

**DEBATE ON HIV
ENVELOPE AS
A T CELL
IMMUNOGEN
HAS BEEN
GAG-GED**

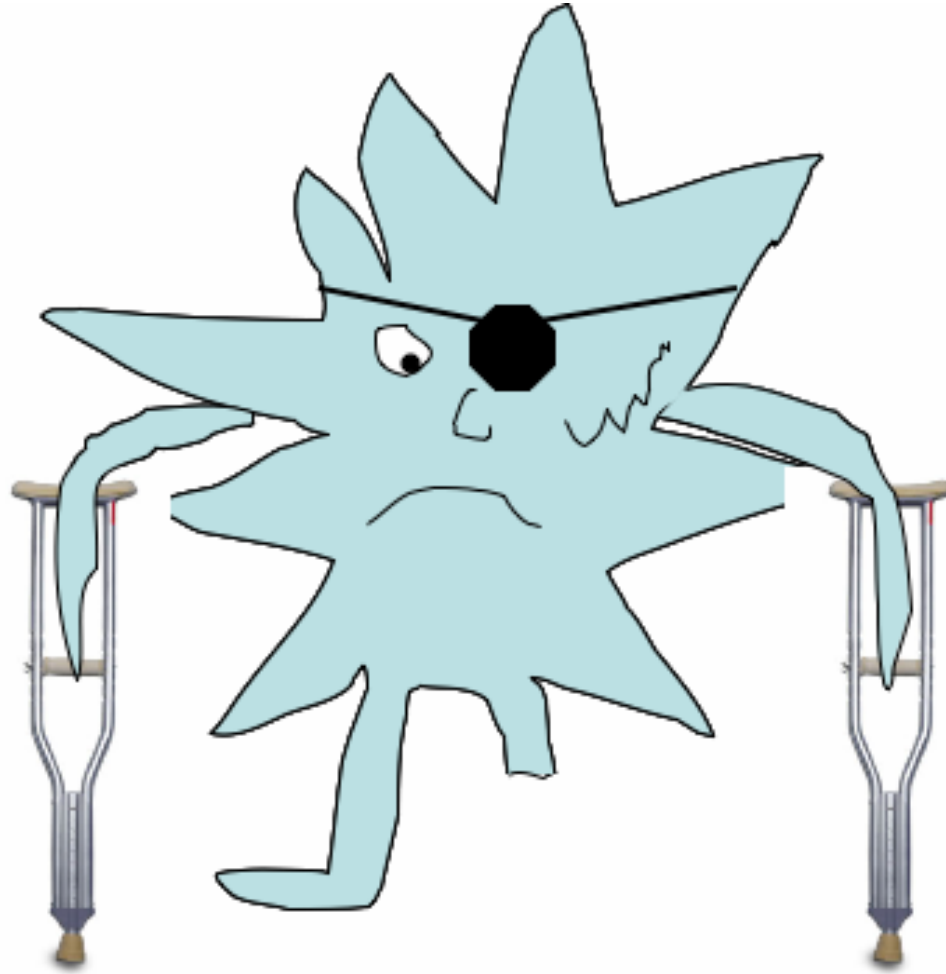
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WHY ENVELOPE?

- Env subject to both humoral and cellular immune responses
- Perhaps multiple rounds of mutation would be required for effective immune escape
- May result in virus with reduced fitness
- Lower viral fitness = Lower viral load (VL)
 - slower progression to disease
 - reduced transmission rates

VERY UNFIT VIRUS



HOWEVER.....

- Gag has recently been shown to elicit a more effective CD8 T cell response in humans.
- Broad Env-specific CTL responses correlated with higher levels of viremia.

(Kiepiela *et al.*, Nat Med 2007)

- Gag-specific CD8 T cell clones more efficient than Env-specific CD8 T cells in limiting viral replication *in vitro*.

(Chen, Walker, 4th IAS Conference, Sydney, 2007)

- Gag presented much earlier than other HIV proteins.

