

Rapid induction of protection against homologous challenge by SIV Δ nef

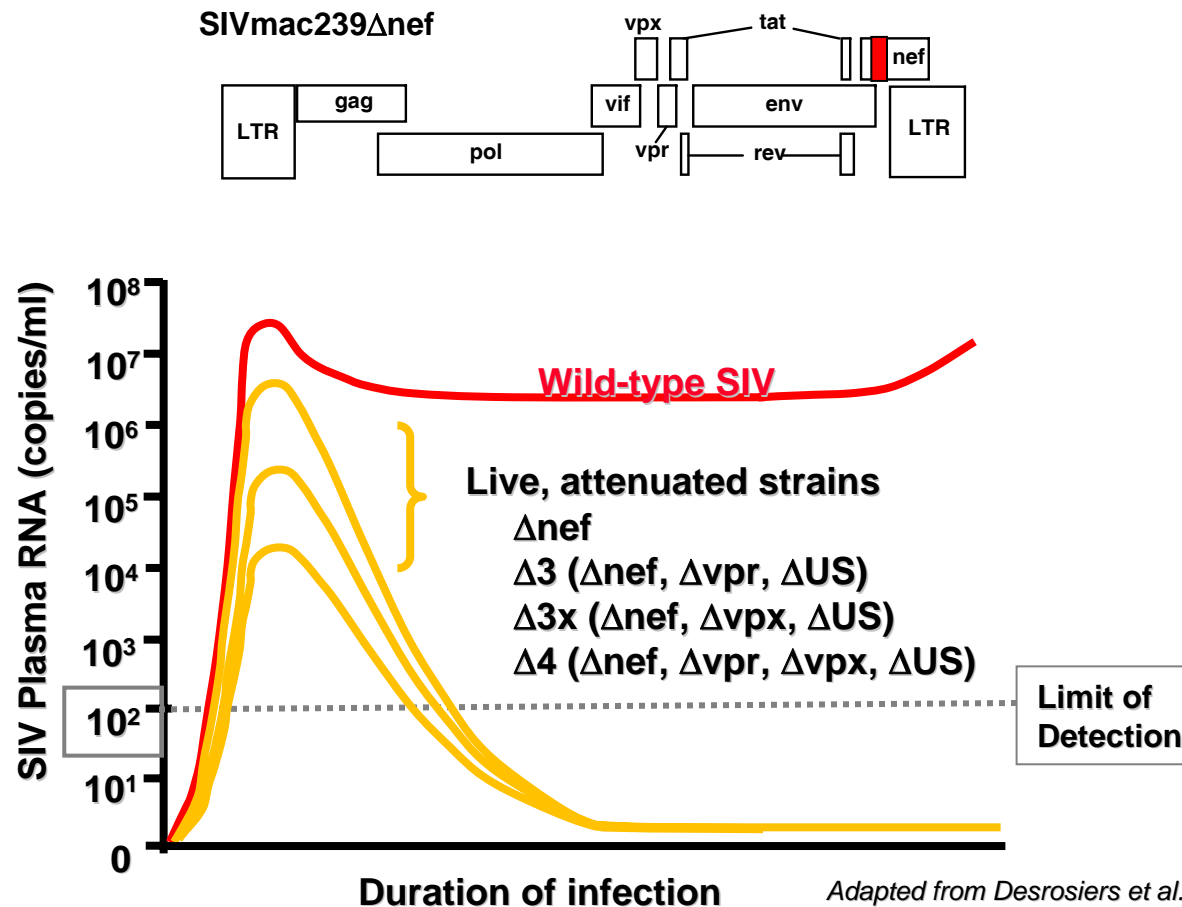
R. Keith Reeves

**New England Primate Research Center
Harvard Medical School**

Live attenuated SIV: SIV Δ nef

Structure and properties:

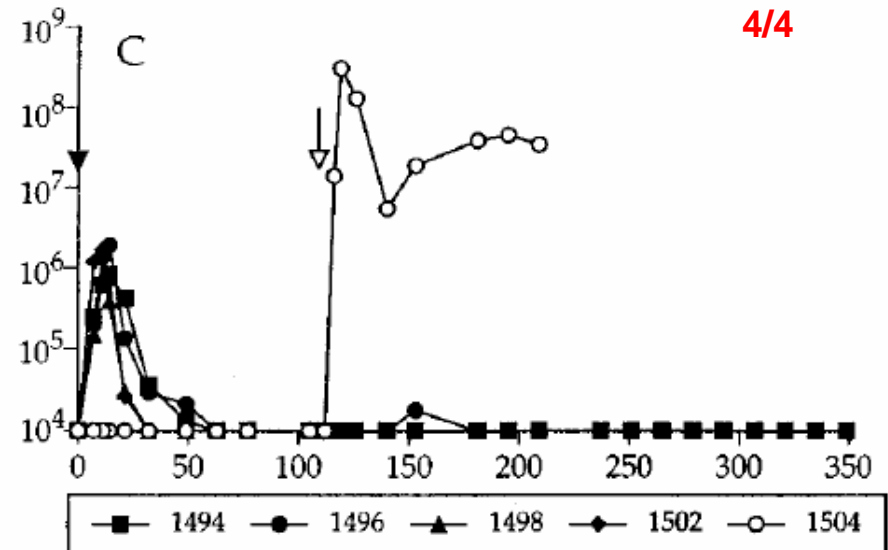
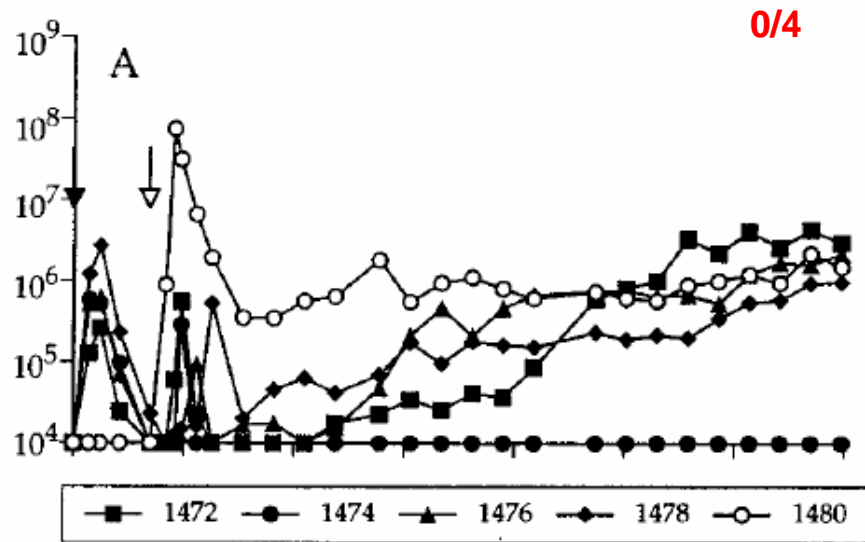
- SIV Δ nef: molecular clone of SIVmac239, premature stop codon in nef.



