

# Exposed, uninfected rhesus monkeys: immune correlates of protection

- **Exposed, uninfected humans**
  - Cohorts
    - Discordant couples
    - commercial sex workers
  - Immune correlates of protection → vaccine strategies
- **Immune correlates of protection**
  - Virus-specific cellular, humoral immunity
  - Systemic, mucosal
- **Skepticism**
- **Macaque model**

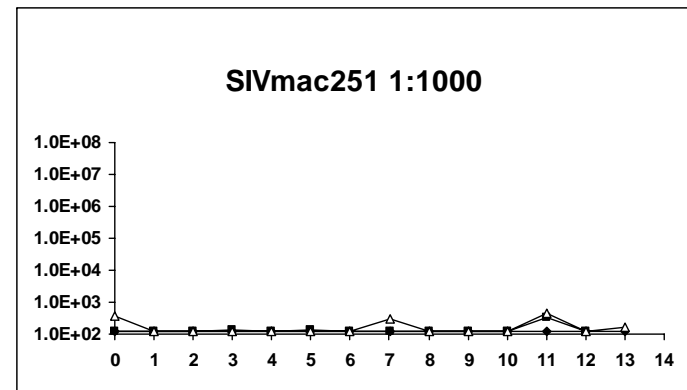
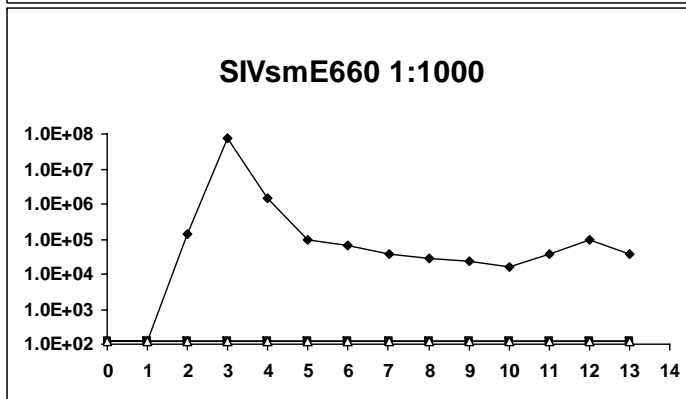
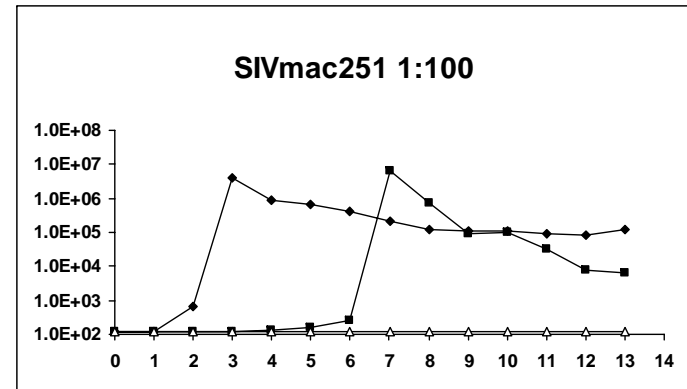
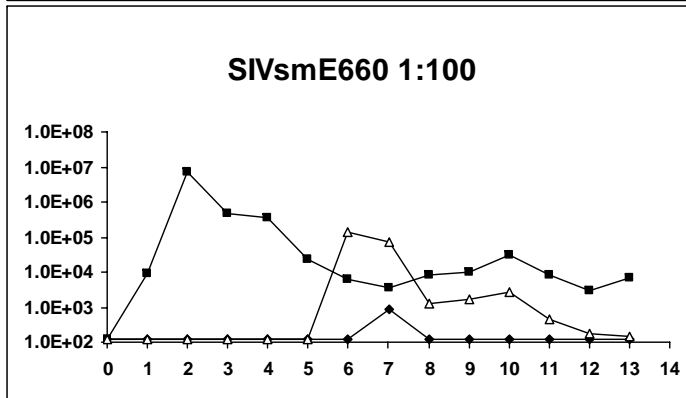
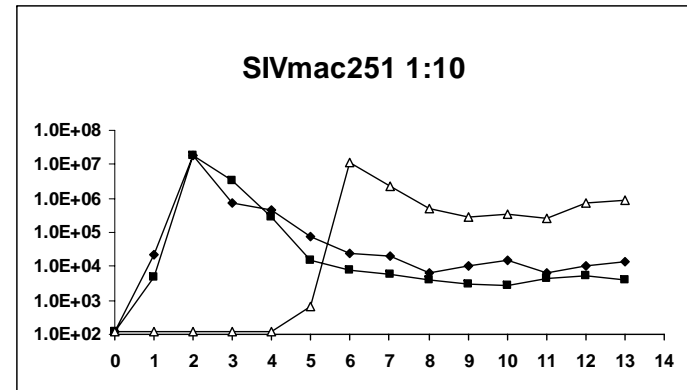
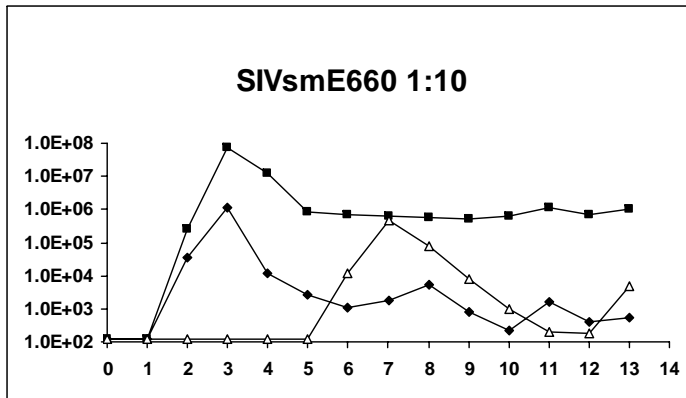
## Cohort of exposed, uninfected rhesus monkeys

