

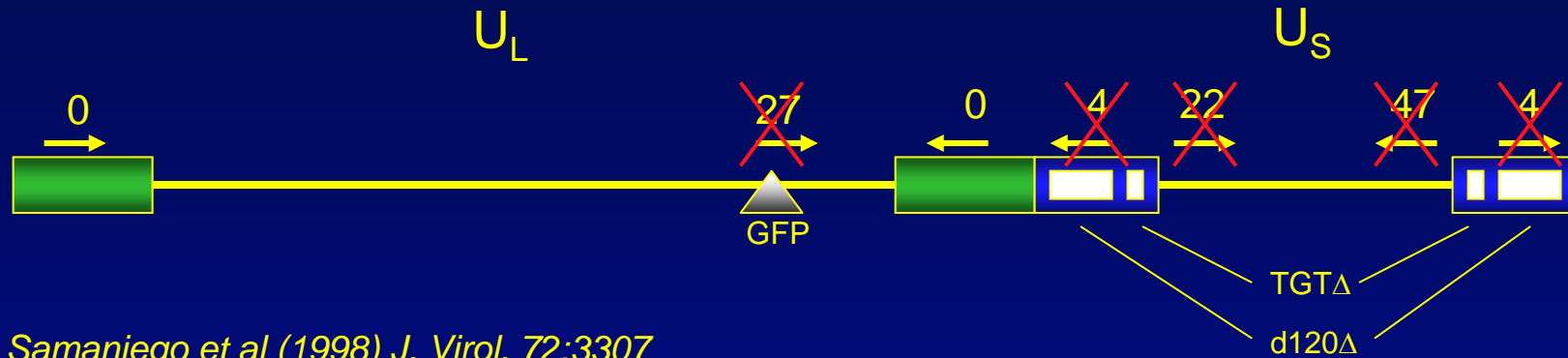
**Immunogenicity of different prime-boost
regimens using recombinant DNA and
replication-defective herpes simplex virus
(HSV)d106 vectors**

**Kenneth Chan PhD
New England Primate Research Center
August 22nd, 2007.**

Rationale for HSV recombinants as vaccine vectors

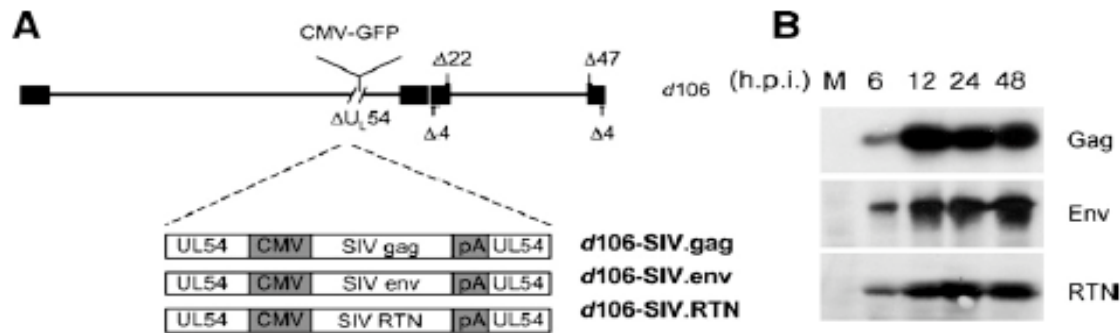
- PERSISTENT infection with potential to induce strong, durable immunity
- SAFETY with replication-defective vectors
- High levels of foreign gene expression in the absence of viral replication with replication-defective vectors
- Broad tropism
- Mucosal route of immunization

HSV-1 KOS $d106$ mutant



Samaniego et al (1998) J. Virol. 72:3307

D. Watanabe et al. / Virology 357 (2007) 186–198



ELSEVIER

Virology 357 (2007) 199–214

www.elsevier.com/locate/yviro

Ability of herpes simplex virus vectors to boost immune responses to DNA vectors and to protect against challenge by simian immunodeficiency virus

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Goals - CURRENT STUDY

- To determine the relative immunogenicity of different prime-boost vaccine regimens using recombinant HSV and DNA vectors
- To determine protective efficacy against intra-rectal SIVmac239 challenge

DNA vectors

- CATE SIV239gag
- MCP3 SIV239gag
- SIV239env
- MCP3 SIV239env
- SIV239rev-tat-nef fusion
- CATE SIV239rev-tat-nef fusion