Kinetics of protection against IV SIVmac251 in SIV Δ nef-vaccinated macaques

5 week challenge

15 week challenge



“Sterile” protection

Connor et al., J. Virol. 1998

Challenges in identifying correlates of protection induced by LASIV

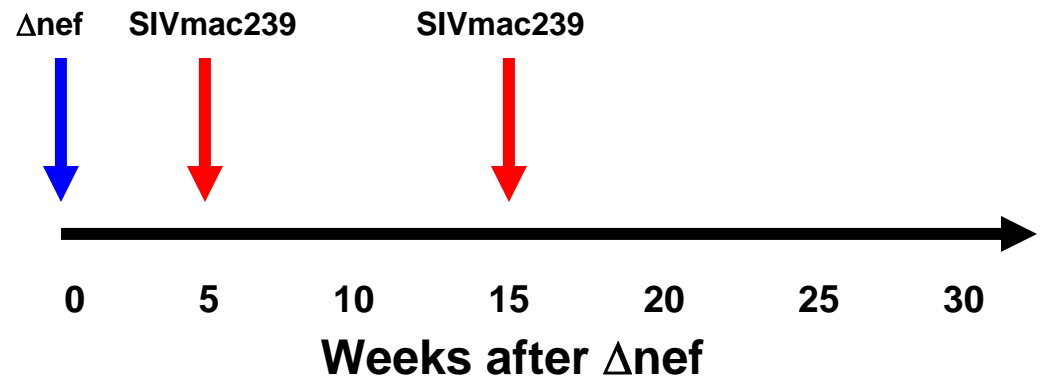
- Induction of broad array of SIV-specific immune responses by SIV Δ nef
- Landmark studies conducted prior to advent of modern assays of cell-mediated immune responses and MHC typing of study animals, study groups often 2-4 animals
- Protection against homologous challenge in SIV Δ nef-vaccinated animals generally “sterile”, and not associated with anamnestic T cell responses

Objectives

- **To evaluate the kinetics of protection induced by SIV Δ nef against a homologous challenge**
- **To identify changes in humoral and cellular immune responses that correlate with sterile protection 5 and 15 weeks after SIV Δ nef vaccination**

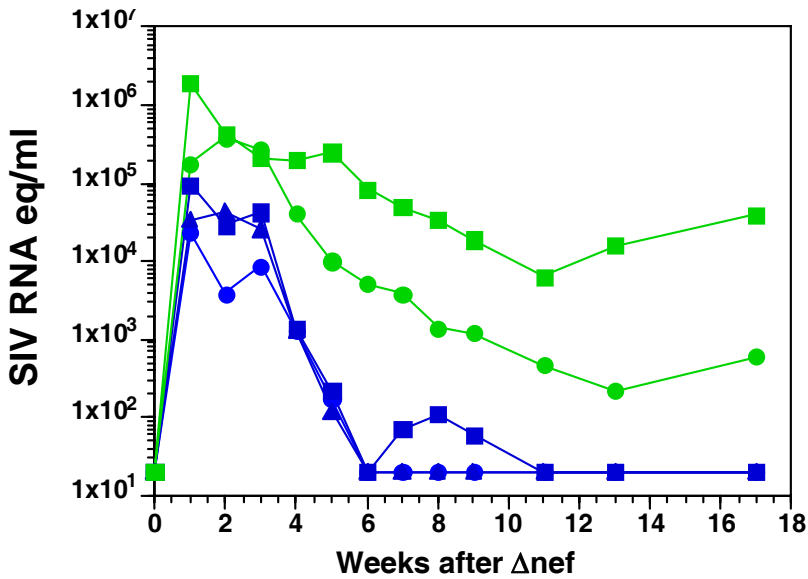
Study design

- **5 week challenge**
 - **SIV Δ nef: n=5, 3 A*01+**
 - **Naïve: n=1**
- **15 week challenge**
 - **SIV Δ nef: n=5, 3 A*01+**
 - **Naïve: n=1**
- **Challenge with SIVmac239**
 - **10 AID**



