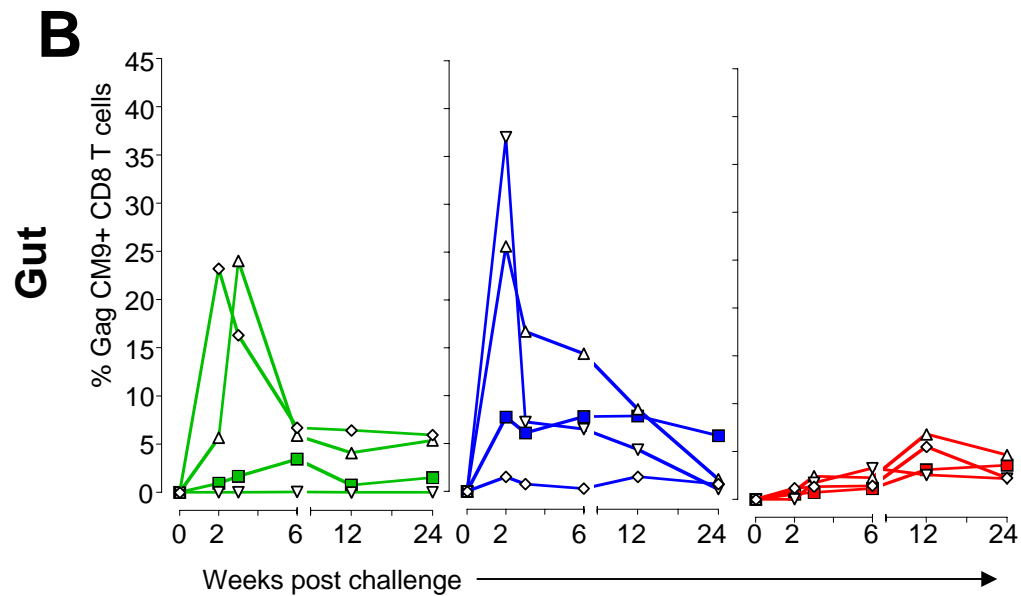
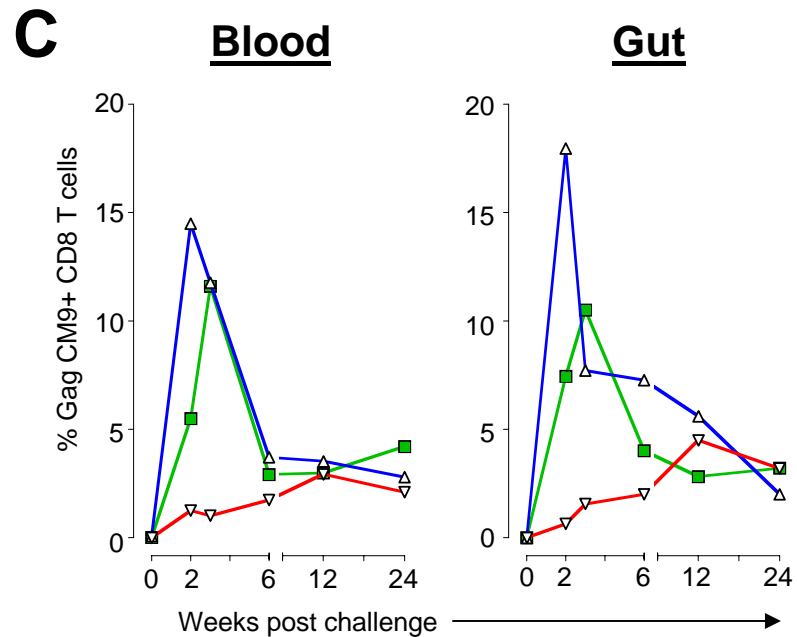
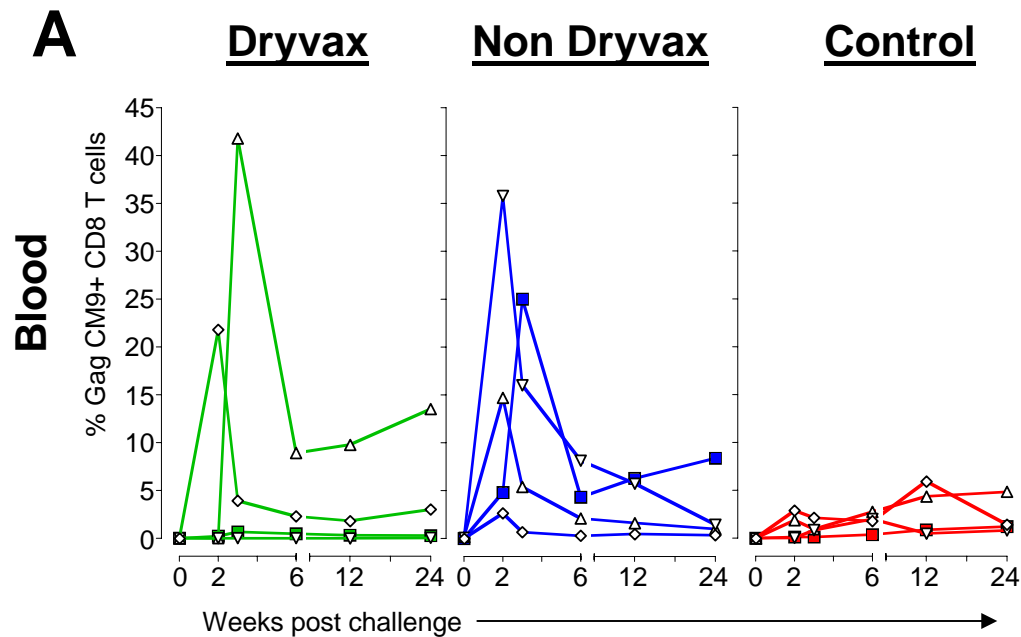
**Efficacy post SIVmac251
challenge**