- Repeated mucosal exposure
  - SIVmac251, SIVsmE660
  - doses of virus: 1:10 ( $6 \times 10^7$  copies), 1:100 ( $6 \times 10^6$ ), 1:1000 ( $6 \times 10^5$ )
  - 3 monkeys/dose
  - 6 weekly intrarectal exposures
- Monitored: plasma SIV RNA

# Infections following mucosal exposures

## weekly rectal x 6

RNA Copies/ml

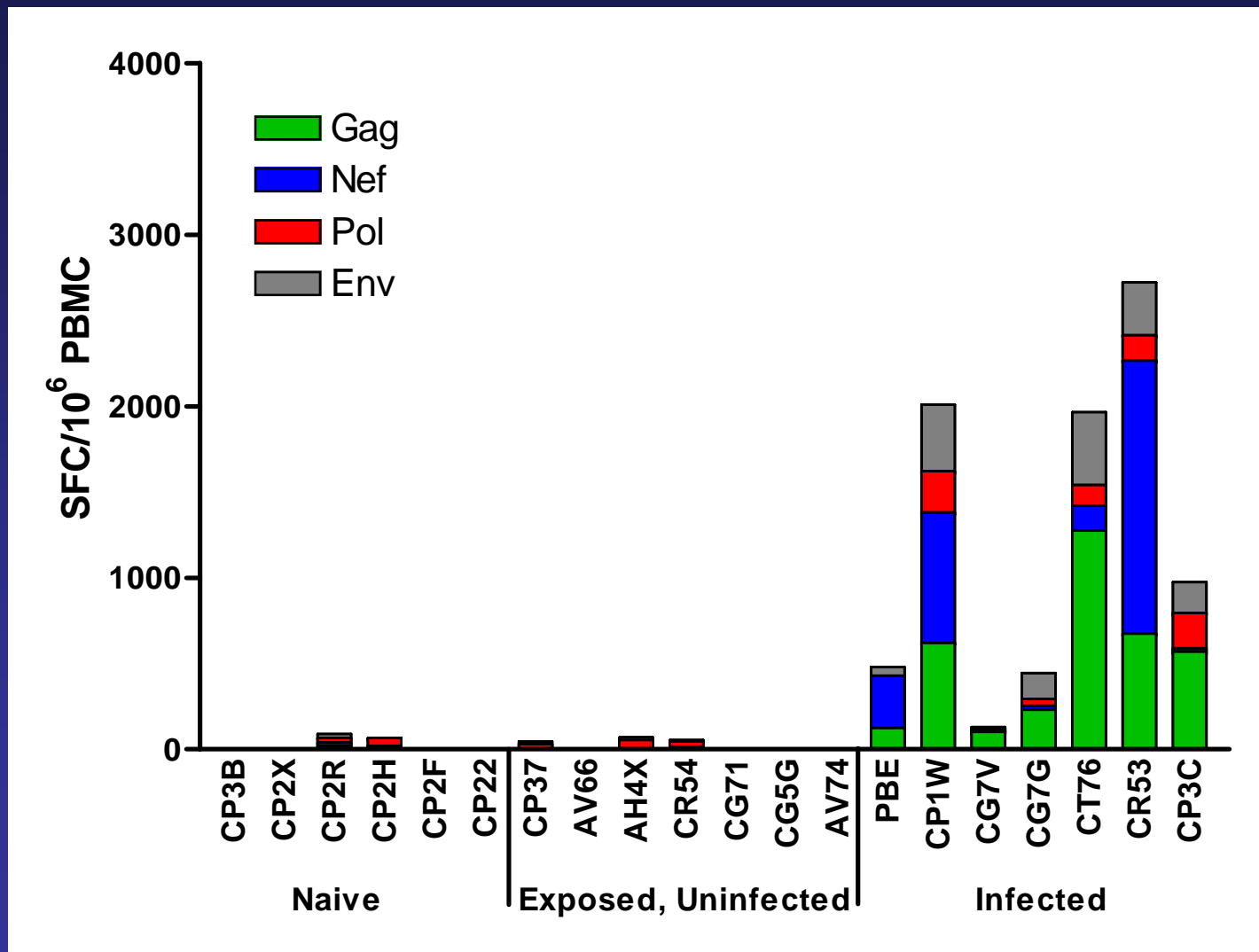


Weeks

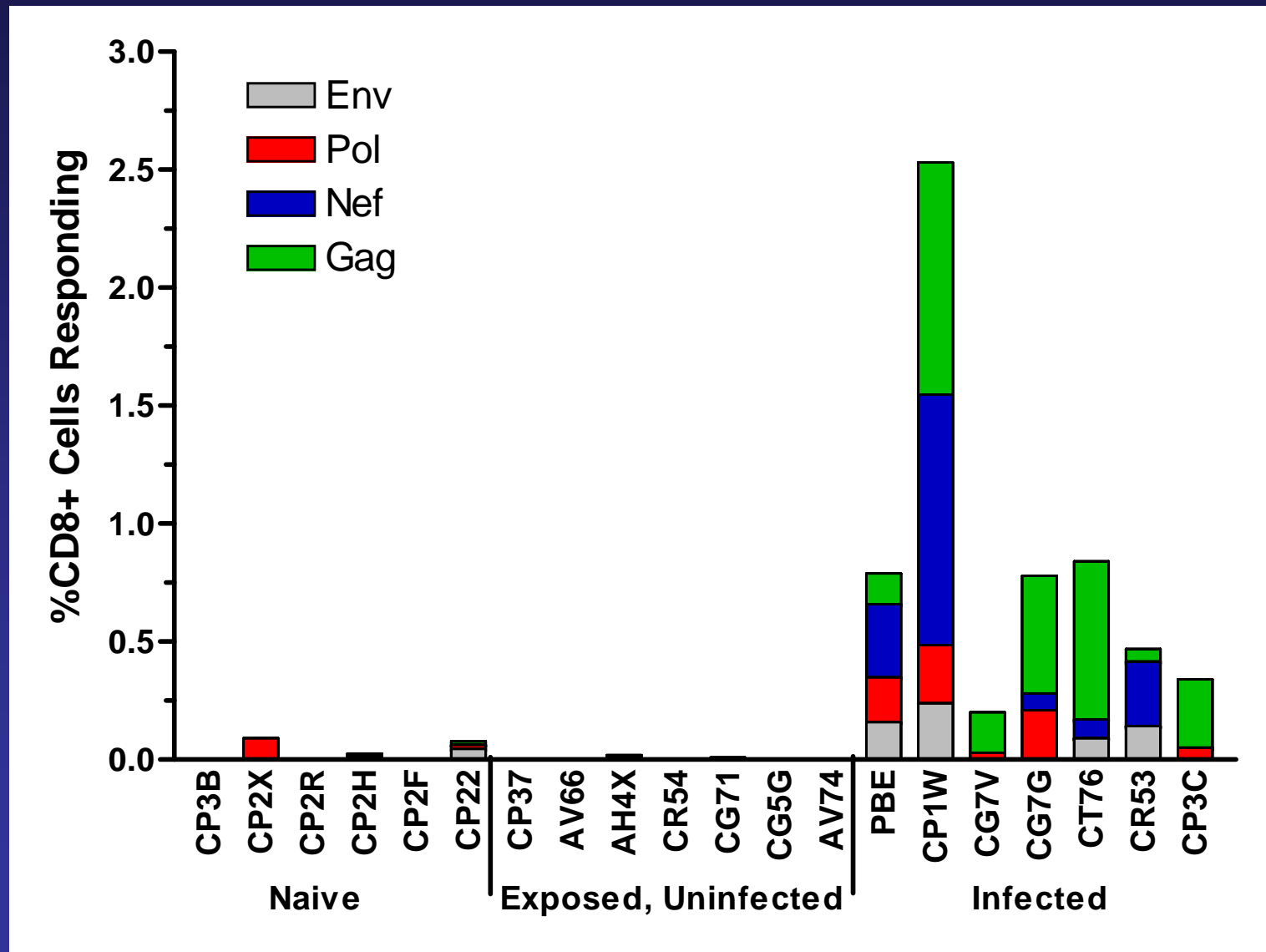
## **Cohort of exposed, uninfected rhesus monkeys**

- **7 exposed, uninfected monkeys**
  - **Evaluate SIV-specific T cell responses**
    - **Routine ICS, Elispot assays**
    - **Cytokine-augmented pooled peptide Elispot assay**