Plasma viremia after SIV Δ nef vaccination

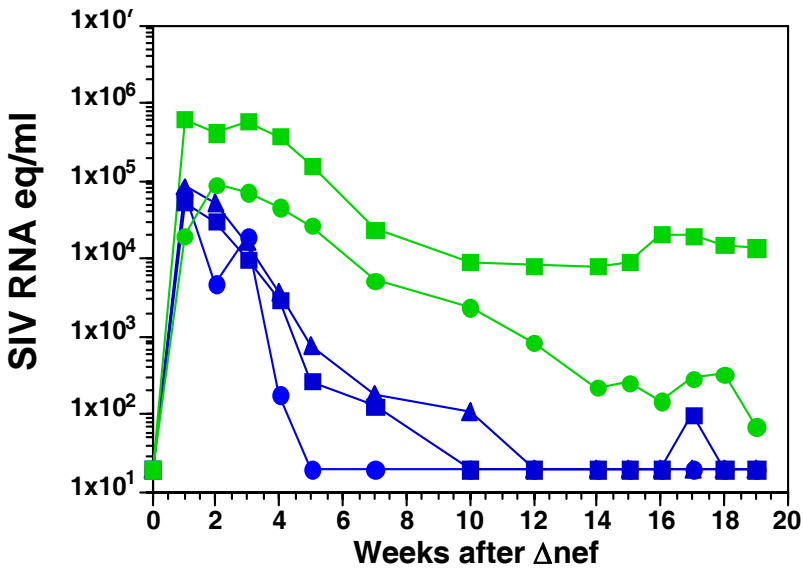
5 week challenge



- 165-03 ● 376-04
- 168-03 ■ 310-04
- ▲ 211-03

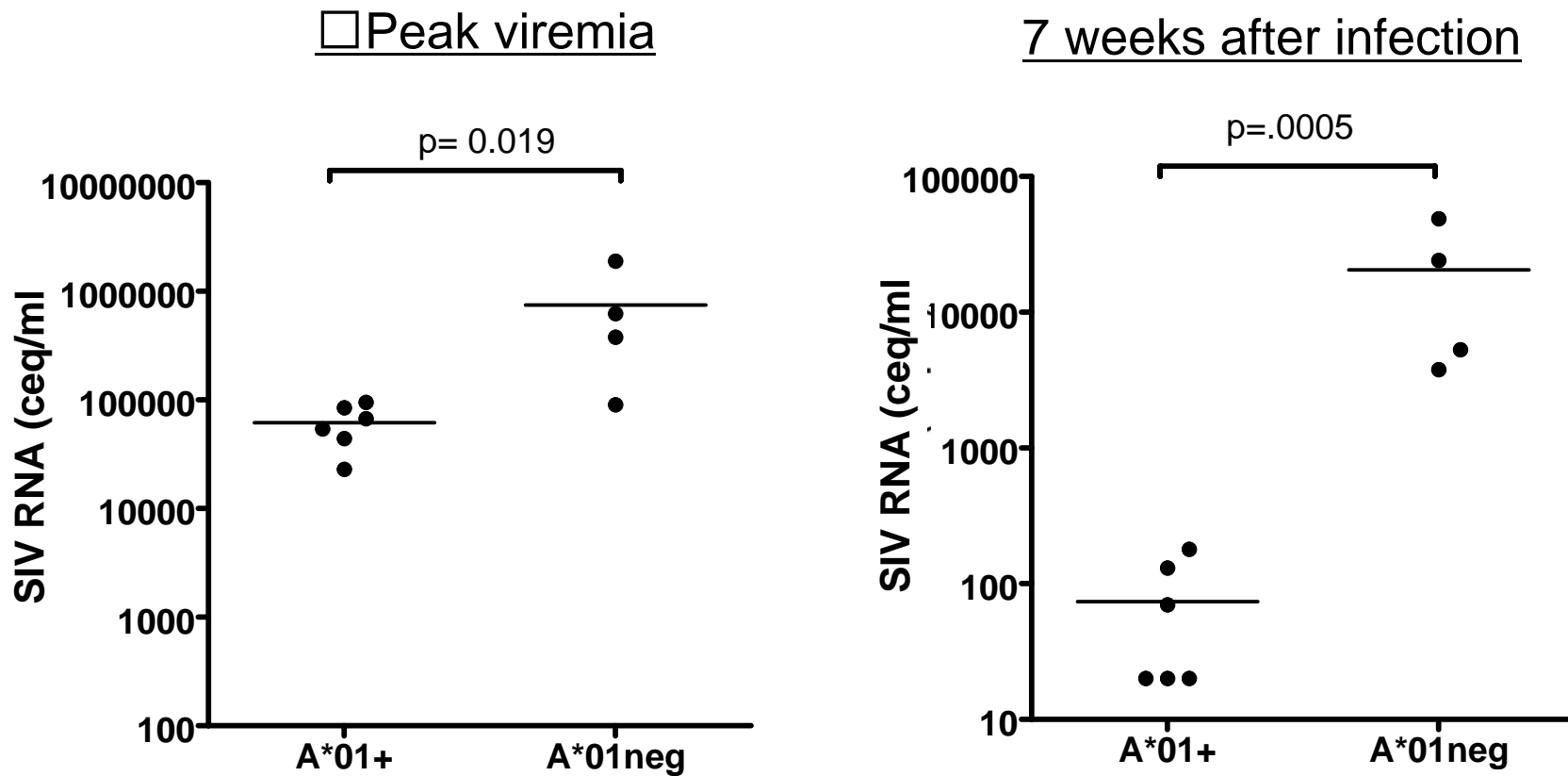
A*01+ Δ nef
A*01- Δ nef

15 week challenge



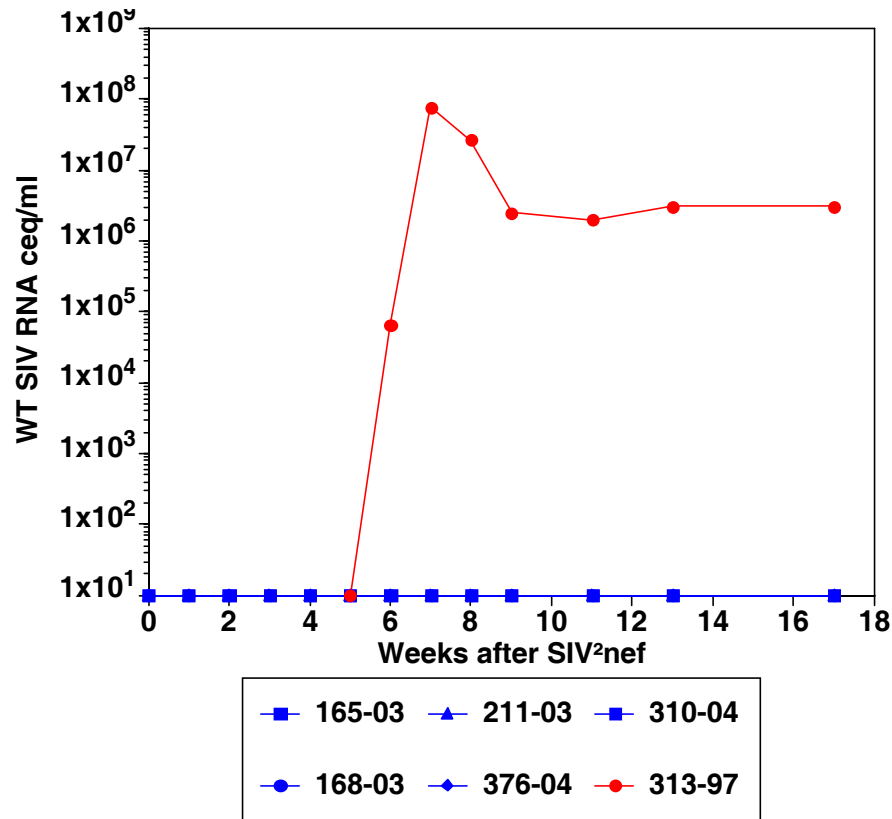
- 283-03 ● 323-06
- 290-03 ■ 350-04
- ▲ 293-01

Significantly lower levels of viremia in Mamu A*01-negative animals following SIV Δ nef vaccination