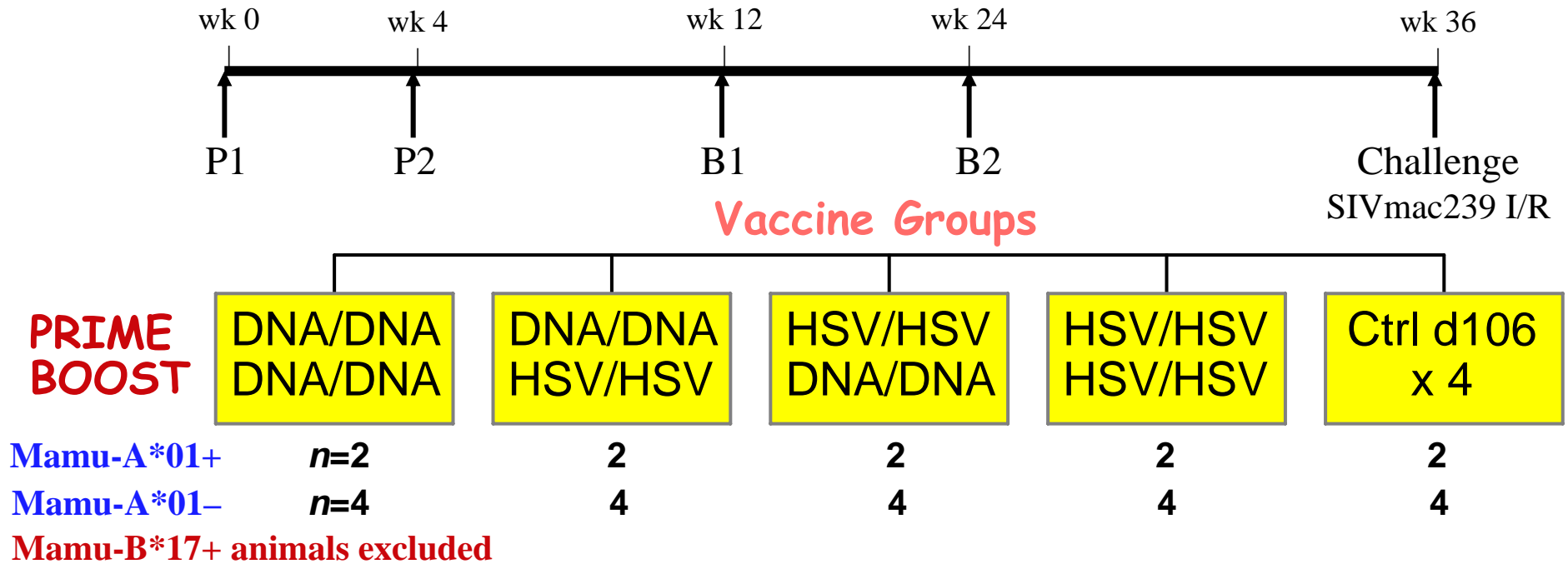
1 mg IM / plasmid / inoculation

d106-HSV vectors

- SIV d106-gag
- SIV d106-env
- SIV d106-rev-tat-nef
- HSV-1 d106 ctrl vector

~5-7 x 10⁸ pfu IM / vector / inoculation

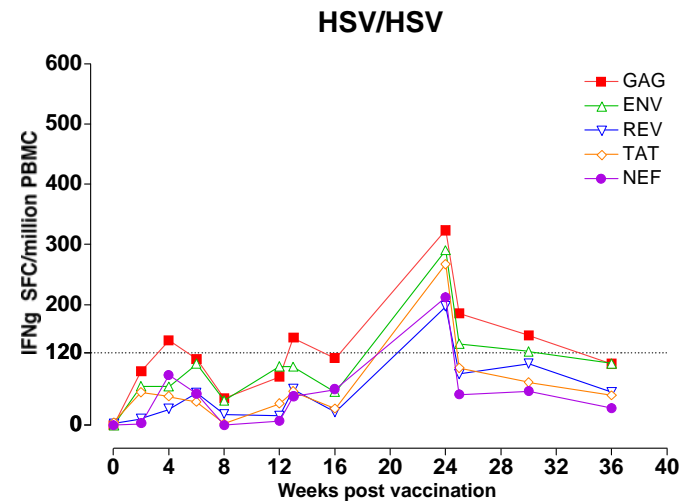
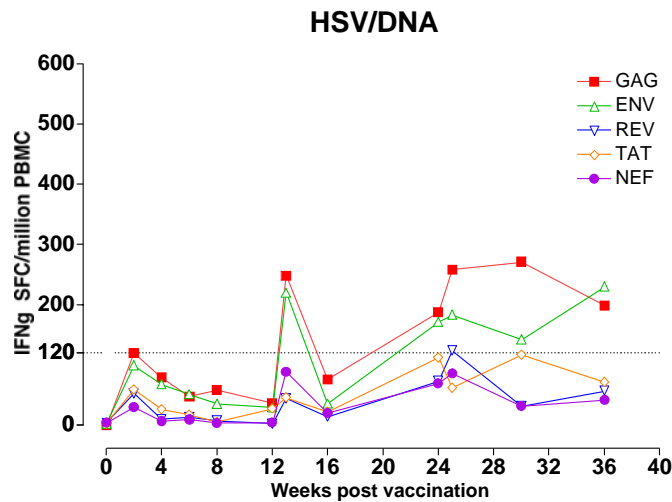
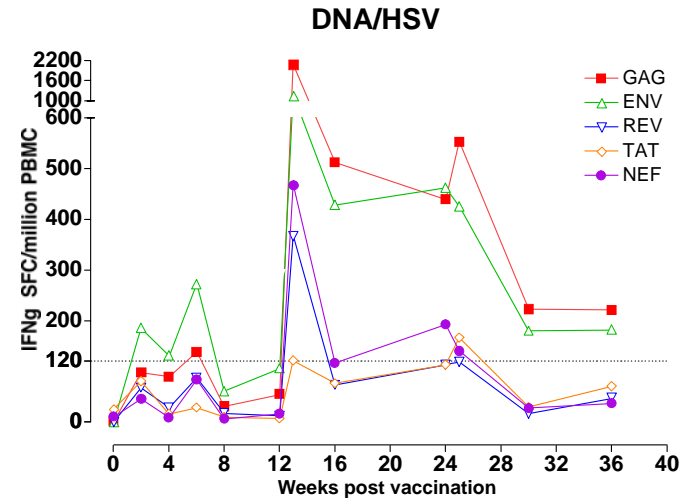
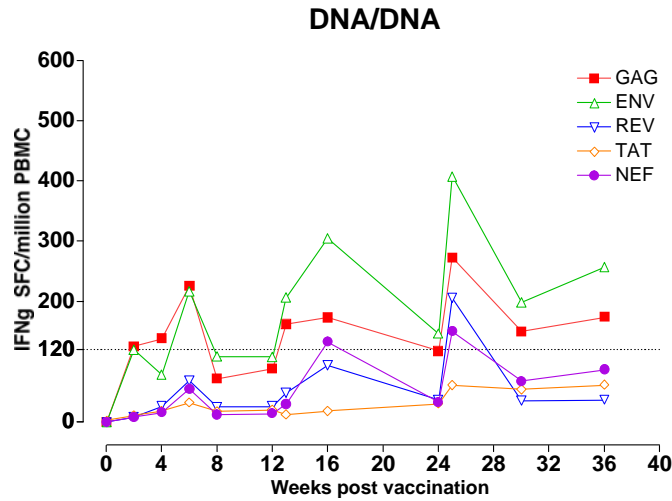
Study design



Monitoring Immunogenicity

- **ELISPOT (IFN- γ , IL-2 and perforin)**
 - PBMC
 - Peripheral LN
- **Tetramers {Mamu-A*01 (Gag CM9 & Tat SL8) and A*02 (Gag GY9 & Nef YY9)}**
 - PBMC
 - Tissues (LN, BAL, rectal tissue)
- **Neutralizing Ab to lab-adapted SIVmac251**

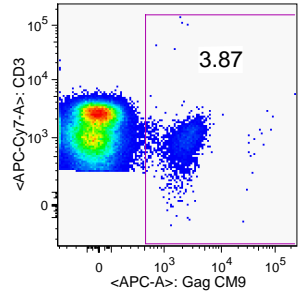
SIV-specific IFN- γ ELISPOT responses in four prime-boost vaccine regimens (Mean values for 4-6 macaques/group shown)



Negative cut-off: 120 SFC/million PBMC

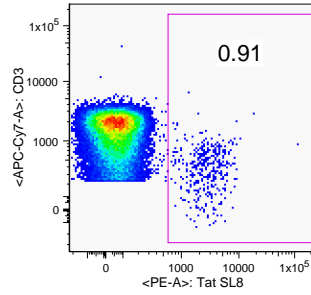
Tetramer-positive SIV-specific CD8+ T cells in the peripheral blood of Mamu-A*01 (n=8) and Mamu-A*02 (n=2) vaccinated macaques