Blood Viral load



Gut Total CD4

**SIV-specific CD8 T cells
post SIVmac251 challenge**



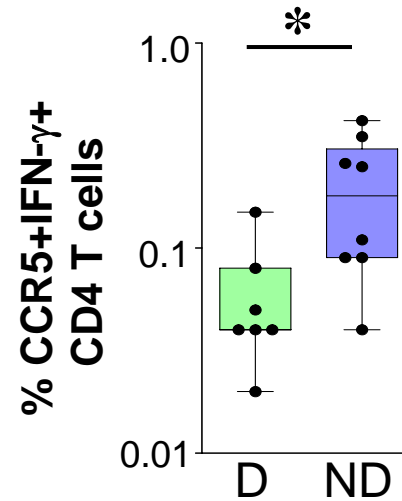
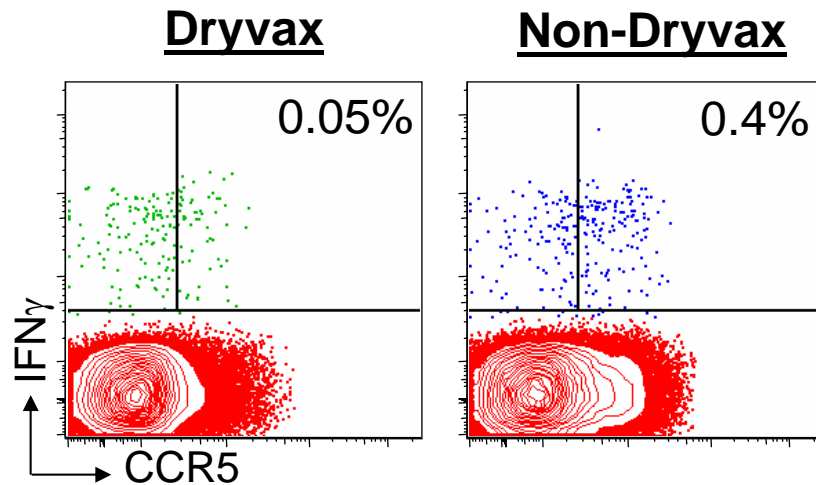
Conclusions for post challenge

- **Dryvax compared to non-Dryvax**
 - Similar levels of SIV-specific immunity
 - Enhanced control of SIV challenge