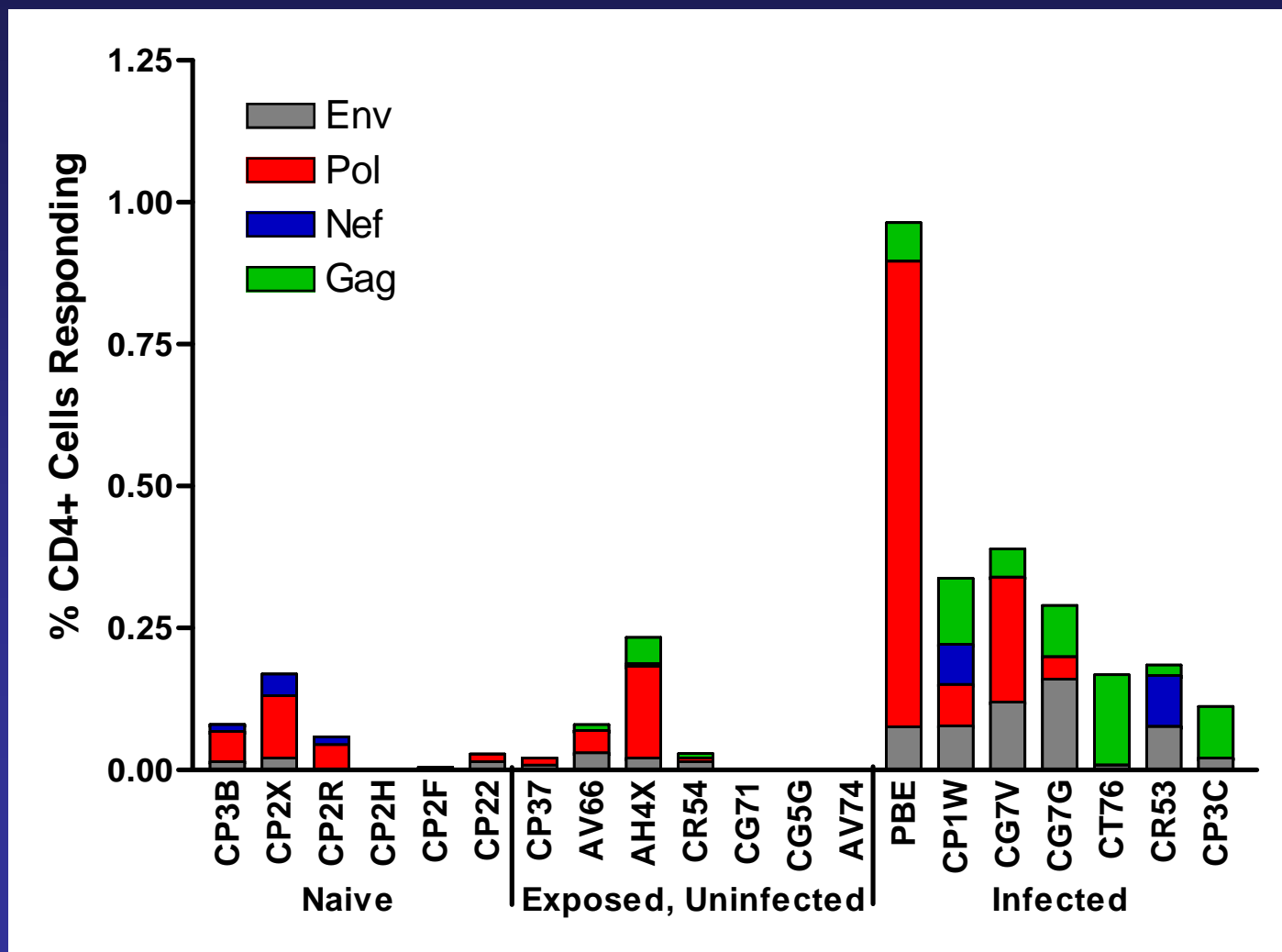
# Exposed, uninfected monkeys do not develop PBMC IFN $\gamma$ Elispot responses to SIV peptide pools