Mamu-A*01 Gag CM9



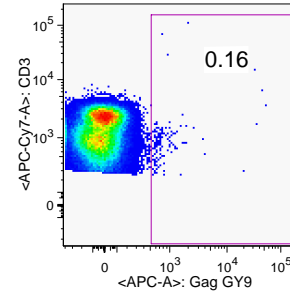
■ GagCM9+

Mamu-A*01 Tat SL8



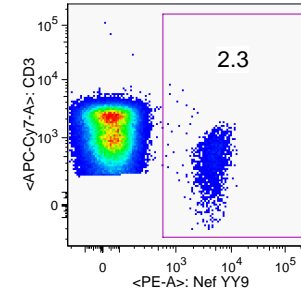
△ TatSL9+

Mamu-A*02 Gag GY9



▽ GagGY9+

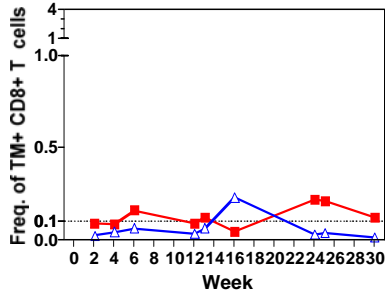
Mamu-A*02 Nef YY9



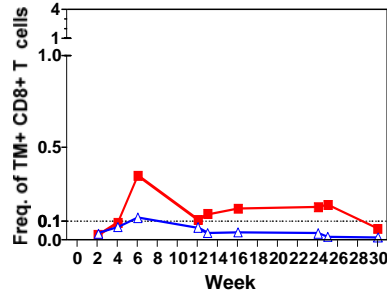
◇ NefYY9+

DNA/DNA

Mm299.03

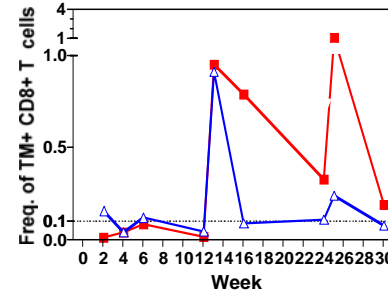


Mm79.04

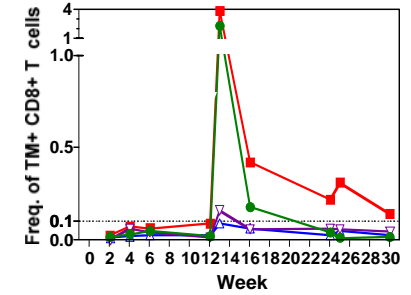


DNA/HSV

Mm381.05

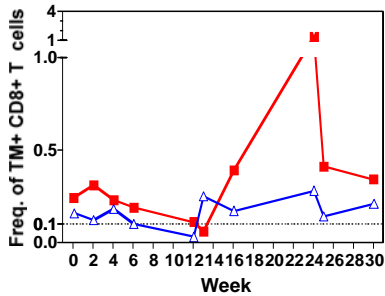


Mm344.03