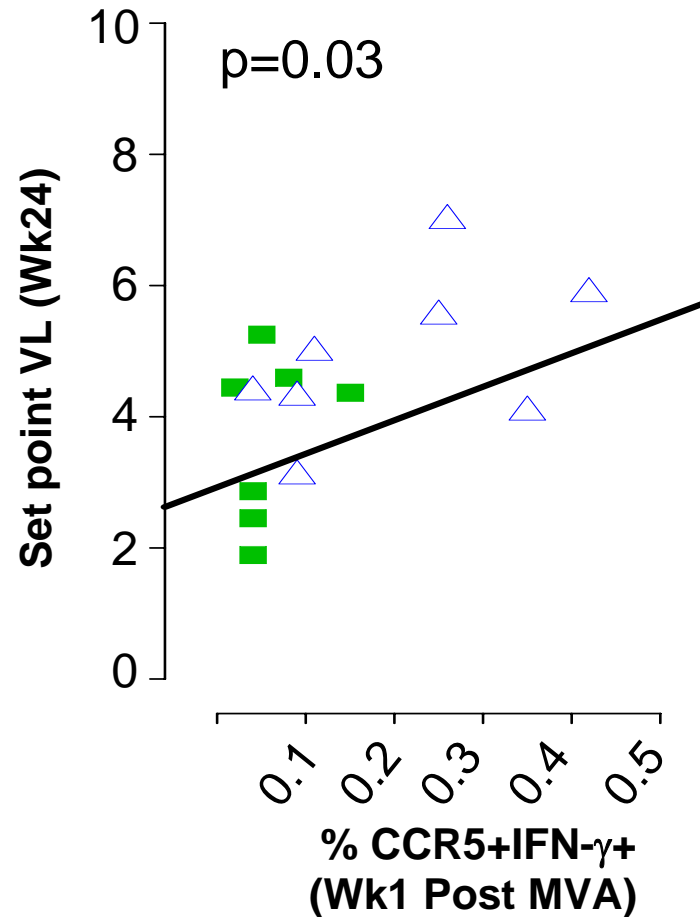
Quality of SIV-specific CD4 and CD8 T cells at 1 week post 1st MVA boost

- CD4 T cells
 - CCR5 expression (target cells for virus)
- CD8 T cells
 - Proliferative capacity in vitro
 - Central memory phenotype (CD28+CCR7+)

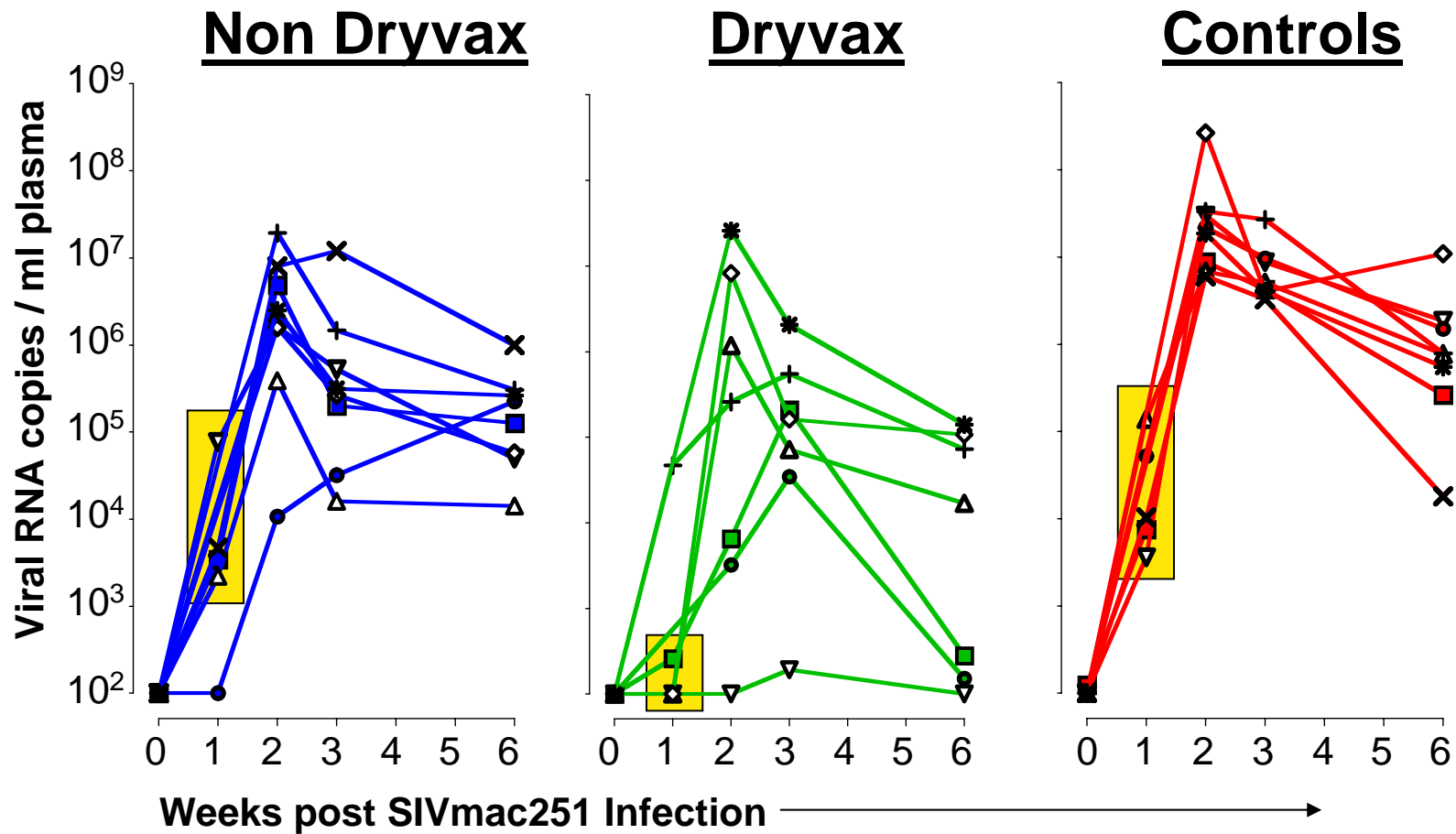
Lower levels of CCR5 positive SIV-specific CD4 T cells post vaccination in Dryvax