# Exposed, uninfected monkeys do not develop CD8+T cell MIP-1 $\beta$ responses to SIV peptide pools



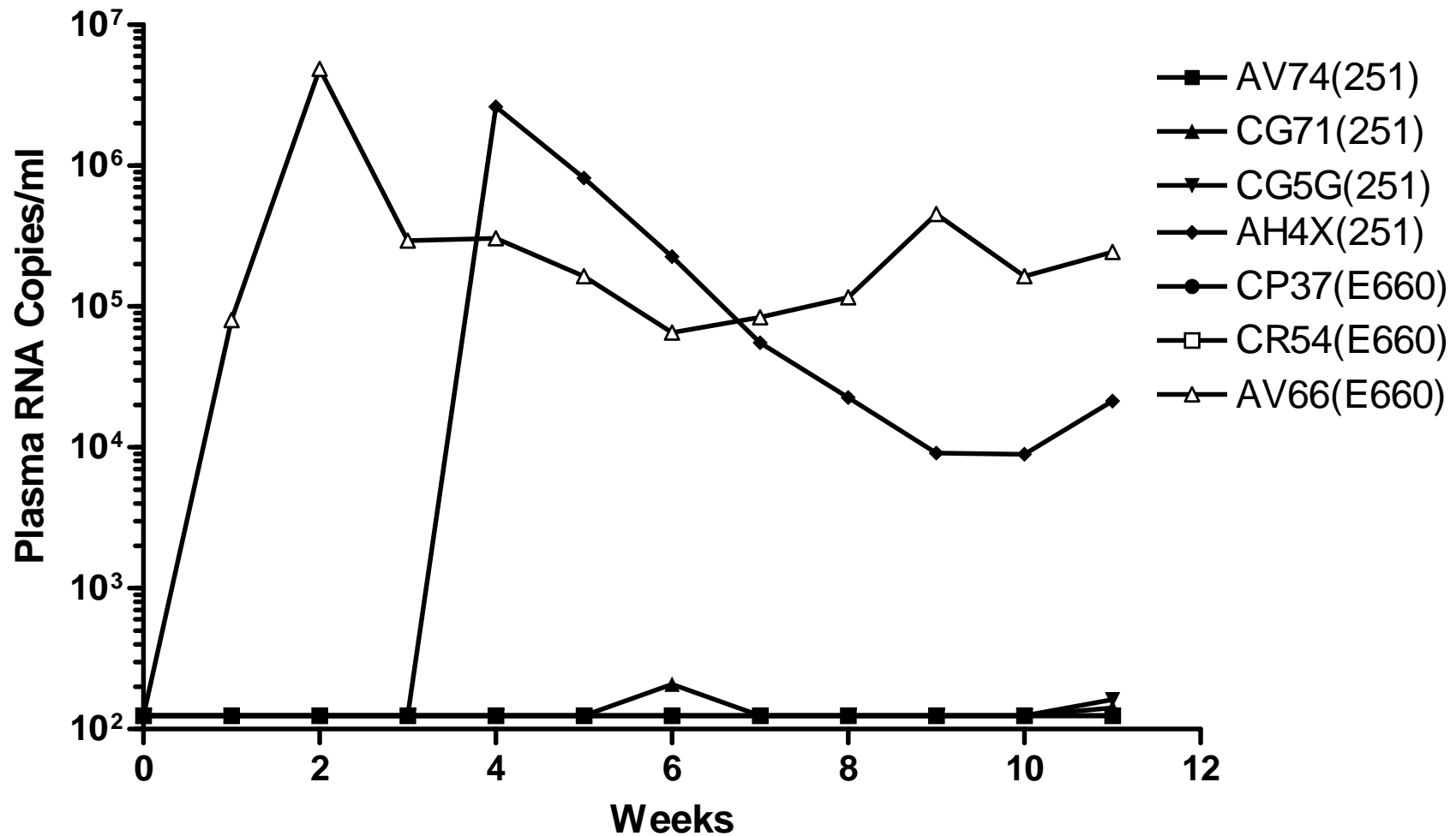
# Exposed, uninfected monkeys do not develop CD4+ T cell IFN- $\gamma$ responses to SIV peptide pools



## Exposed, uninfected monkeys

- Repeated cluster of 6 weekly i.r. exposures in 7 uninfected monkeys
  - Same inoculum
  - Plasma viral RNA monitored
- No further infections
- Another cluster of i.r. exposures with 1/10 dilution of virus

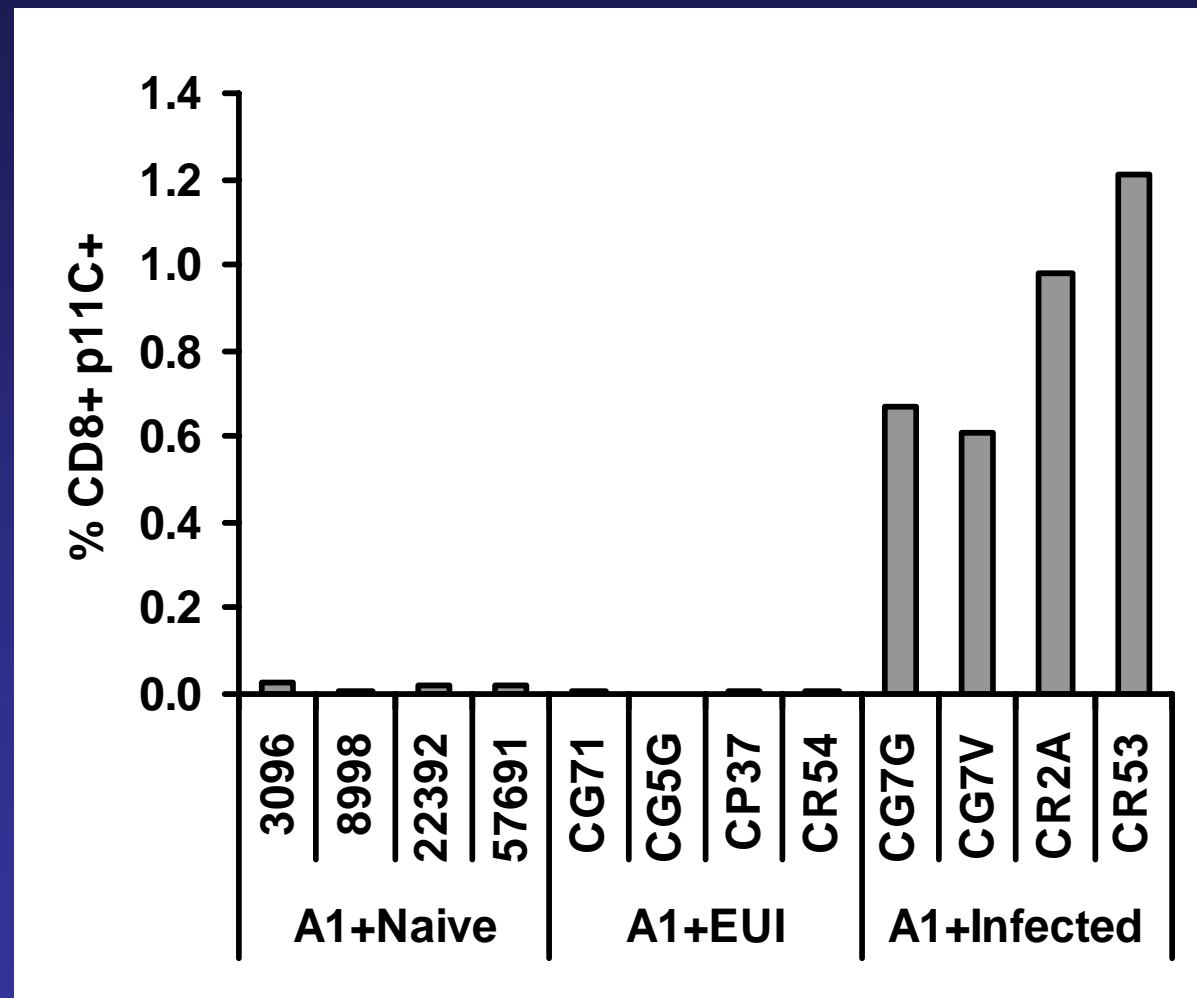
# Only 2 of 7 monkeys infected by 6 weekly i.r. exposures to 1:10 dilution of SIV