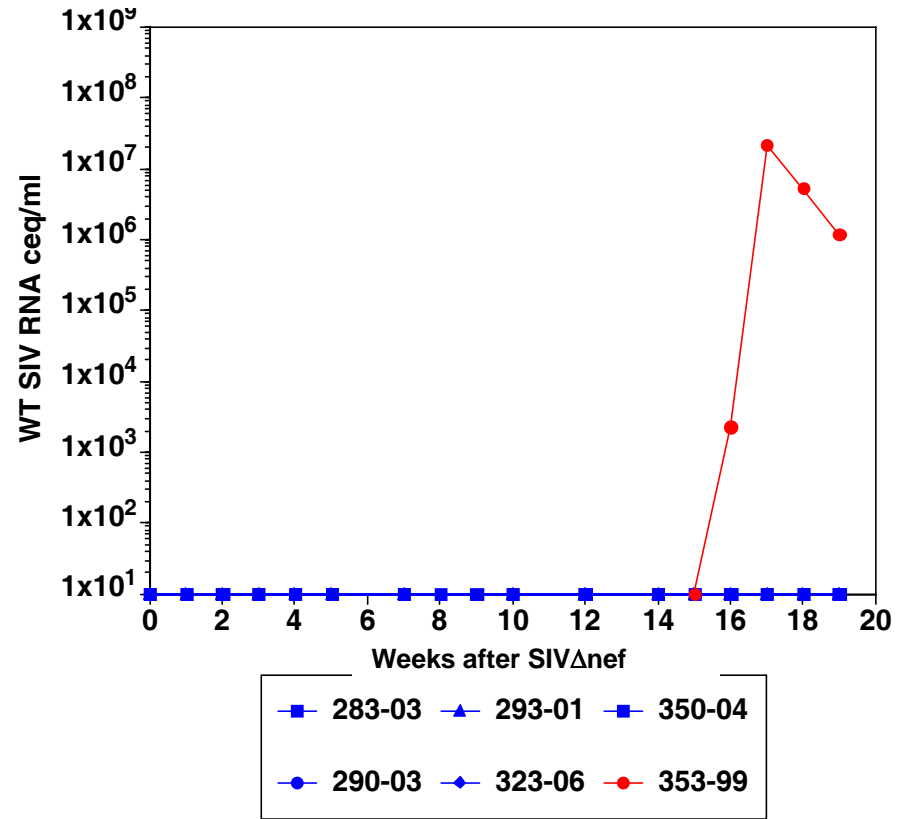


WT Plasma viremia after SIV Δ nef infection and SIVmac239 challenge

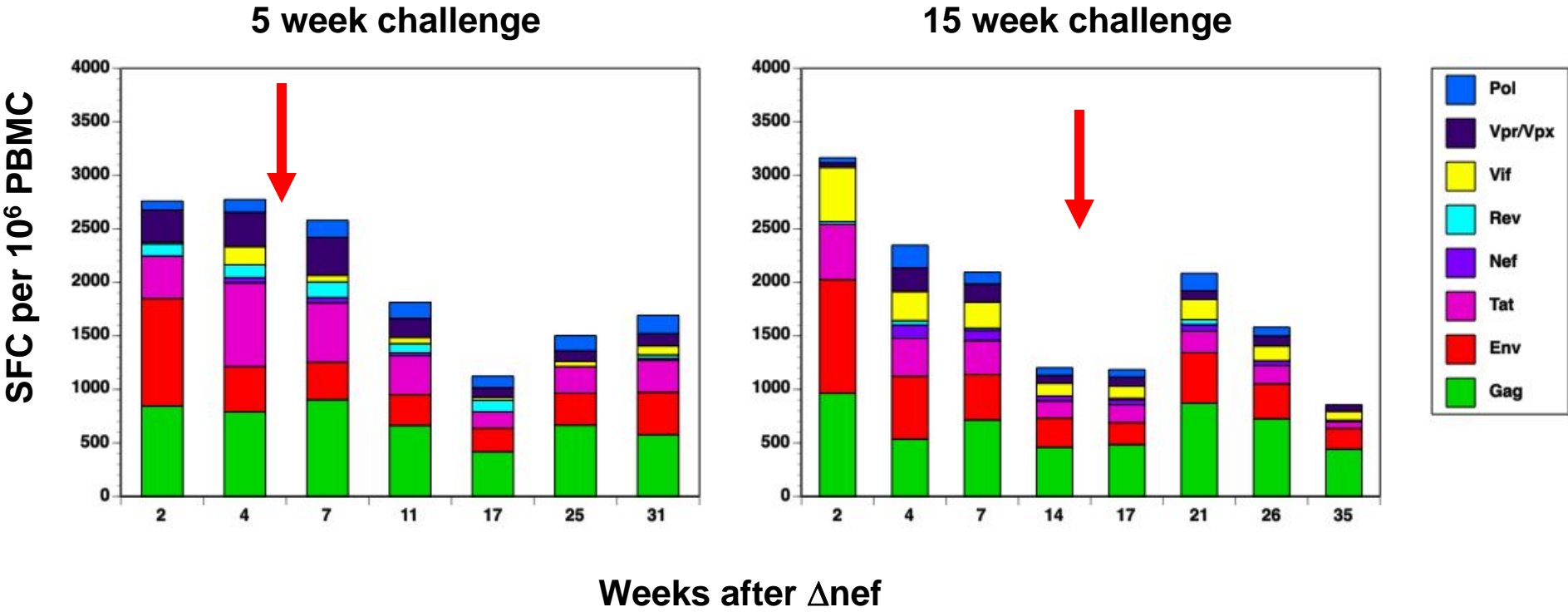
5 week challenge



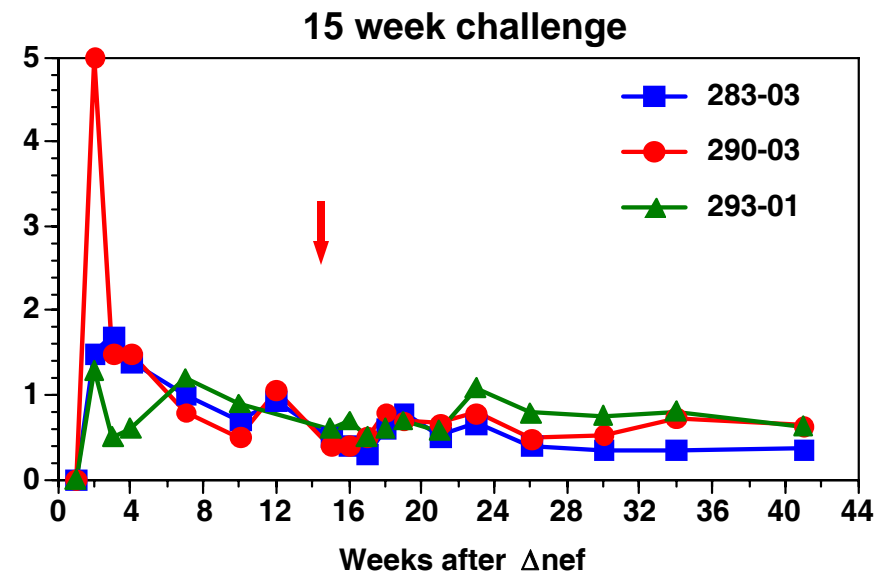
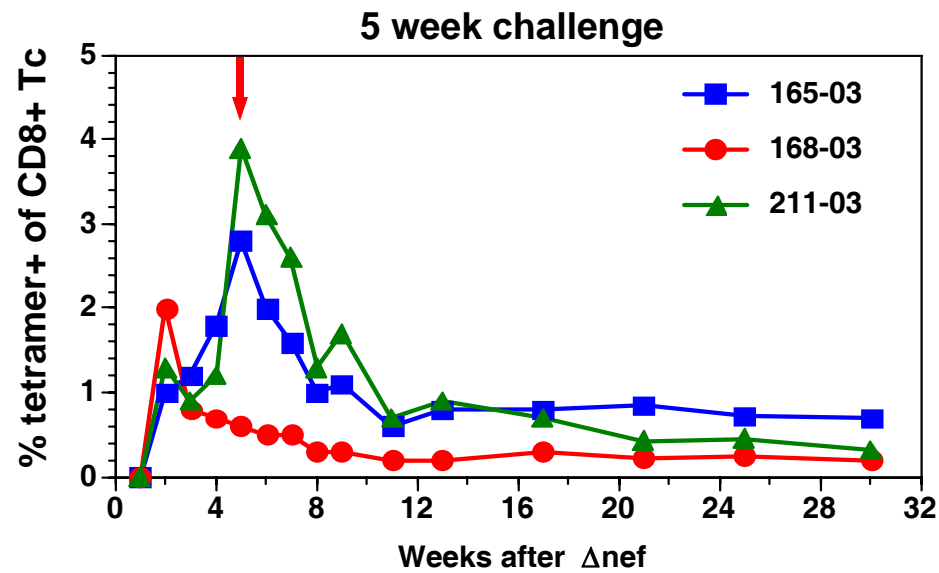
15 week challenge