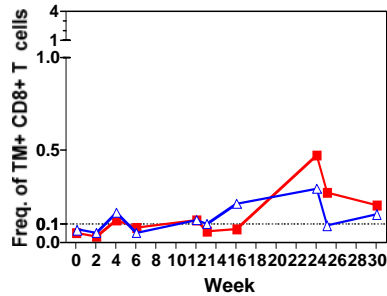


HSV/DNA

Mm402.03

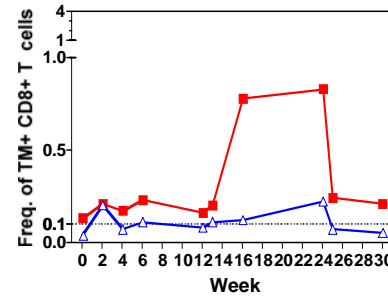


Mm349.05

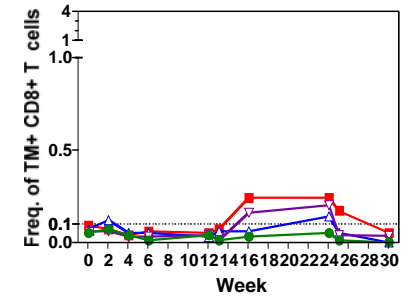


HSV/HSV

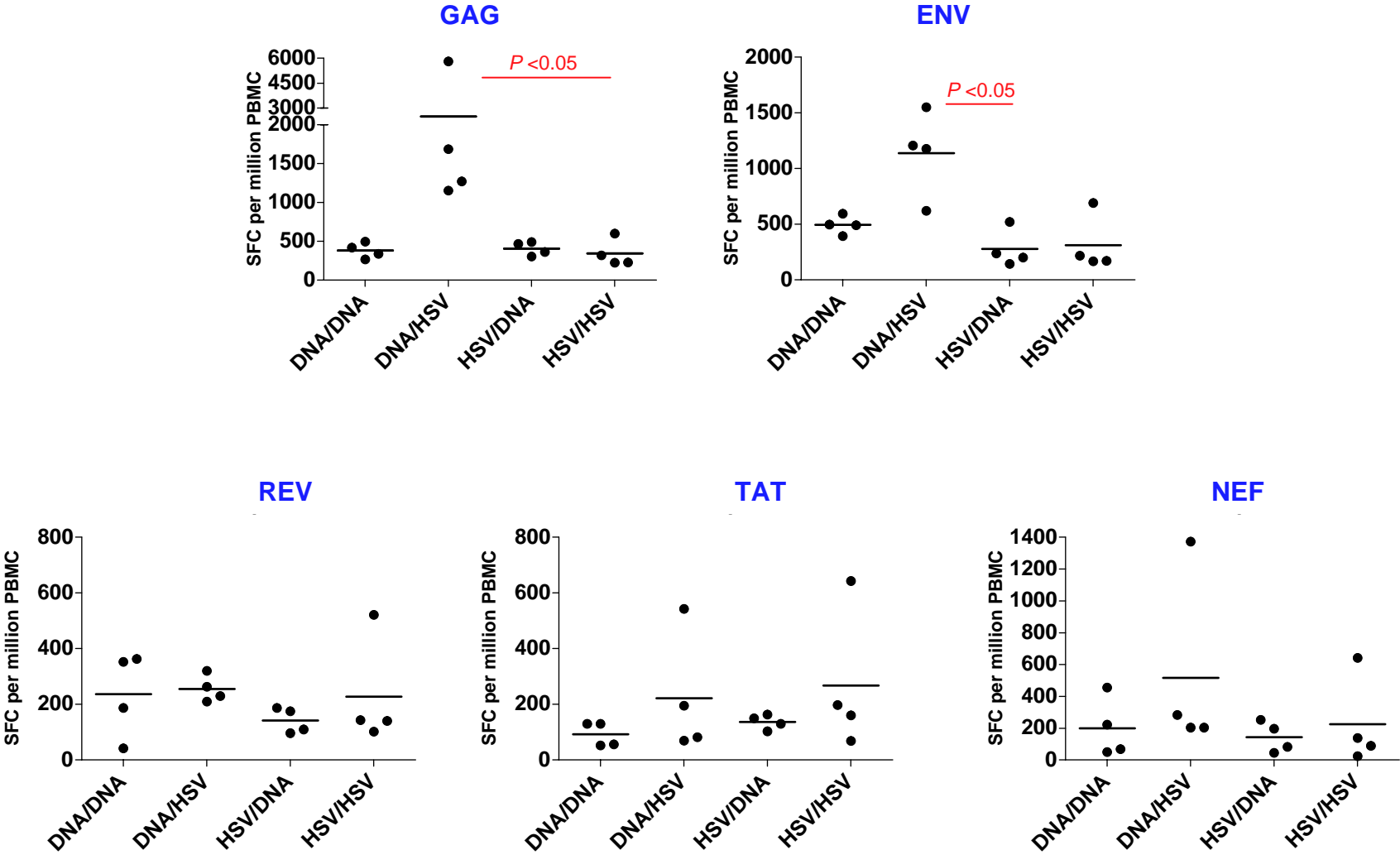
Mm541.03



Mm467.03

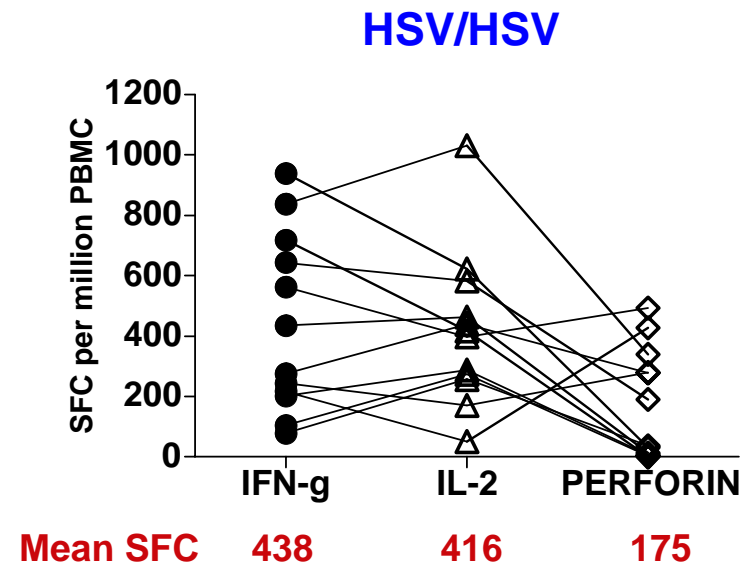
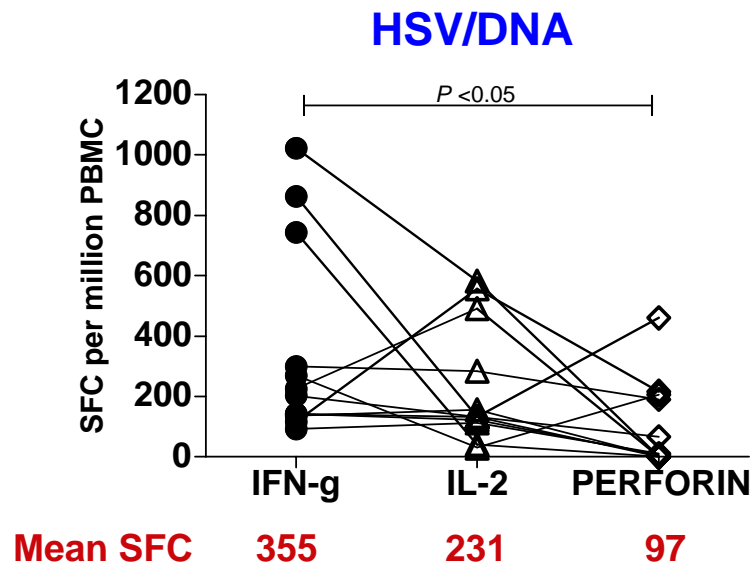
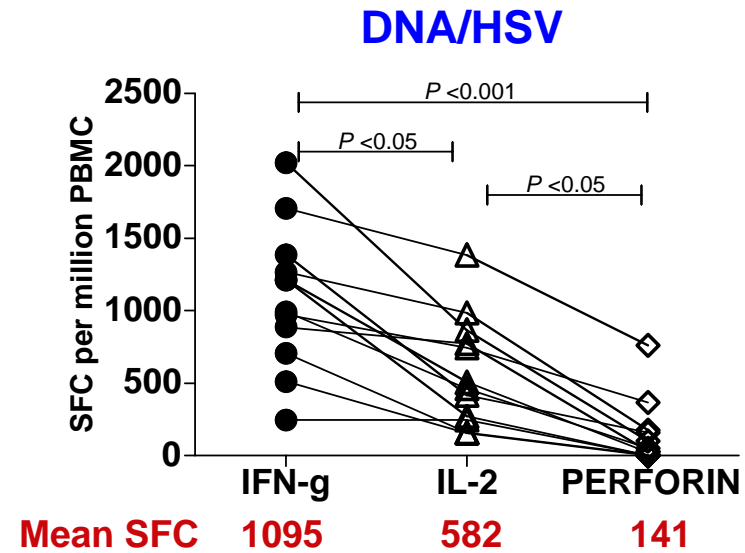
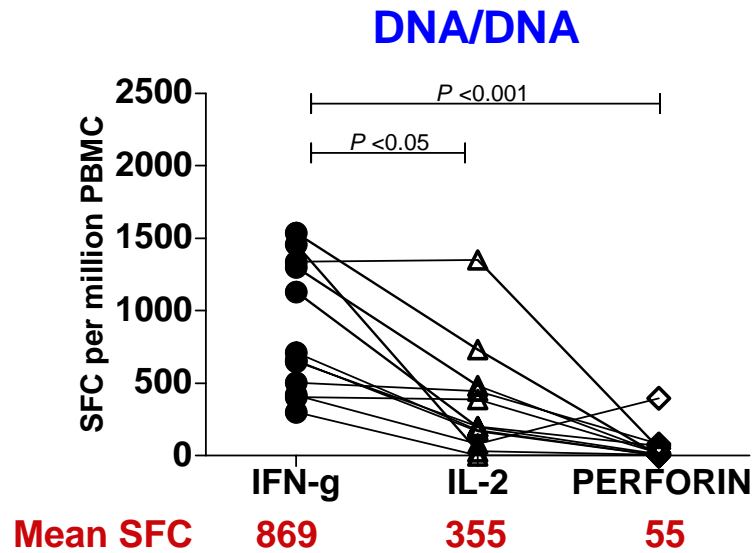


Significantly higher peak Gag- and Env-specific IFN- γ ELISPOT responses induced in DNA/HSV vaccinated macaques