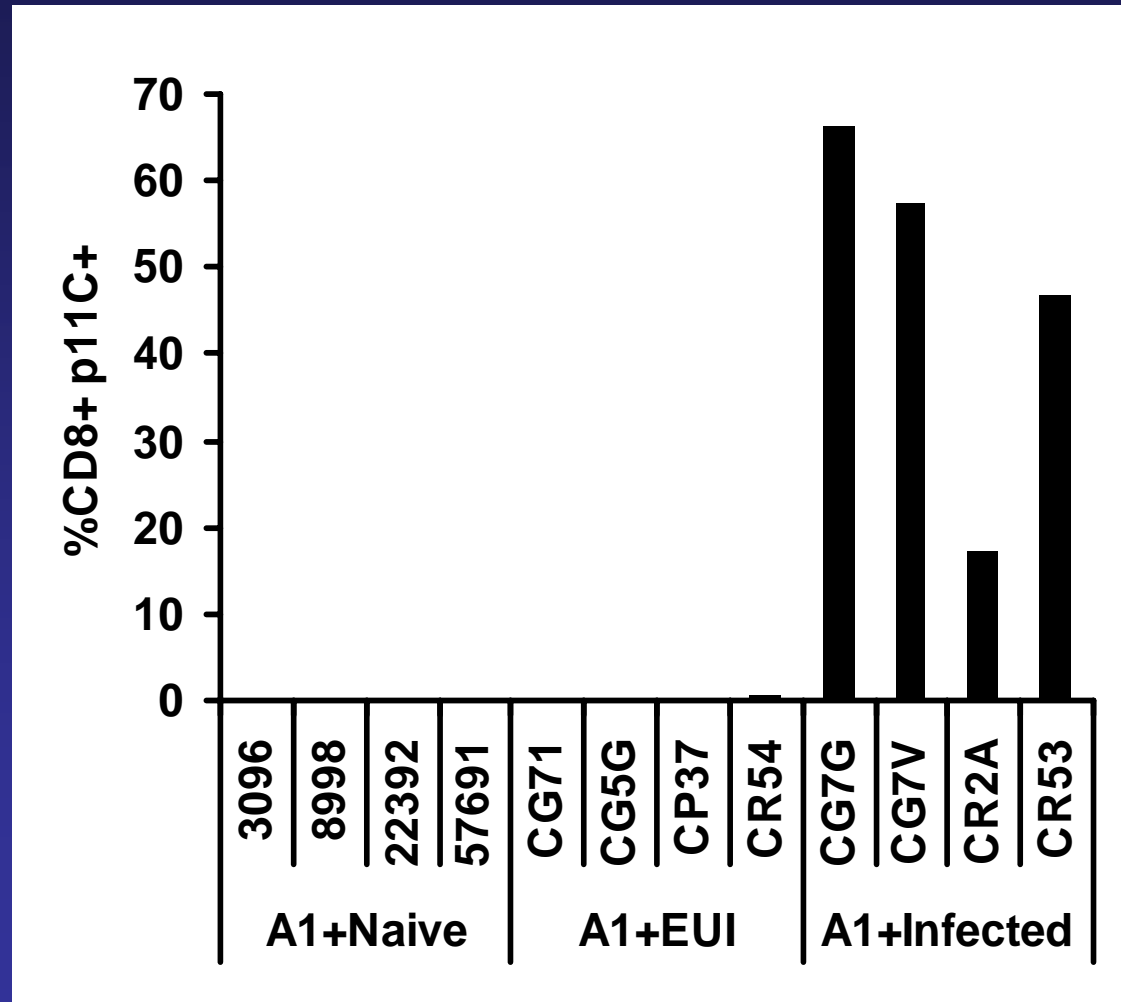
## Further evaluation of remaining uninfected monkeys