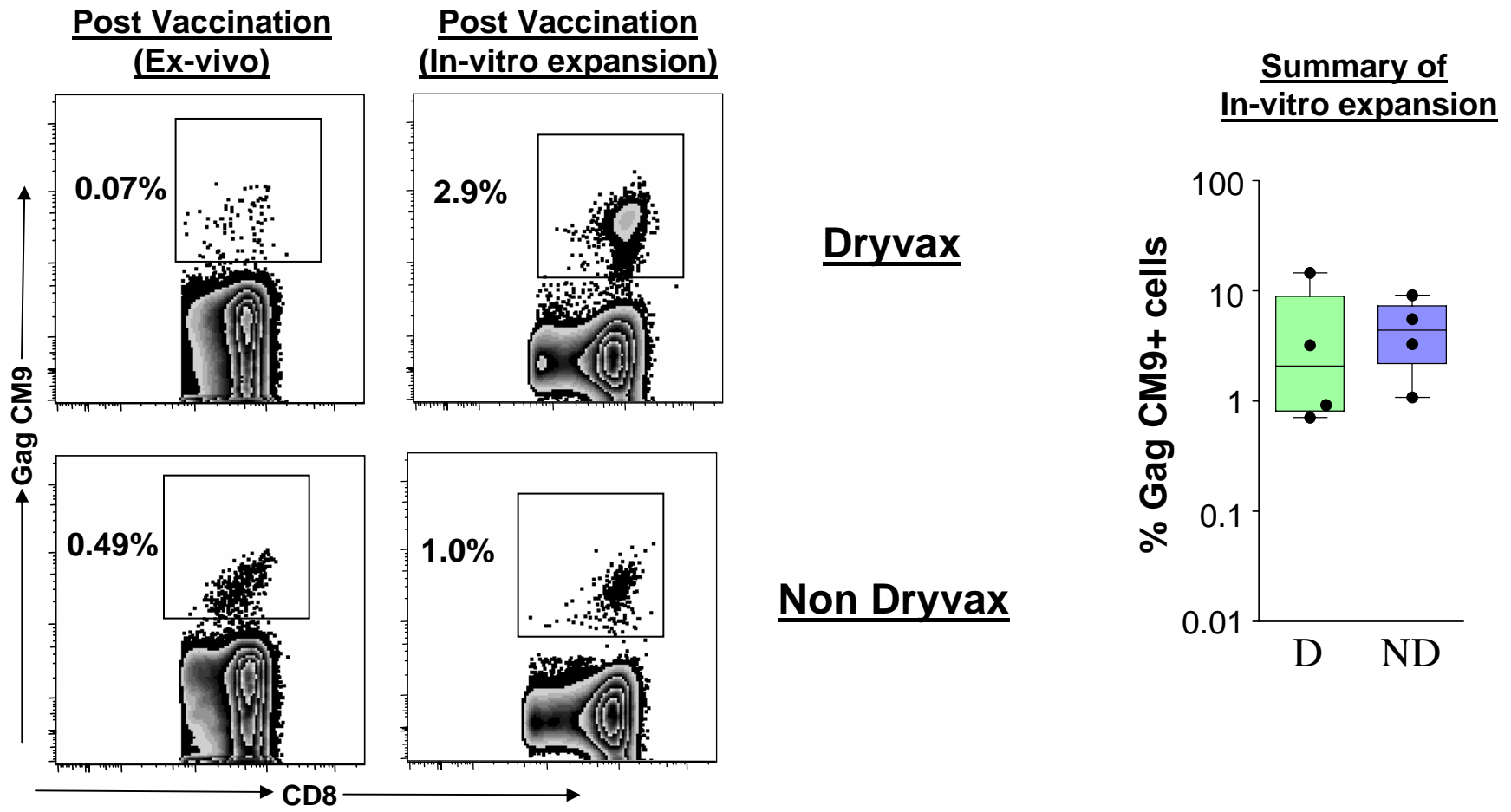
**Inverse Correlation between levels of CCR5
positive SIV-specific CD4 T cells post
vaccination and
set point viremia post challenge**