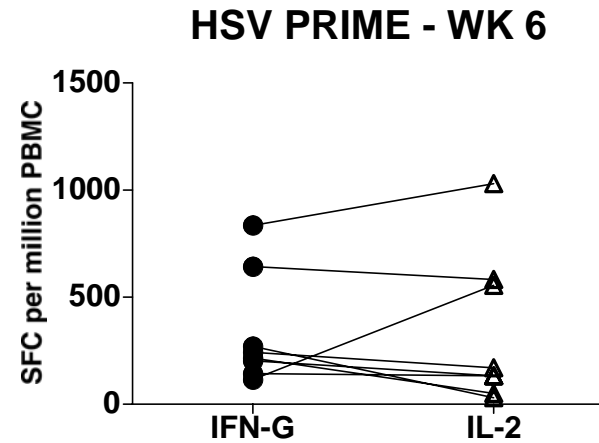
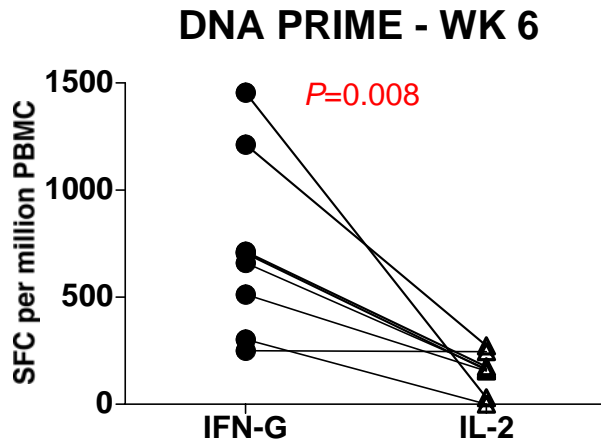
SIV-specific ELISPOT responses in peripheral blood are skewed towards IFN- γ production in the DNA-primed macaques

(Data at weeks 6, 16, 25 and 36 in four macaques/group shown)

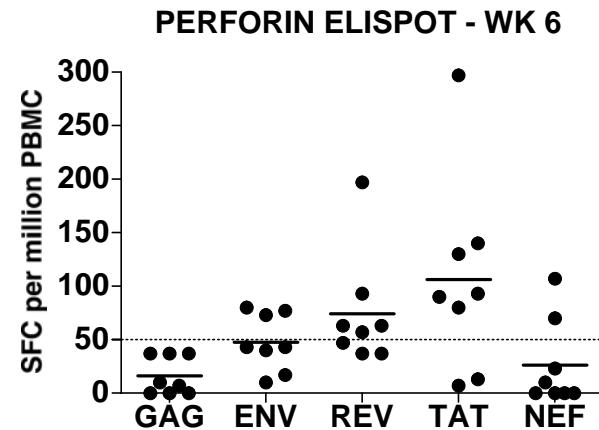
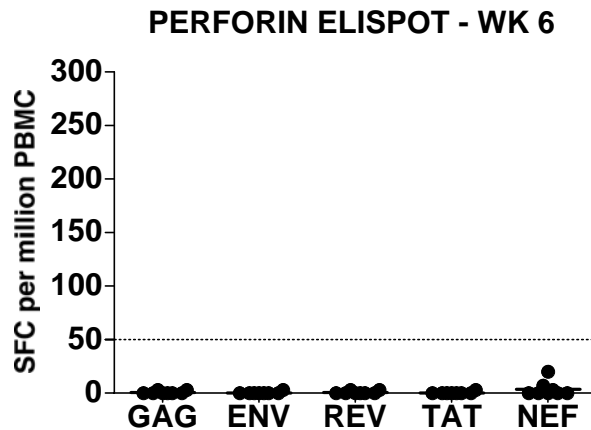


Differences in the “quality” of the SIV-specific T cell response between DNA-primed and HSV-primed macaques are evident two weeks after the second primary inoculation

More “balanced” IFN- γ and IL-2 response in HSV-primed groups

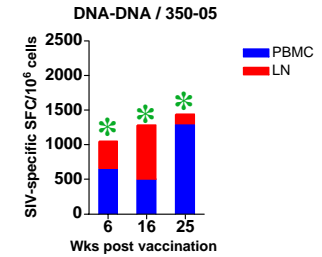
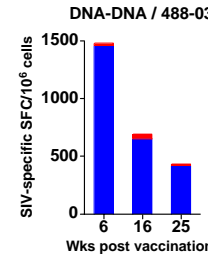
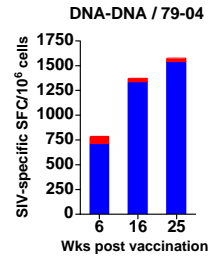
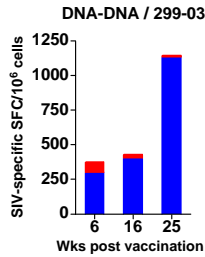


Induction of perforin ELISPOT responses after HSV but not DNA immunization

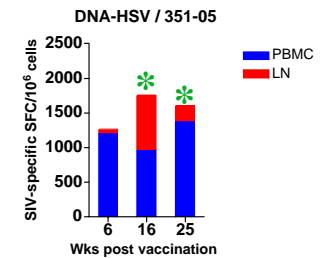
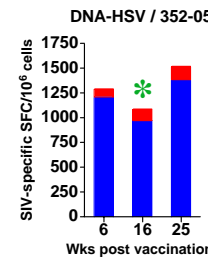
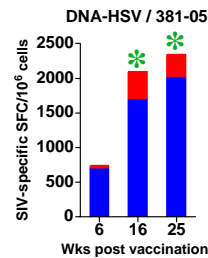
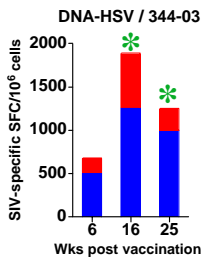


Induction of SIV-specific IFN- γ ELISPOT responses in lymph nodes

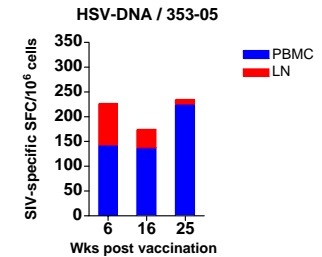
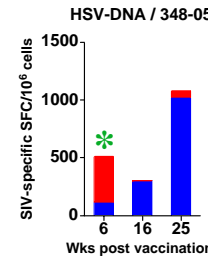
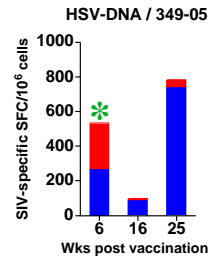
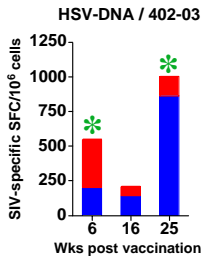
**DNA prime
DNA boost**