- **More sensitive T cell assays**
  - High frequency of Mamu-A\*01 allele in cohort
    - Original: 13/18
    - Remaining uninfected: 4/5
  - Tetramer assays: fresh and peptide-stimulated PBMC
- **Local mucosal immune responses**
  - Tetramer staining of rectal mucosal T cells

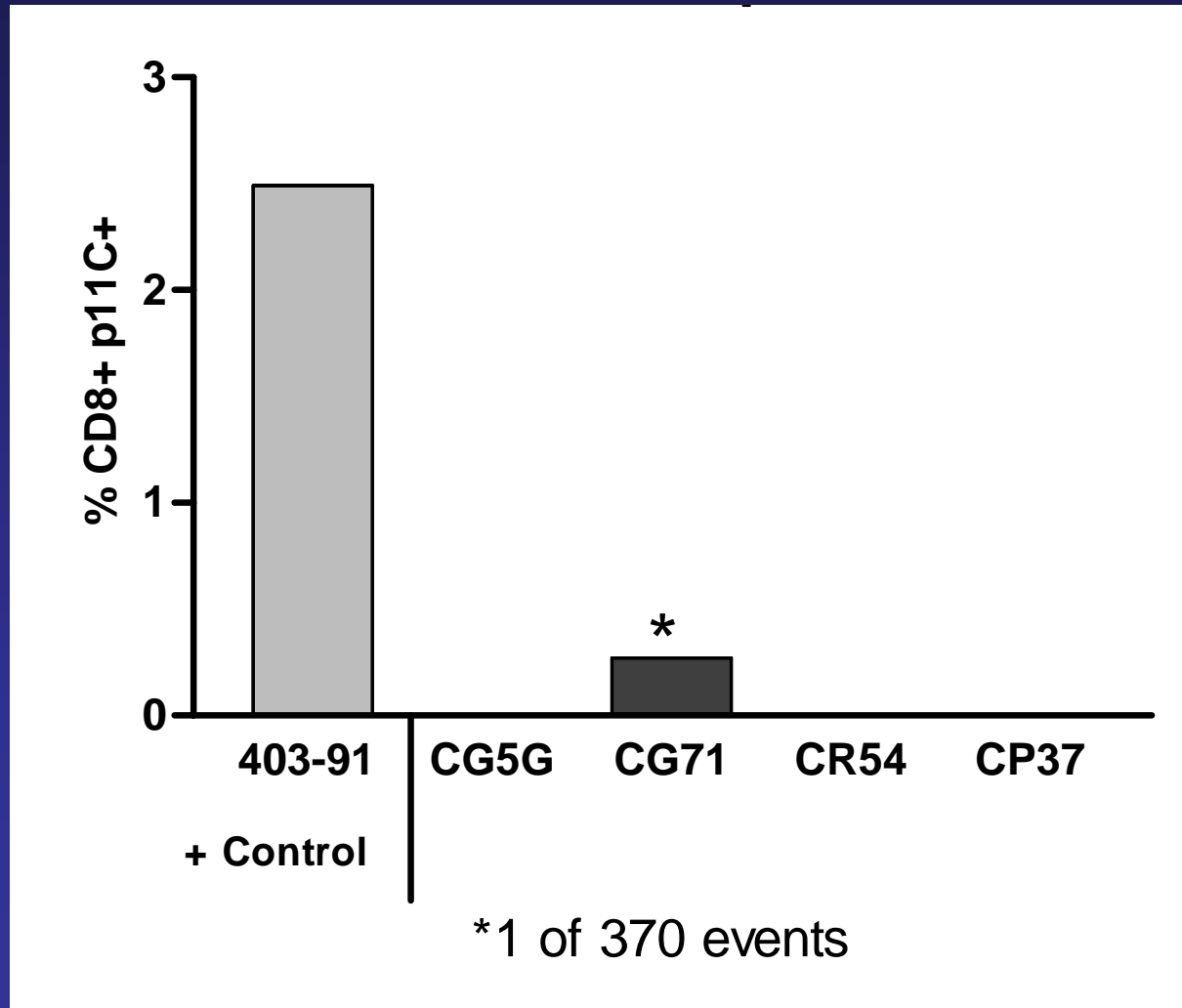
# Exposed, uninfected monkeys demonstrate no peripheral blood p11C tetramer-binding CD8+ T cells