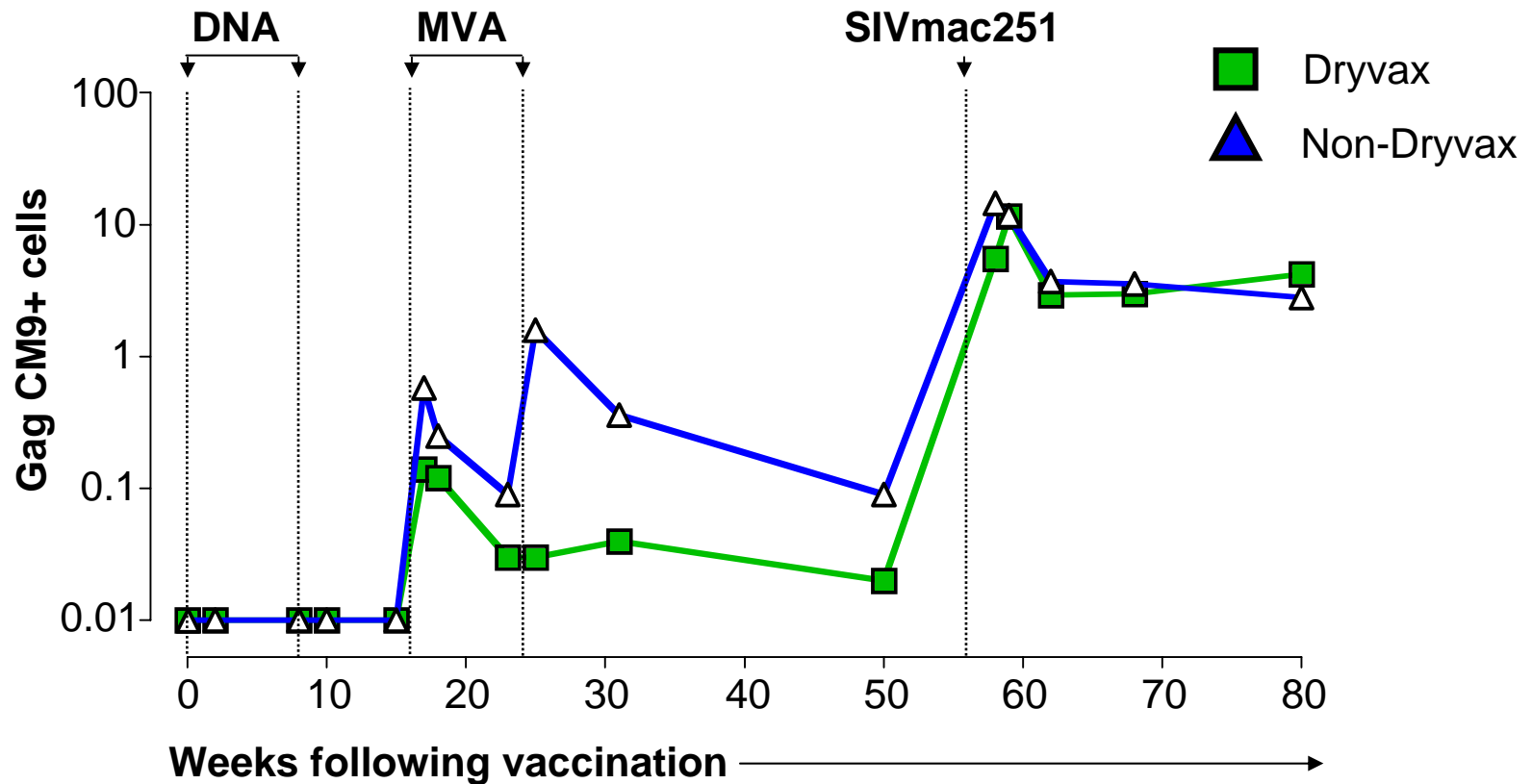
Delayed expansion of viremia in Dryvax group post SIV251 challenge challenge