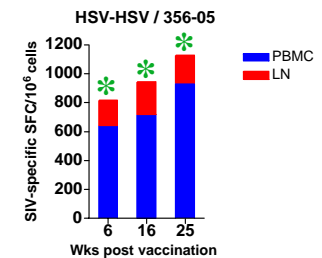
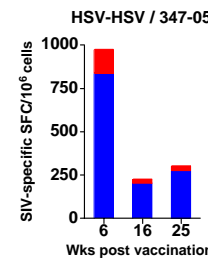
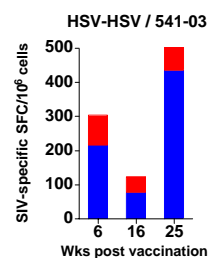
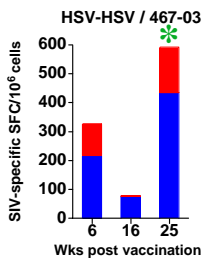
**DNA prime
HSV boost**



**HSV prime
DNA boost**



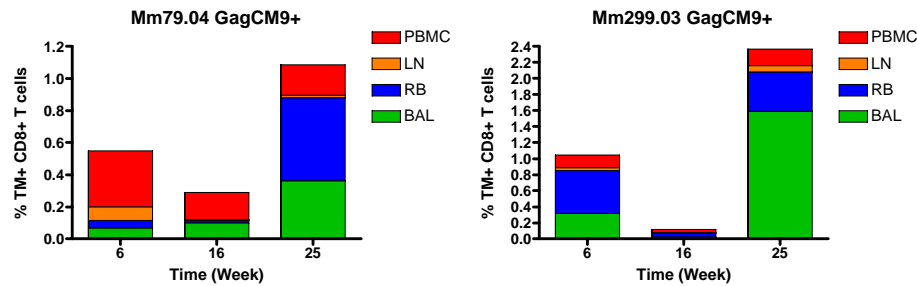
**HSV prime
HSV boost**



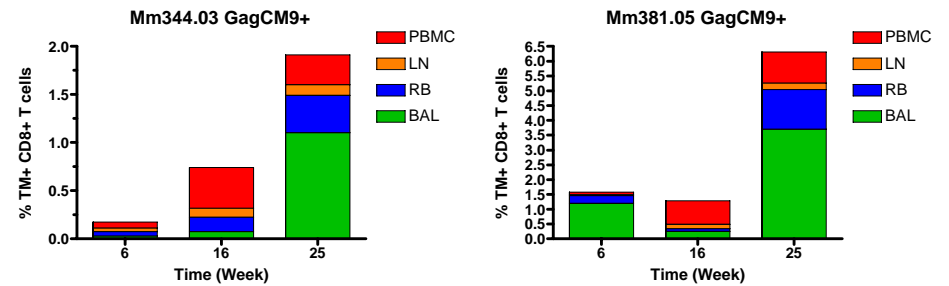
* positive LN response (>50 SFC/10⁶ cells to at least one SIV protein)

Mamu-A*01/Gag CM9 tetramer+ CD8+ T lymphocytes in peripheral blood vs lymphoid and extra-lymphoid tissue