(Sacha *et al.*, J Immunol, 2007)

OUTLINE OF TALK

- What is VL outcome of macaques responding to Env vs those responding to Gag?
 - X4-SHIV trial analyzed
- What is the pattern of immune escape at Env compared to Gag?
 - Kinetics of escape
 - Diversity of escape motifs
- What is effect of therapeutic immunization with only Gag vs all SIV proteins?
 - R5-SIVmac251 study
 - Viral load
 - Immunodominance

THE SHIV_{mn229} TRIAL IN 30 PIGTAIL MACAQUES



Vaccination

SHIV DNA and fowlpoxvirus vaccines expressing Gag and Env (De Rose *et al.*, J Virol, 2007)

- HIV-1 Env truncated - no induction of neutralizing antibodies (NAb)

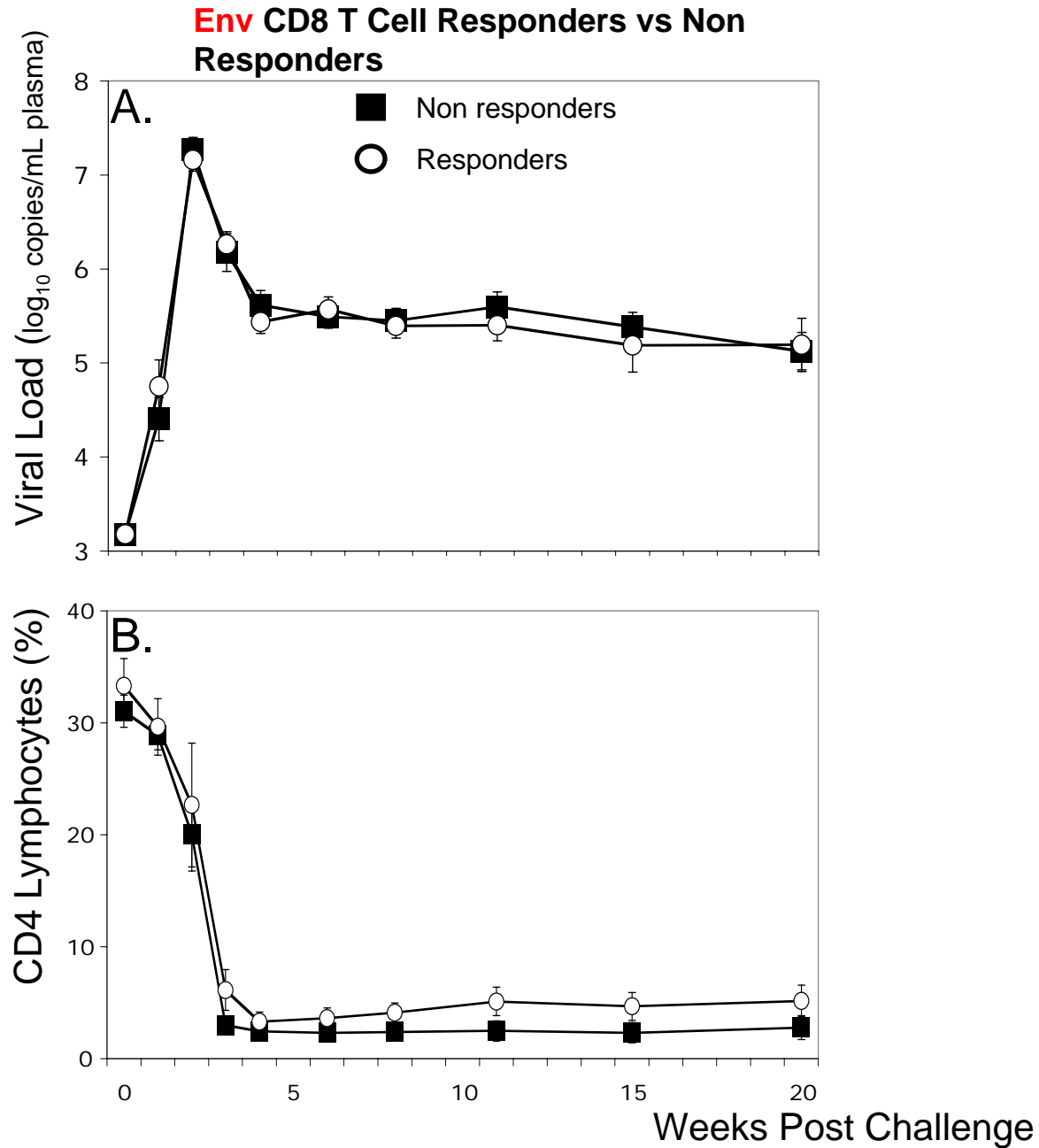
Challenge

Heterologous X4-utilising SHIV_{mn229}

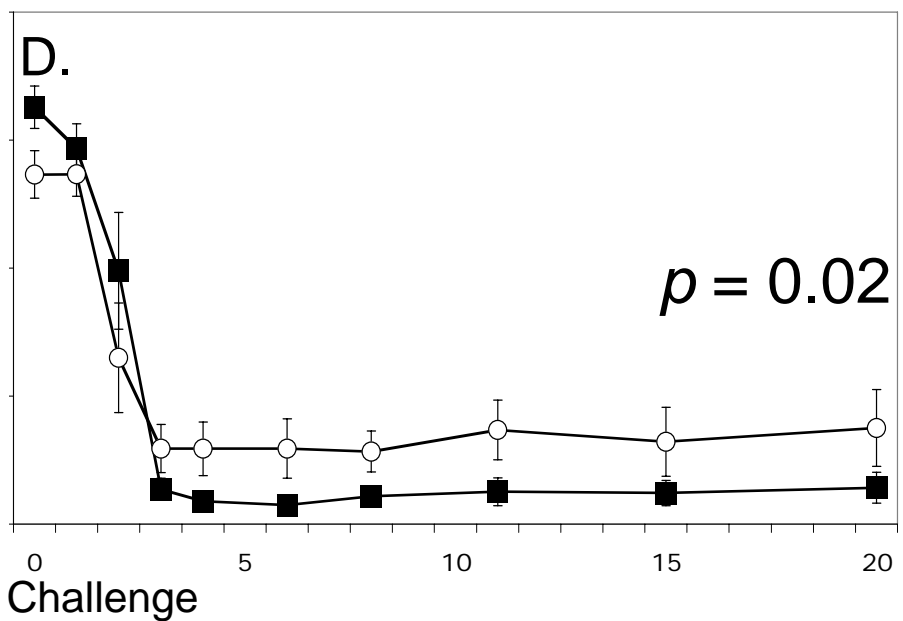
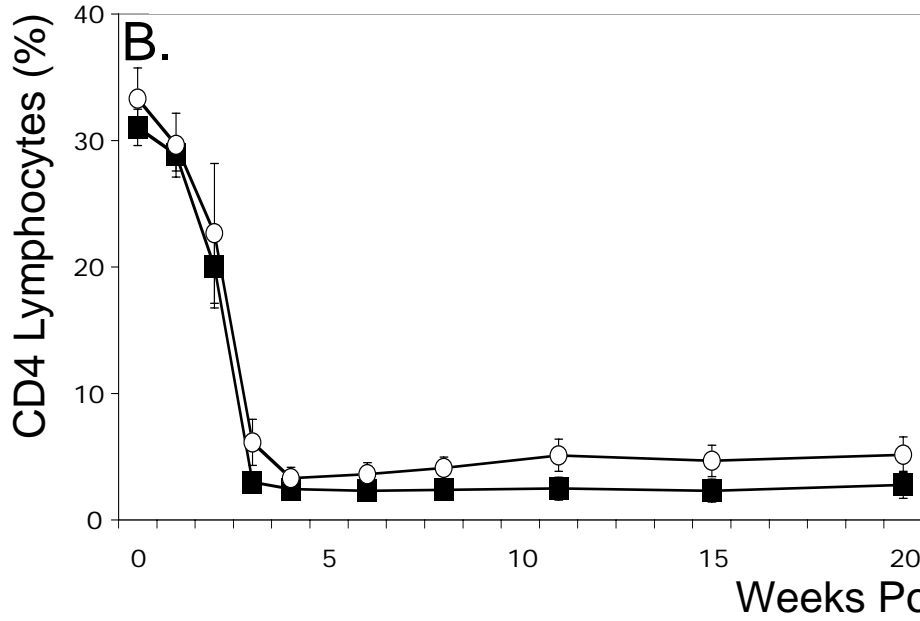
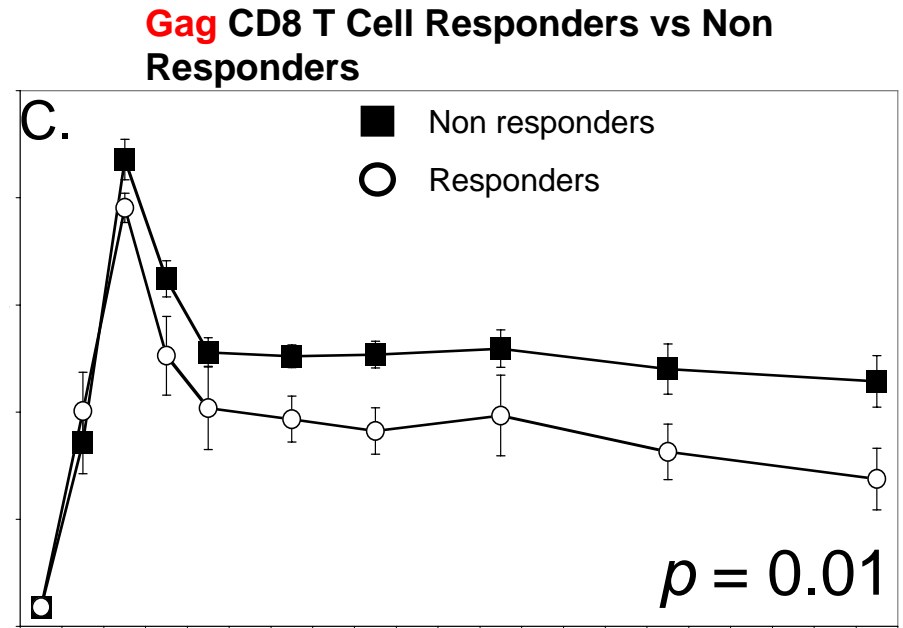
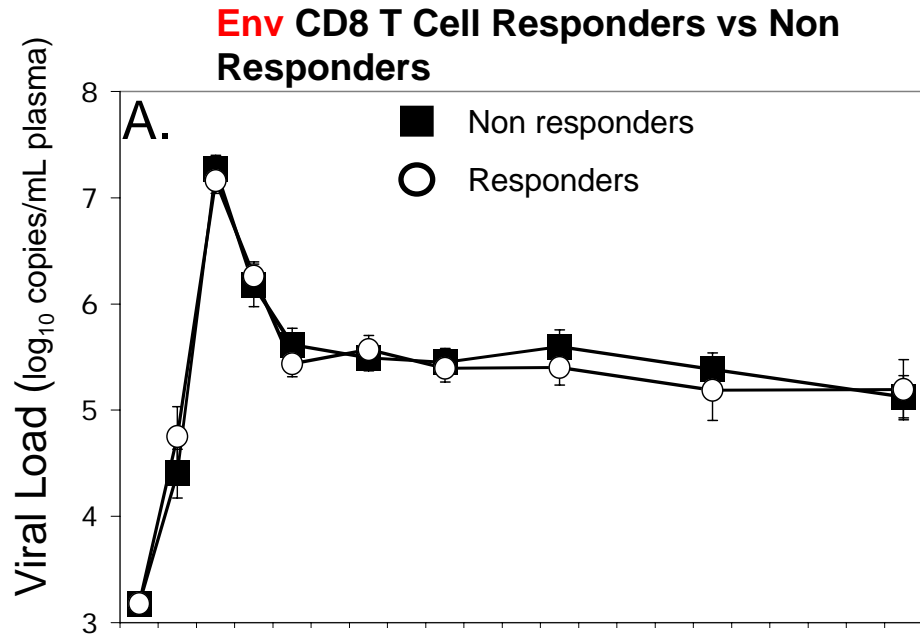
Env-specific T cell epitope identification