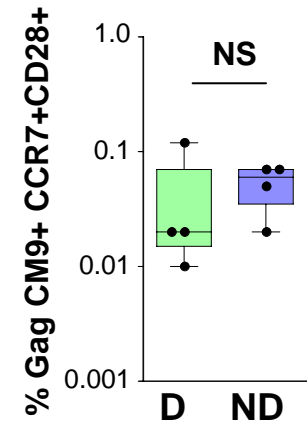
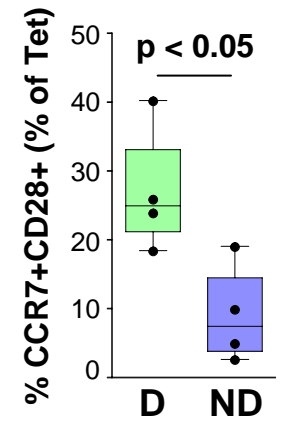
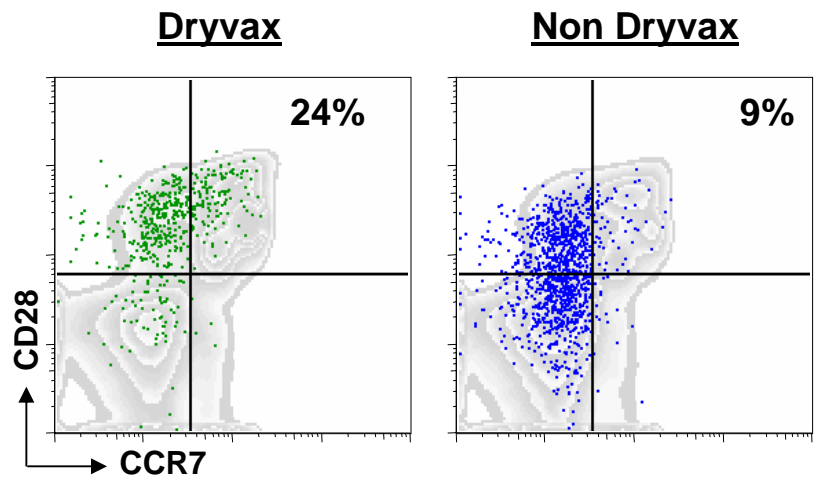
Better expansion of SIV-specific CD8 T cells in vitro in Dryvax group



Similar levels of SIV-specific CD8
T cells
in blood post challenge - Geomean



Higher proportion but similar levels of CCR7 positive SIV-specific CD8 T cells at Wk1 post MVA in Dryvax



Conclusions for the study

- **Preexisting immunity to the vector**
 - reduced the magnitude of insert-specific immunity
 - influenced the quality of insert-specific immunity

CD4 T cells

- Lower levels of IFN- γ positive cells
- Lower levels of CCR5 positive cells (fewer target cells)

CD8 T cells

- Lower levels of IFN- γ positive cells
- Similar levels of CCR7 positive cells (proliferative capacity)

Hypothesis

Pre-existing immunity to the vector may result in rapid clearance of the vaccine vector



Shorter duration of antigen exposure to insert-specific T cells



Elicitation of
higher proportion (similar number) of T cells that
co-expresses CCR7
and Lower number of T cells that co-express CCR5

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Similar levels of CCR7 positive SIV-specific CD4 T cells post vaccination