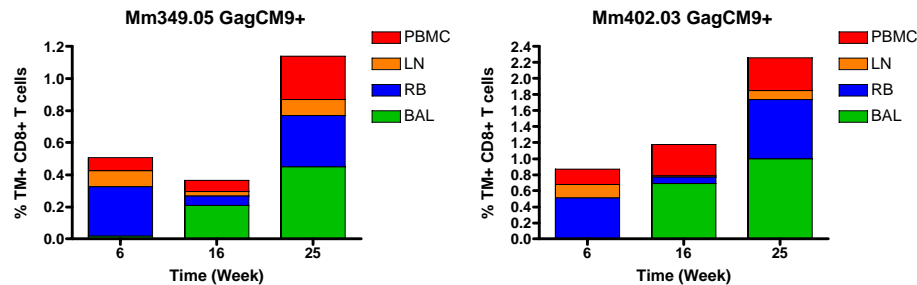
DNA/DNA



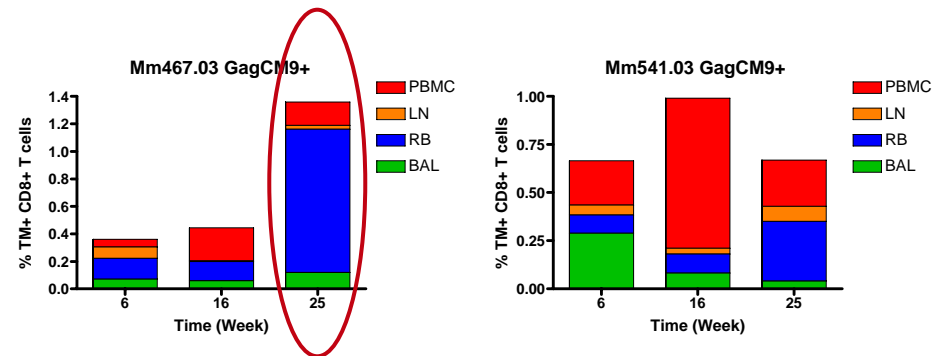
DNA/HSV



HSV/DNA

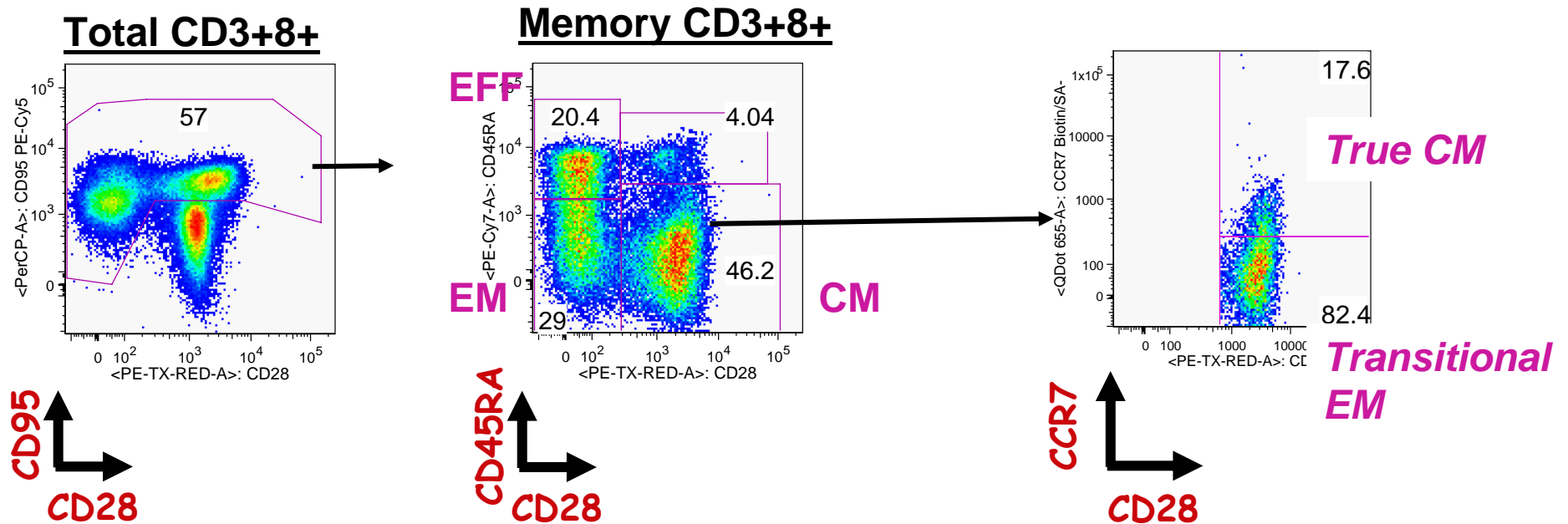


HSV/HSV

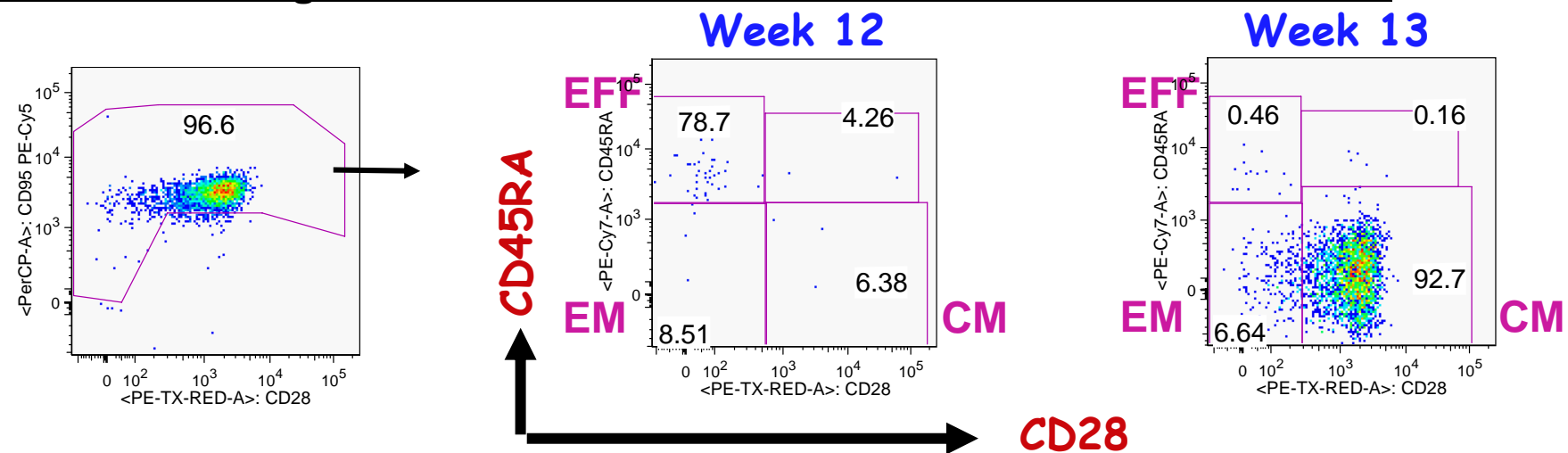


BAL - sampled one week after other sites

Induction of central memory (CD95+28+45RA-CCR7+) and transitional effector memory (CD95+28+45RA-CCR7-) TM+ cells after HSV boost



Mamu-A*01/GagCM9 TM+ CD8s (representative data in one DNA/HSV-vaccinated macaque)