Eight Env-specific CD8 T cell epitopes mapped in 10 animals identified by Intracellular cytokine staining (ICS)

VL AND CD4 LEVELS - ENV vs GAG

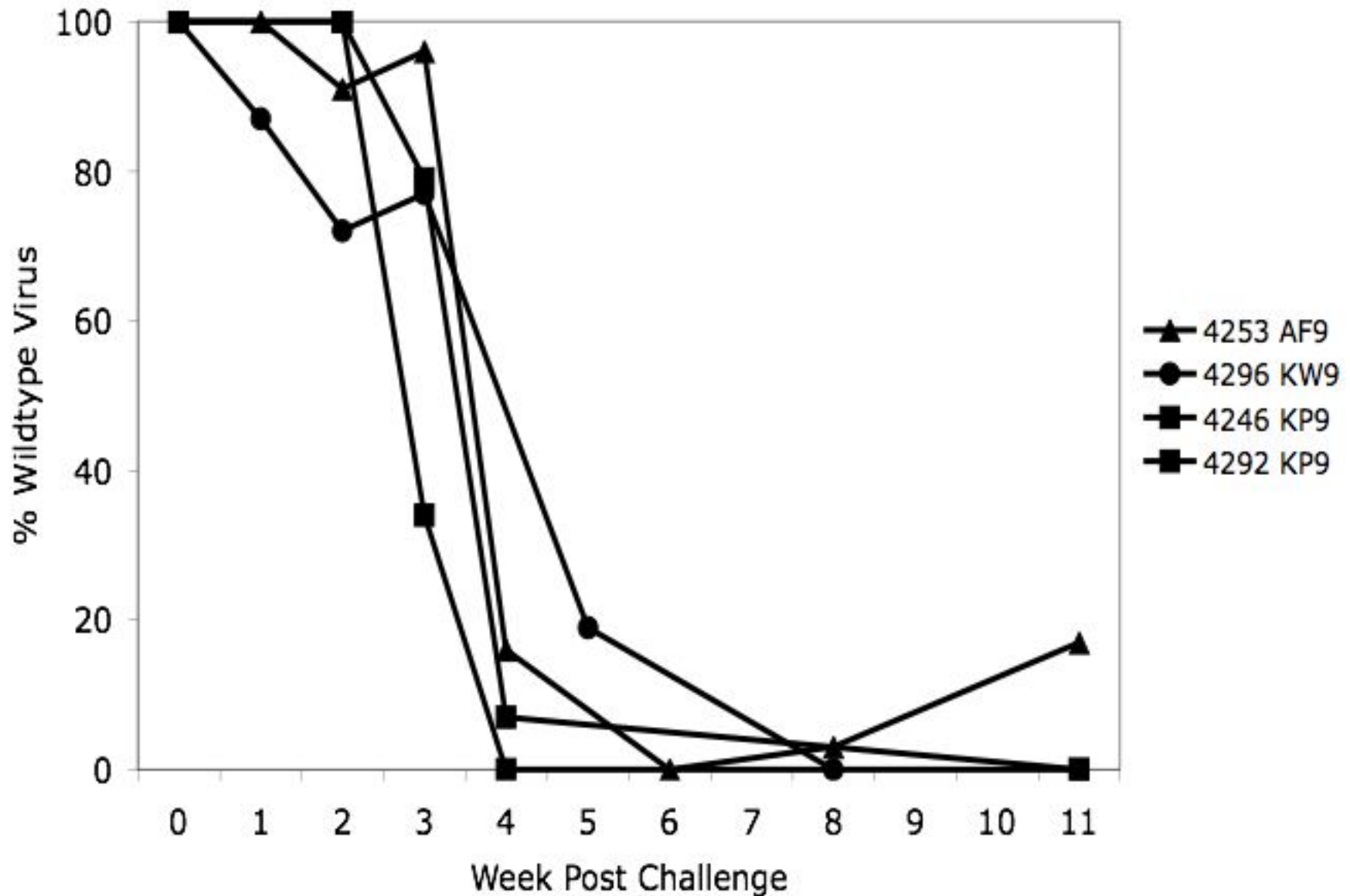


VL AND CD4 LEVELS - ENV vs GAG