Whole proteome ELISPOT responses after SIV Δ nef

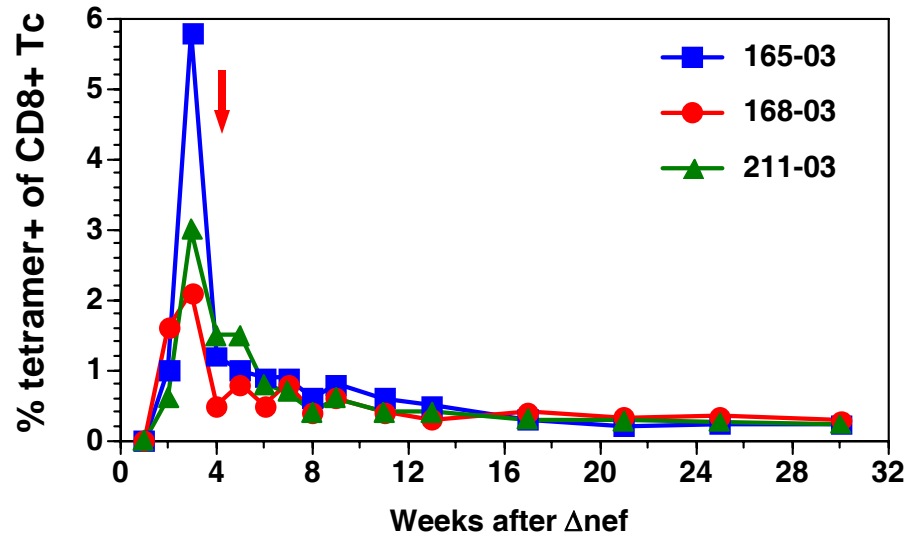


A*01 Gag CM9 tetramer-binding cells after SIV Δ nef vaccination

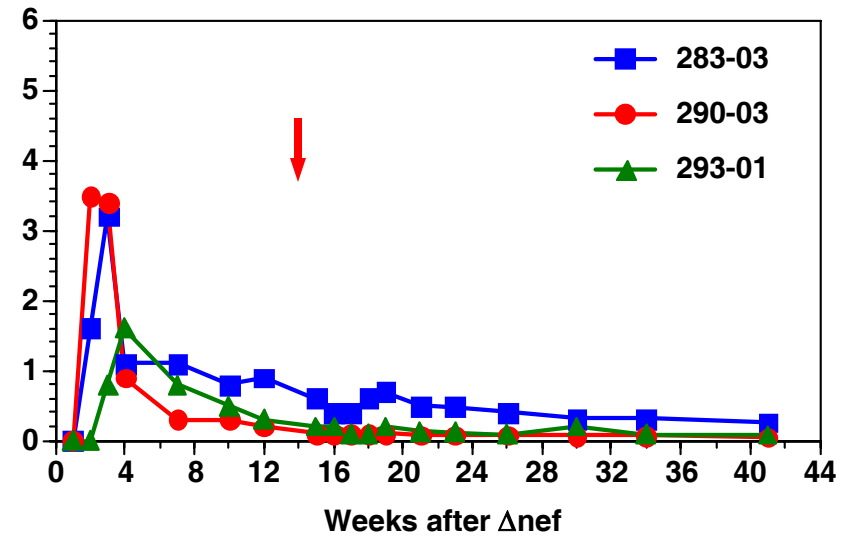


A*01 Tat SL8 tetramer-binding cells after SIV Δ nef vaccination

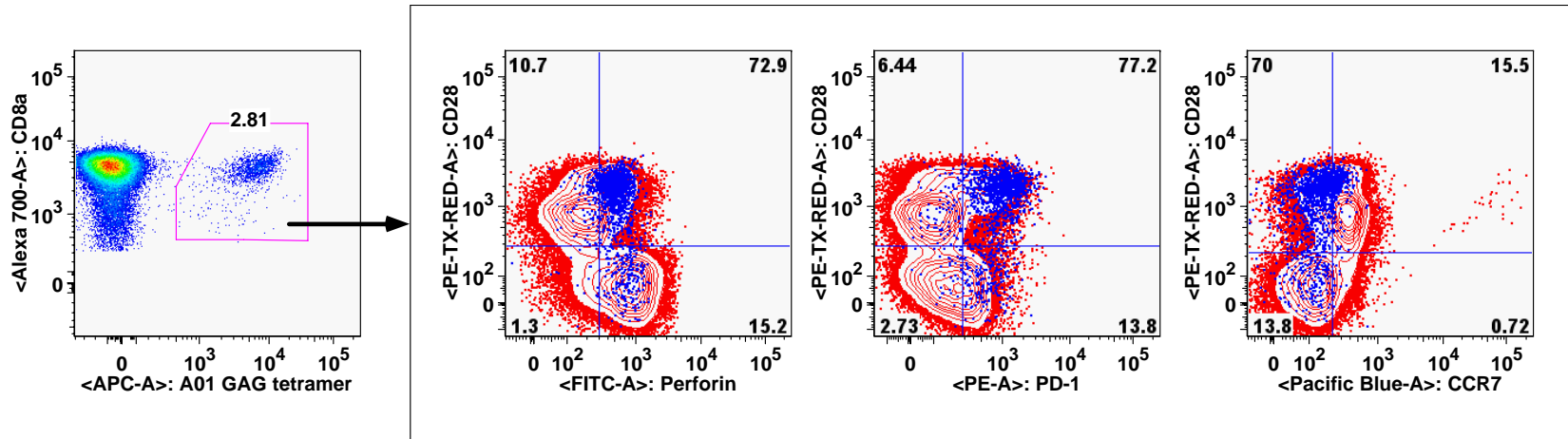
5 week challenge



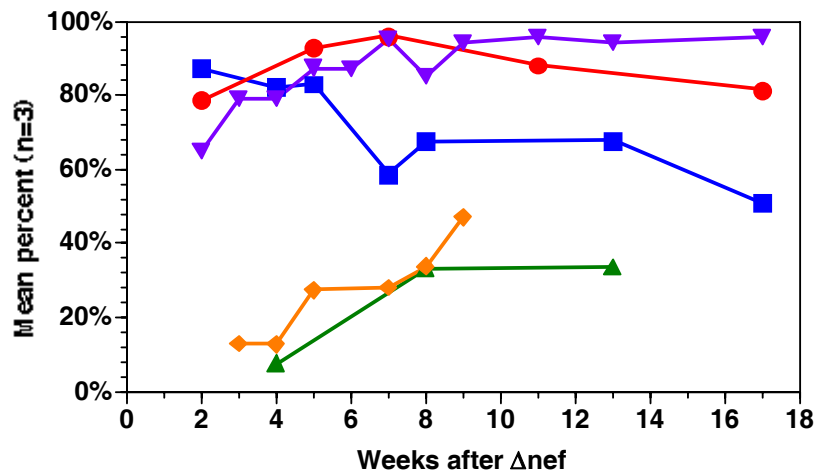
15 week challenge



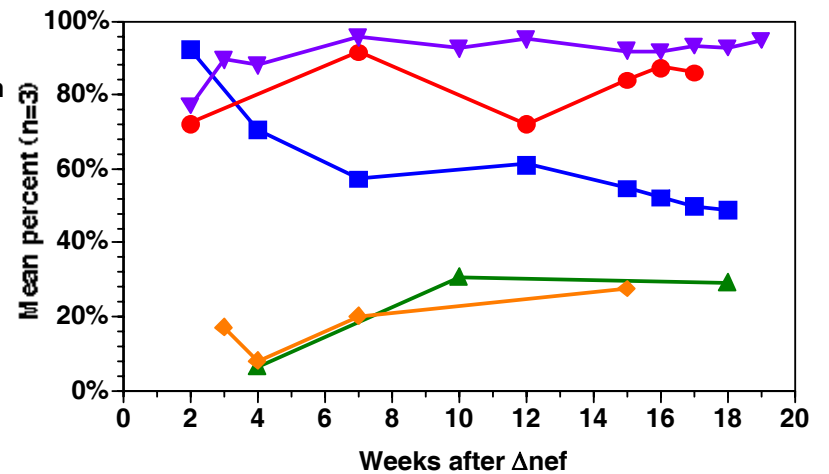
Phenotypic analysis of tetramer-binding CD8⁺ T cells