# Exposed, uninfected monkeys demonstrate no peptide-stimulated tetramer-binding CD8+ T cells



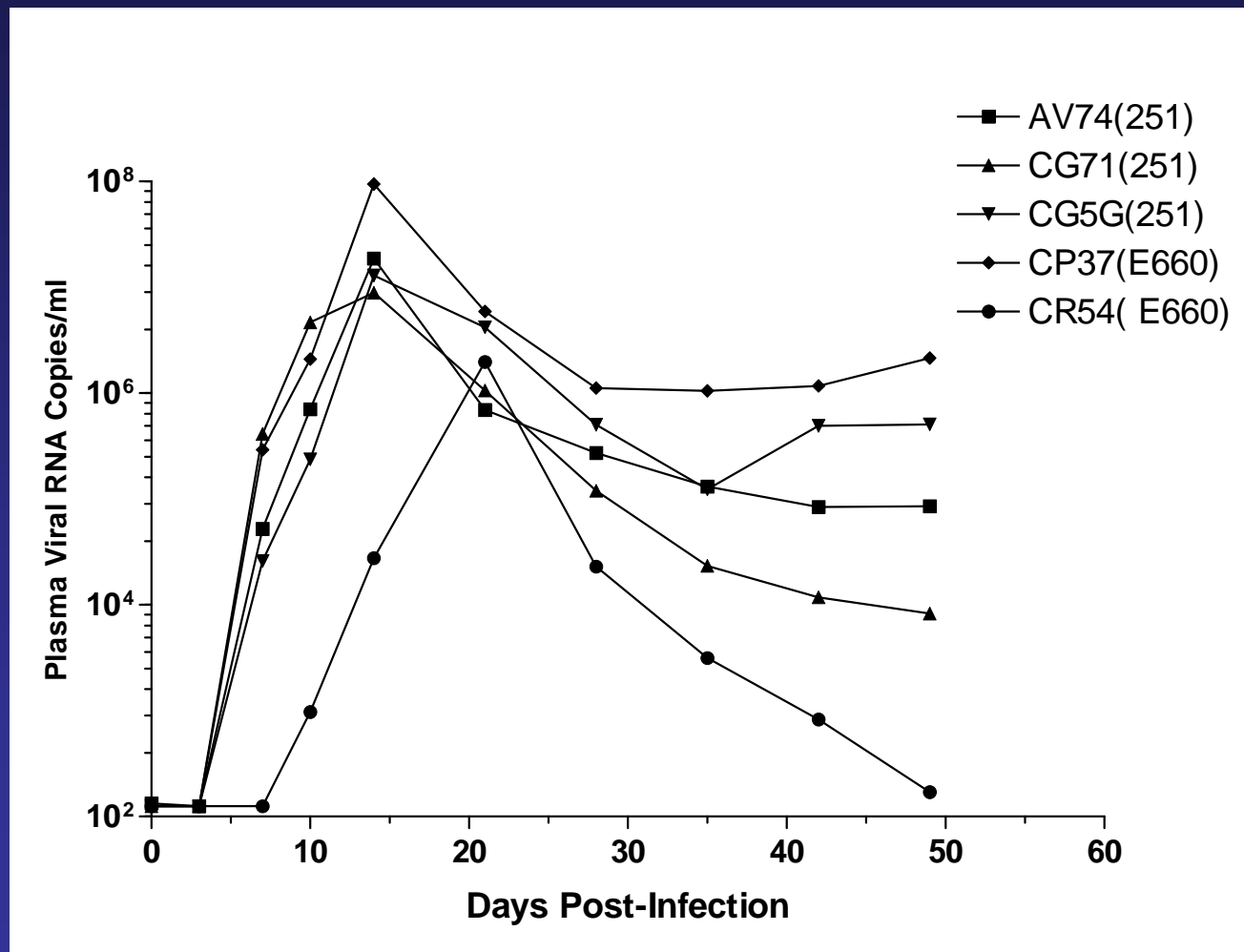
# Exposed, uninfected monkeys demonstrate no rectal mucosal p11C tetramer-binding CD8+ T cells



## Evaluation of mucosal antibody response in exposed, uninfected monkeys

- **New cohort of 6 monkeys**
  - 6 weekly intrarectal exposures to SIVE660
  - 1 week later sampled rectum with a sponge
- **5/6 remained uninfected**
- **No association between finding of low titer anti-SIV IgA antibody in rectal secretions and virus acquisition**

# Exposed, uninfected monkeys readily infected following i.v. virus inoculation



## Exposed uninfected rhesus monkeys

- **No virus-specific adaptive immunity**
  - **T lymphocyte responses**
    - **Elispot, routine and cytokine augmented**
    - **Intracellular cytokine**
    - **Tetramer**
    - **Mucosal tetramer**
  - **Antibody responses**
    - **Mucosal**
- **Readily infected by intravenous exposure**

# Exposed, uninfected rhesus monkeys

- **Exposed, uninfected SIV/macaque model**
  - 18 mucosal exposures → no infection
- **No convincing SIV-specific adaptive immune response**
  - Systemic
  - Mucosal
- **Mechanism other than adaptive immunity mediates resistance?**

# Acknowledgements

## Vaccine Research Center

Srini Rao

Vi Dang

John Mascola

Gary Nabel

## NIAID

Vanessa Hirsch

## Tulane University

Pam Kozlowski

## Harvard Medical School

Adam Buzby

Dilani Dombagoda

Jenny Parvani

Keith Reimann

Ryon Clarke

Liat Bar

Birgit Koriath-  
Schmitz