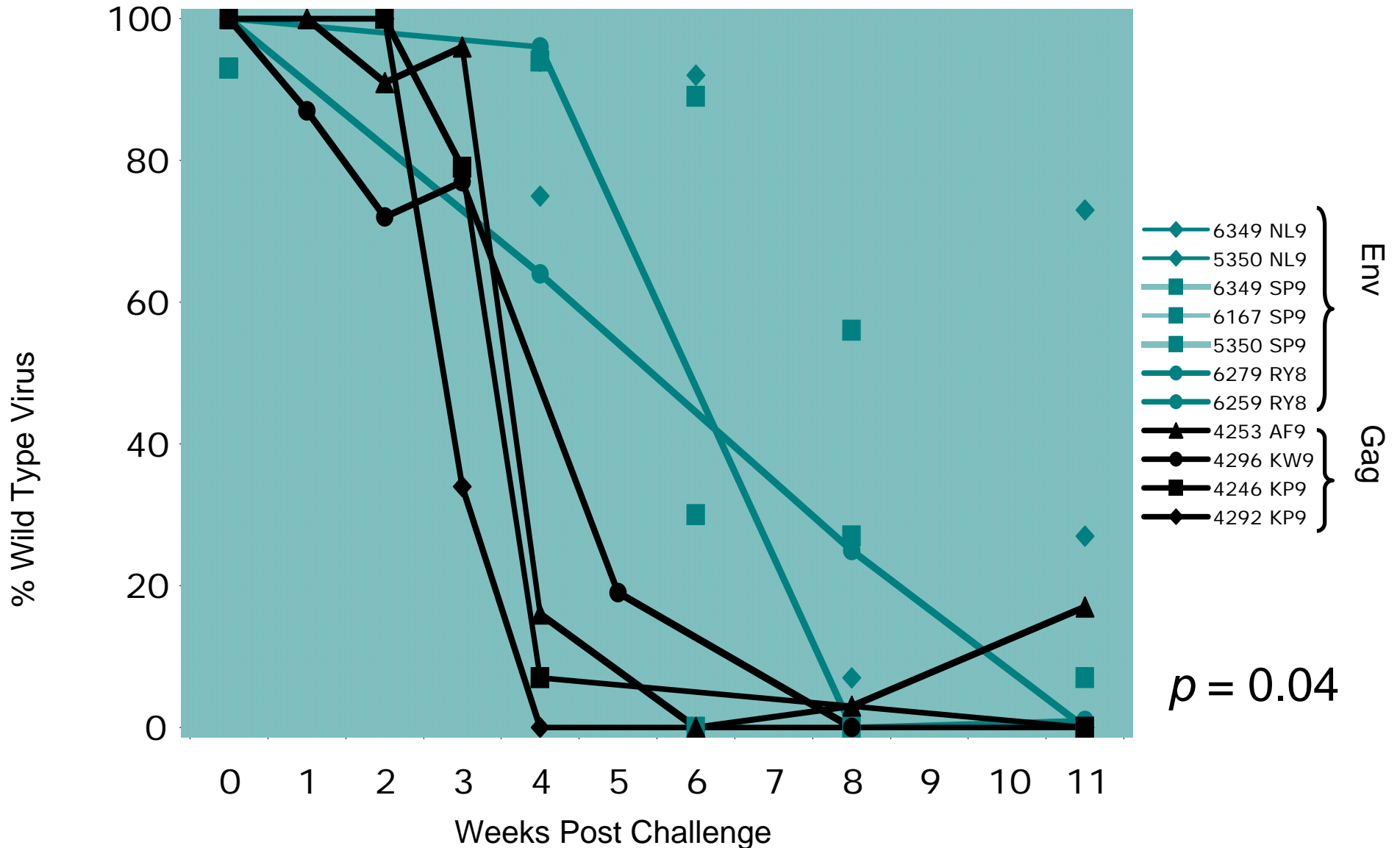
KINETICS OF ESCAPE - ENV vs GAG

Gag epitope kinetics (Loh *et al.*, J Virol, 2007) Poster #PO8-08

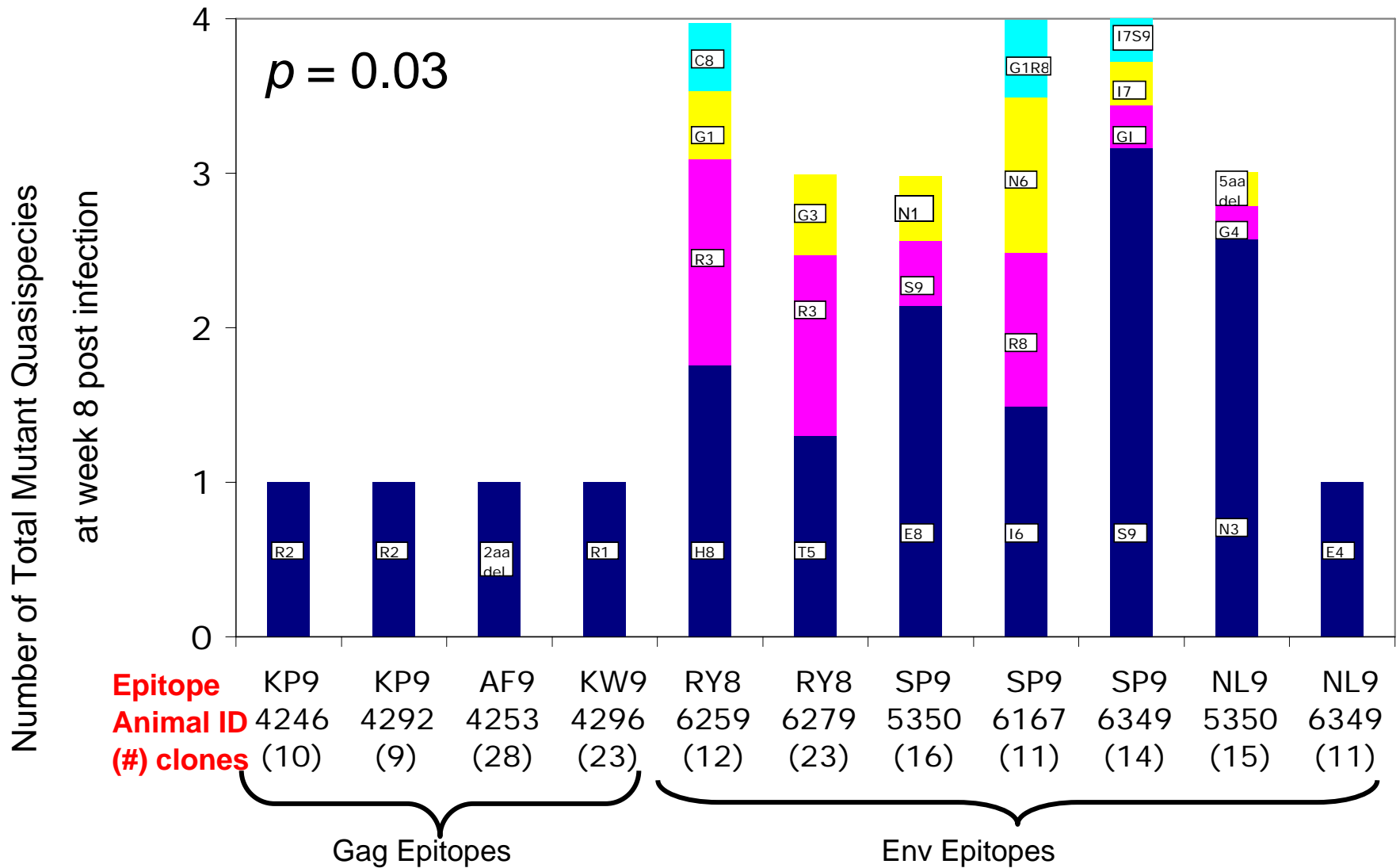


KINETICS OF ESCAPE - ENV vs GAG

Gag vs Env epitope escape kinetics