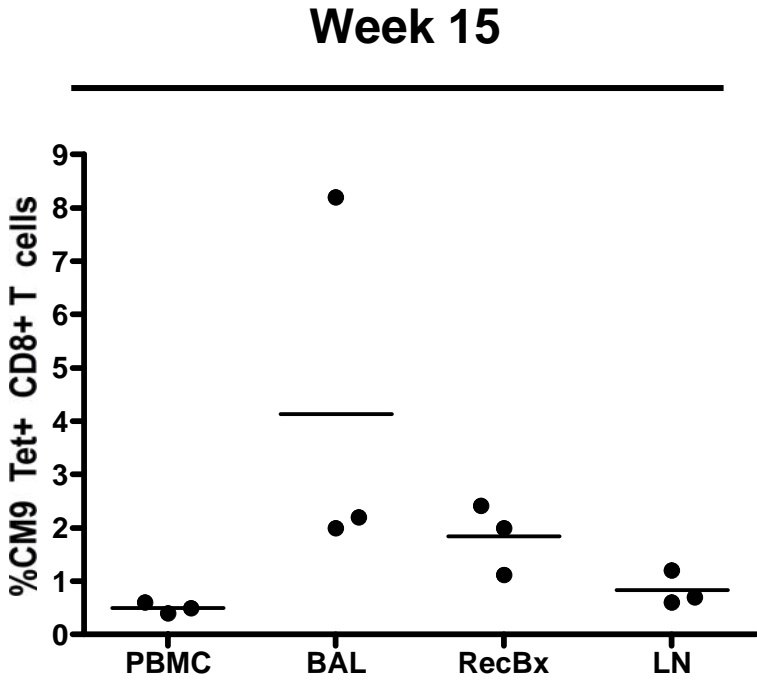
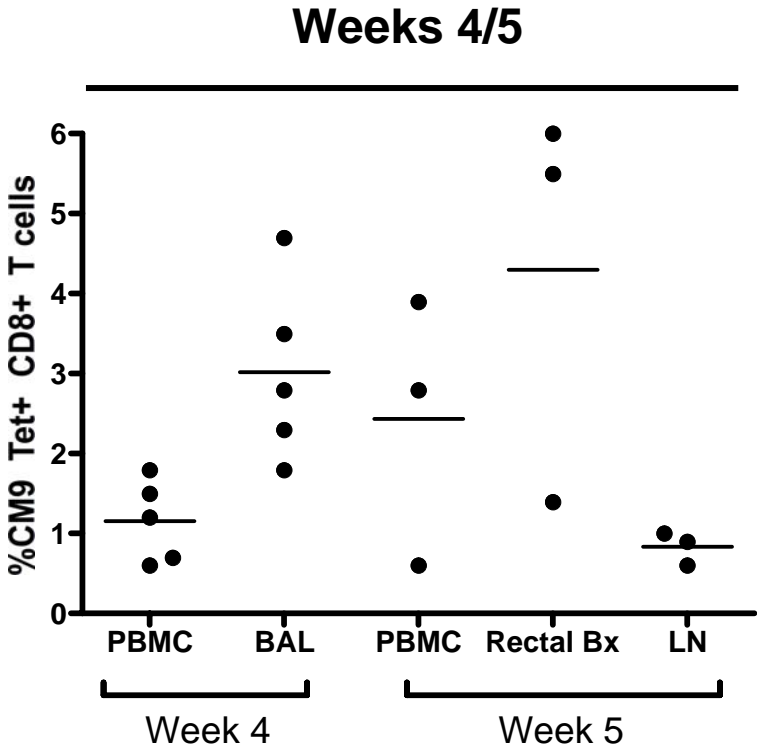
5 week challenge



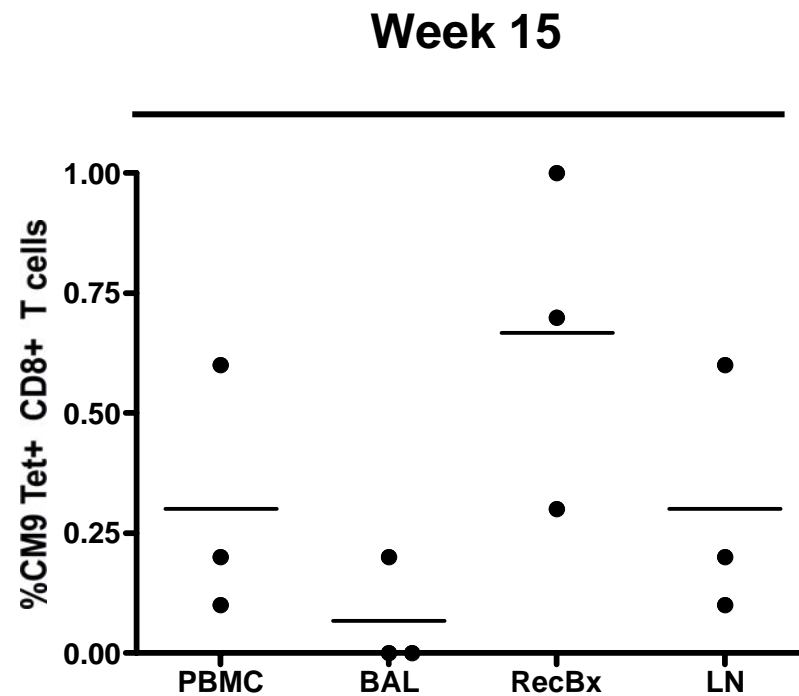
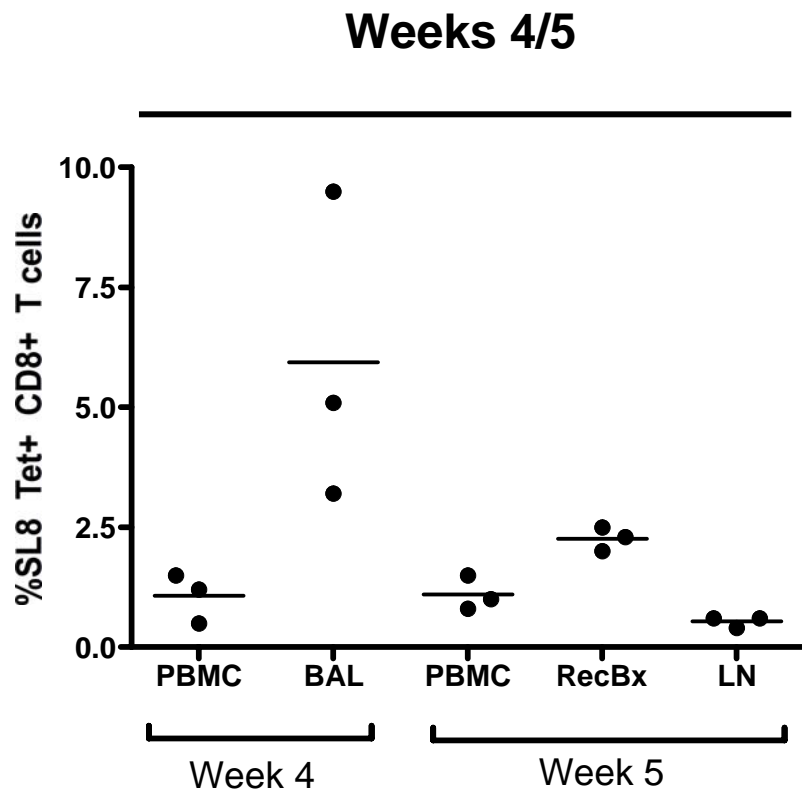
15 week challenge