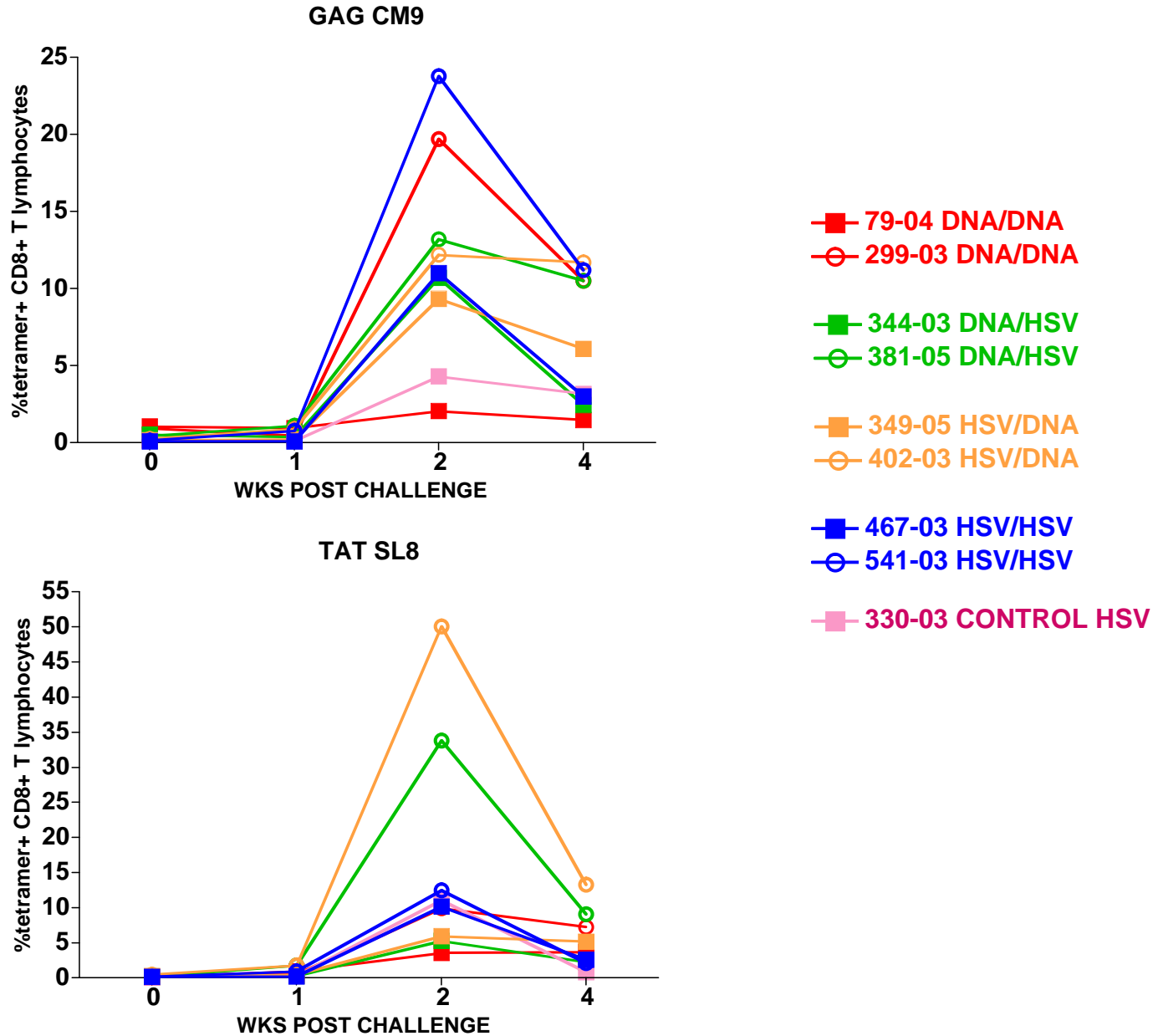


Summary - Vaccine phase

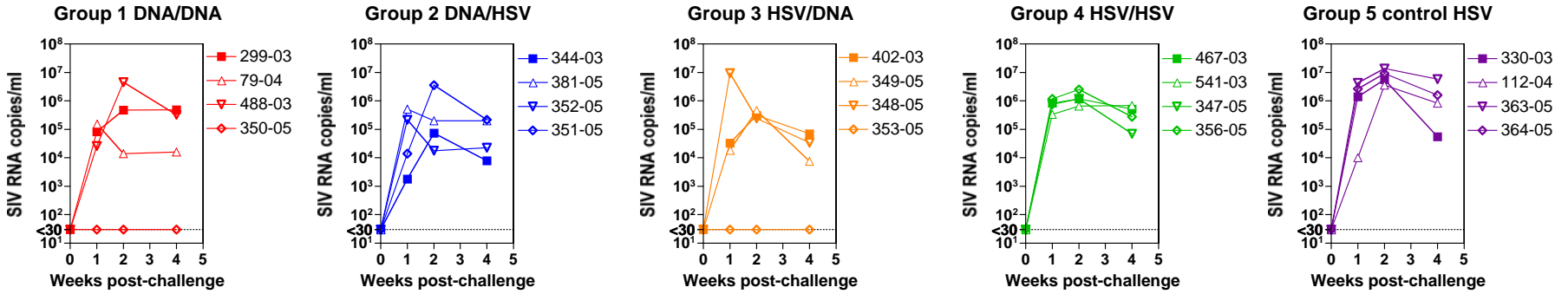
- All four vaccine regimens induced moderate to strong SIV-specific cellular immune responses to one or more SIV proteins in all rhesus macaques
- The highest magnitude of Gag- and Env specific IFN- γ ELISPOT responses were observed in DNA/HSV-vaccinated animals one week after first booster inoculation
- **Features unique to recombinant HSV α 106 immunization**
 - A 'balanced' IFN- γ and IL-2 immune response after HSV priming
 - Induction of perforin ELISPOT responses
 - Induction of Central Memory SIV-specific CD8+ T cells
 - Induction of LN ELISPOT responses
 - Induction of neutralizing Ab to SIVmac251

POST SIVmac239 CHALLENGE

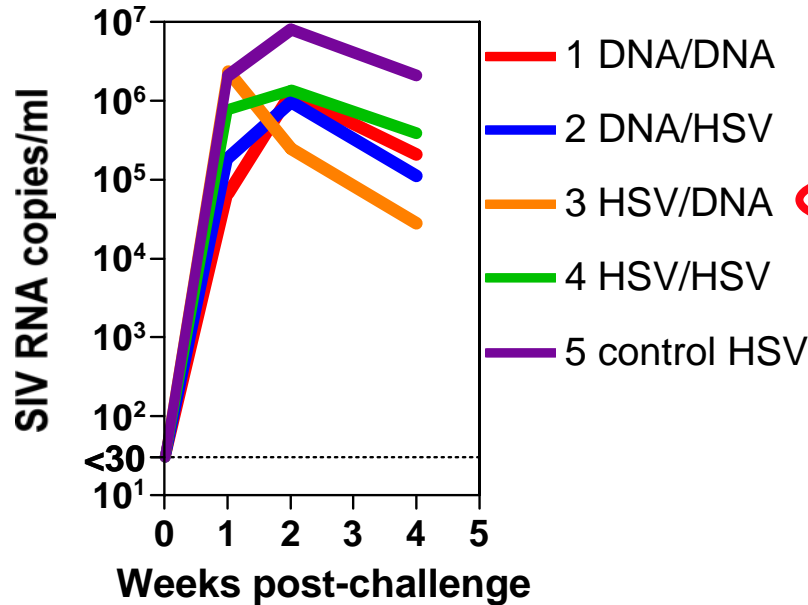
- peripheral blood tetramer responses in Mamu-A*01+ macaques



POST SIV_{mac239} CHALLENGE - SIV viremia



Mean viremia of each group

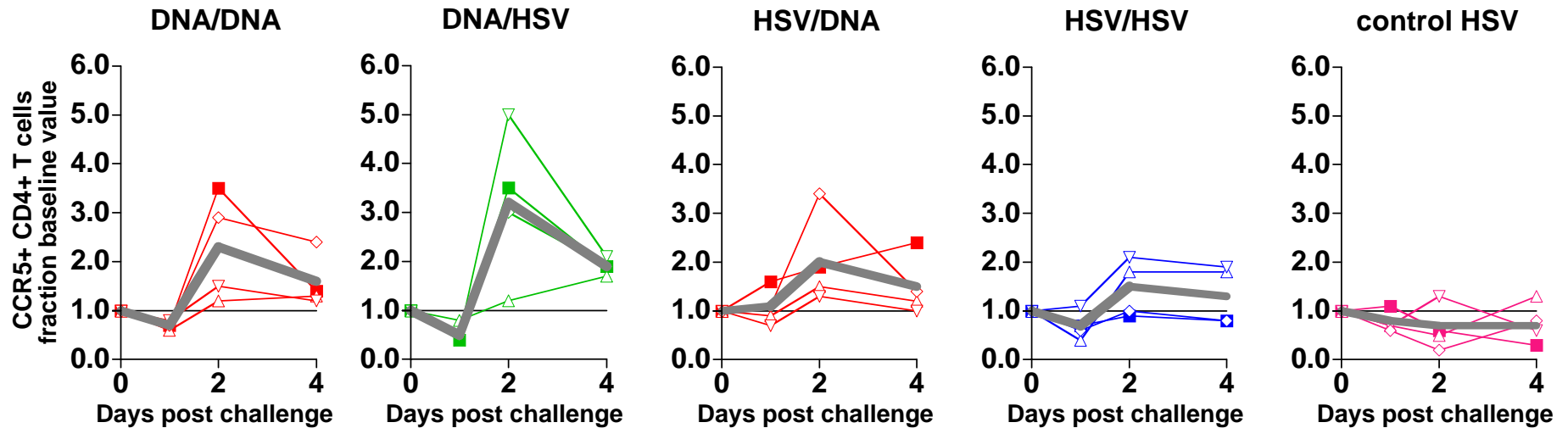


Fold-reduction

	<u>Wk2</u>	<u>Wk4</u>
1 DNA/DNA	6	10
2 DNA/HSV	8	19
3 HSV/DNA	32	75
4 HSV/HSV	6	5

POST SIVmac239 CHALLENGE

- CCR5+ CD4+ T lymphocytes in peripheral blood



Acknowledgements

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NCI - Frederick

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