Trafficking of Gag CM9 tetramer-binding cells to LN and tissues

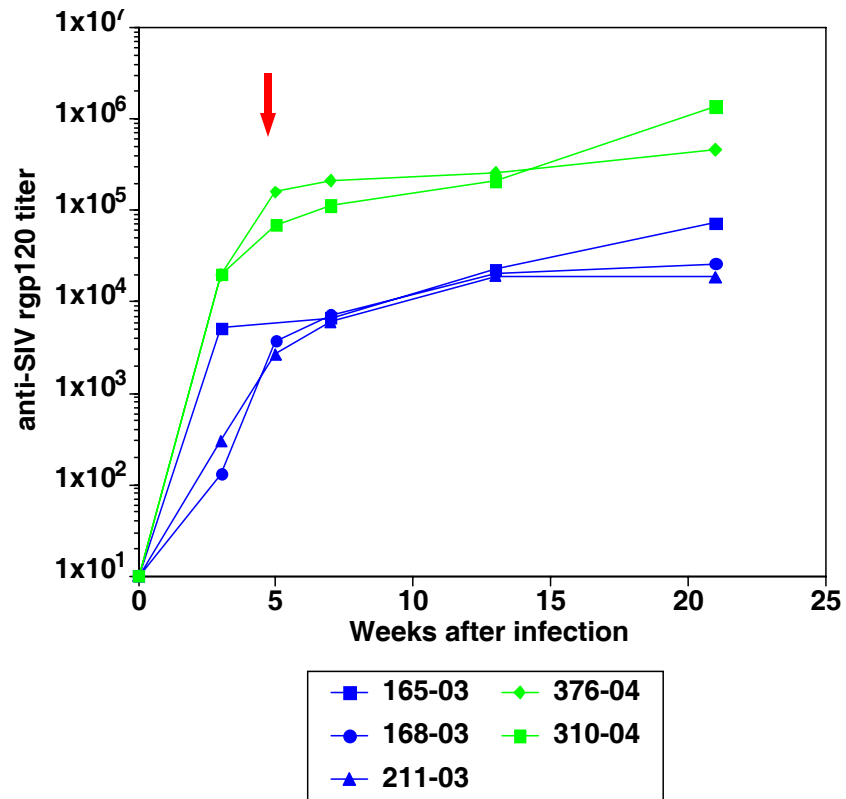


Trafficking of Tat SL8 tetramer-binding cells to LN and tissues

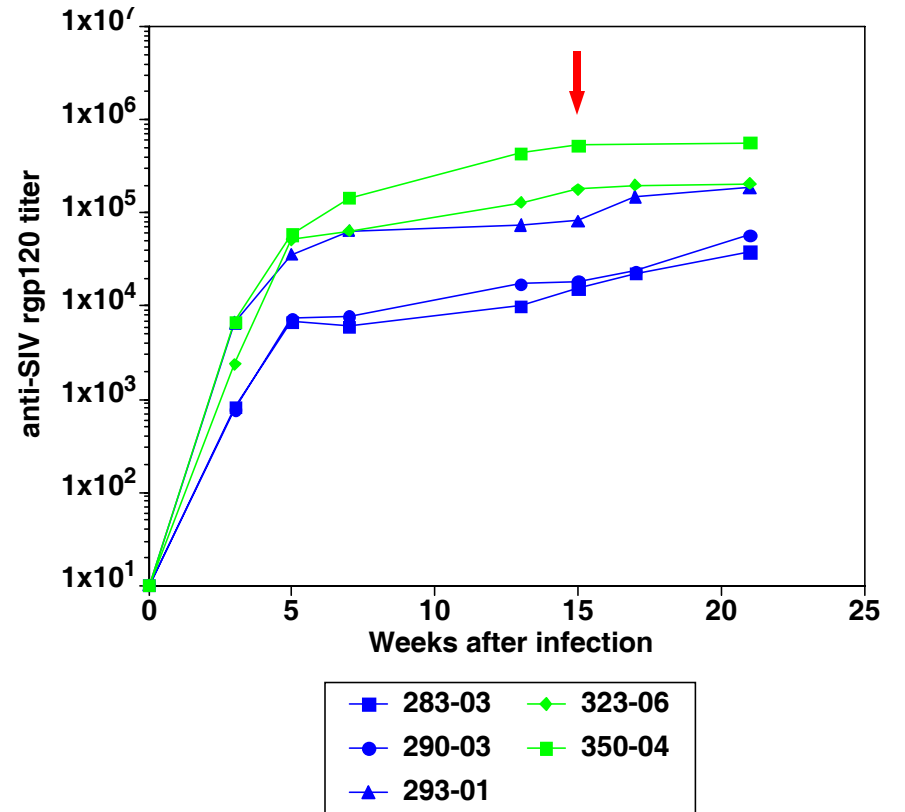


Antibody titers after SIV Δ nef

5 week challenge

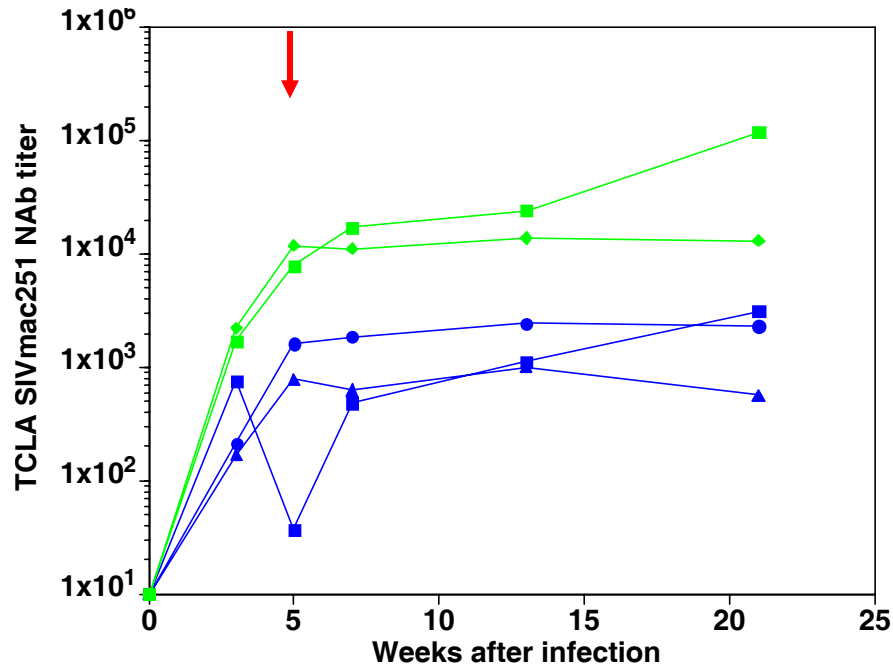


15 week challenge



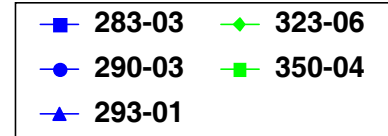
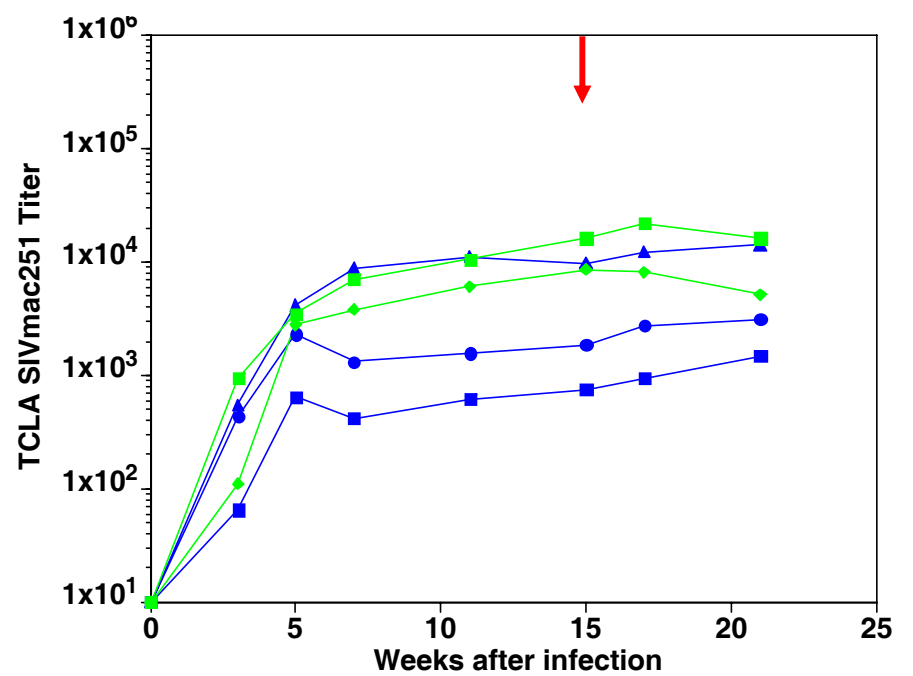
TCLA SIVmac251 Neutralization Titers

5 week challenge



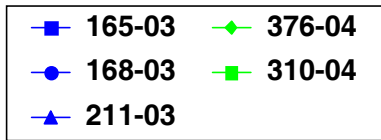
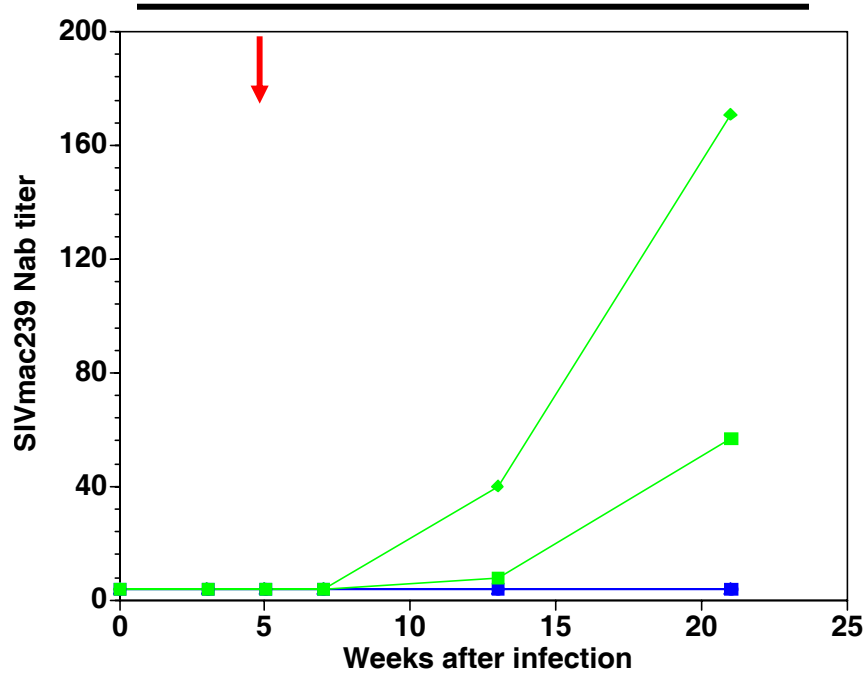
A*01+ Δnef
A*01- Δnef

15 week challenge



SIVmac239 neutralizing antibodies after SIV Δ nef vaccination

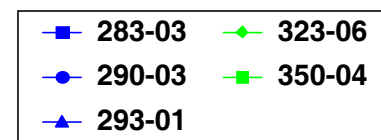
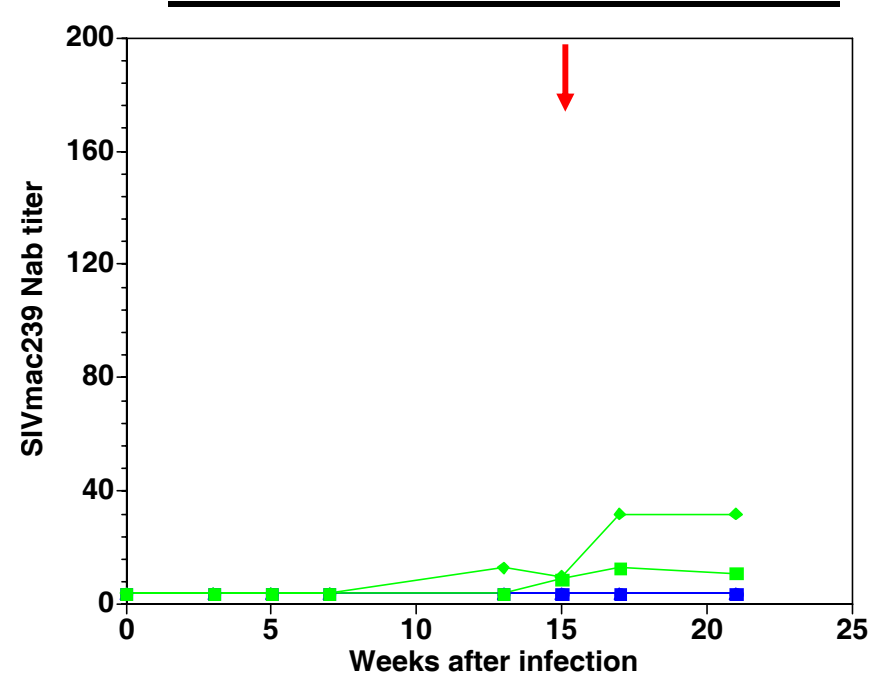
5 week challenge



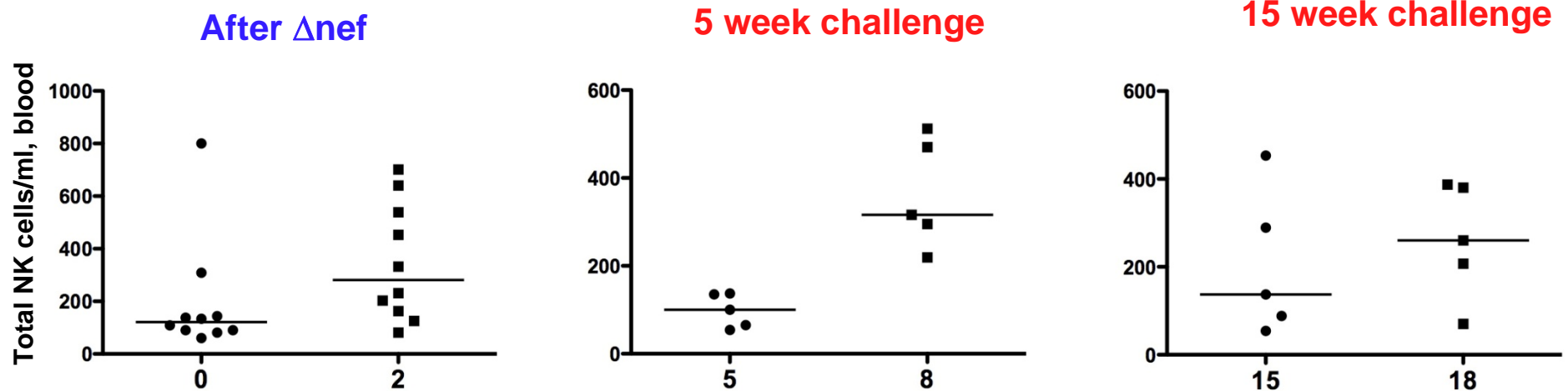
A*01+ Δ nef

A*01- Δ nef

15 week challenge



Modulation of absolute NK cell counts after SIV Δ nef vaccination and challenge



Summary and Conclusions

- **A*01+ animals display significantly better control of SIV Δ nef infection**
- **“Sterile protection” observed against IV SIVmac239 in 5/5 animals at 5 and 15 weeks after SIV Δ nef infection in contrast to SIVmac251 challenges**
- **SIV Δ nef induces a relatively broad and high frequency CD8+ T cell response**
- **Initial SIV-specific CD8+ T cell responses are CD28⁺CD127⁻CCR7⁻PD-1⁺ Perforin⁺ “Transitional memory phenotype”**
 - **Observe upregulation of CD127 and CCR7 at later time points**
- **Efficient homing of Gag and Tat-specific T cells to BAL and rectal mucosa**
- **No detectable anamnestic responses at either 5 or 15 week challenge**

Summary and Conclusions

- **SIV Δ nef induces strong humoral responses to gp120**
- **Neutralizing antibodies to TCLA SIVmac251, but not to SIVmac239**
 - **Suggests neutralizing antibodies may not be necessary to protect against SIVmac239 challenge**
- **Increases in circulating NK cells in first weeks after SIV Δ nef infection**
- **Consistent increases in circulating NK cells observed after challenge**
 - **Suggest challenge may not be silent even in the absence of an anamnestic response**

Future Directions

- **Repeat previous studies challenging macaques with SIVmac251**
- **Functionality of SIV-specific cells**
 - **ICS - IFN- γ , TNF- α , IL-2, 107a**
- **More detailed analysis of contribution of NK cells and innate immunity to Δ nef-mediated protection**

Acknowledgements

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