NUMBER OF MUTANT QUASISPECIES - ENV vs GAG

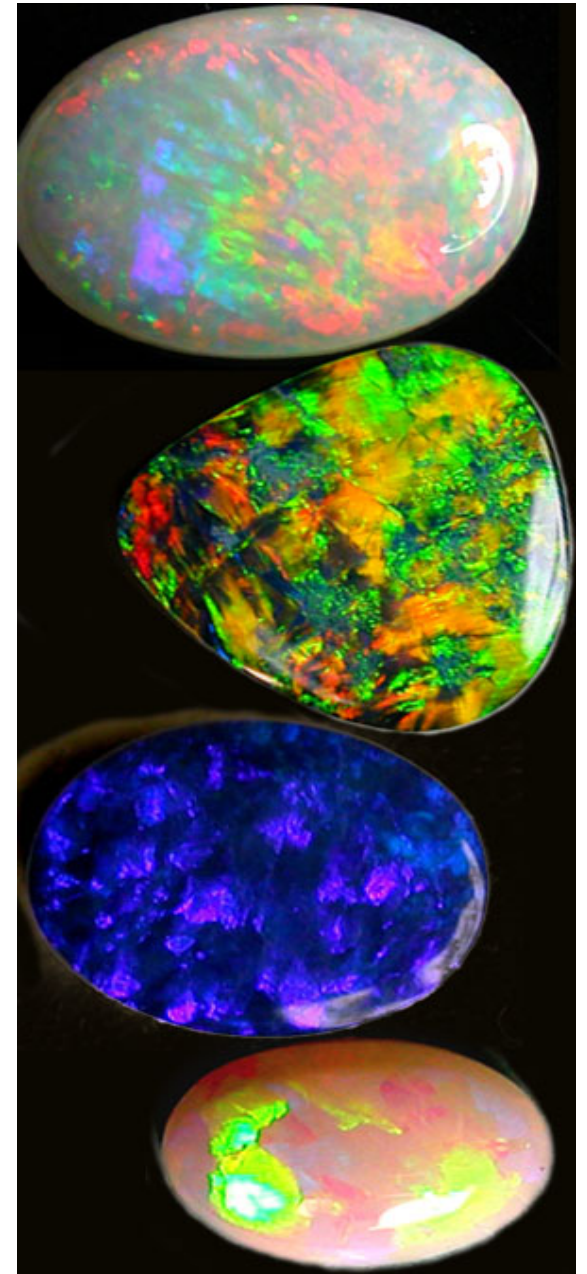


BROAD vs NARROW RESPONSE

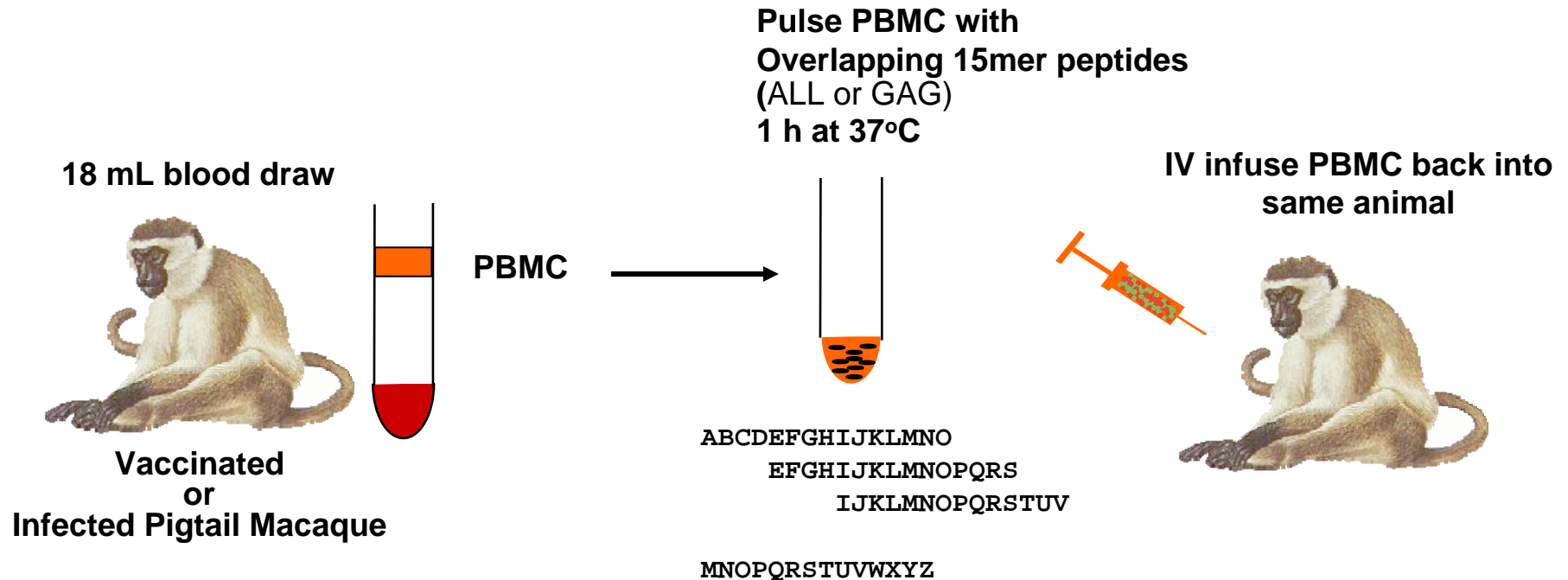
Compare Gag and Env - specific CD8 T cell responses elicited by a Gag, Env, Pol and accessory proteins combined (**OPAL AII**) vaccination with a Gag-alone vaccination (**OPAL Gag**).

Overlapping
Peptide-pulsed
Autologous
Leukocytes

(Kent *et al.*, Poster, #P09-06)



OPAL - WHAT IS INVOLVED

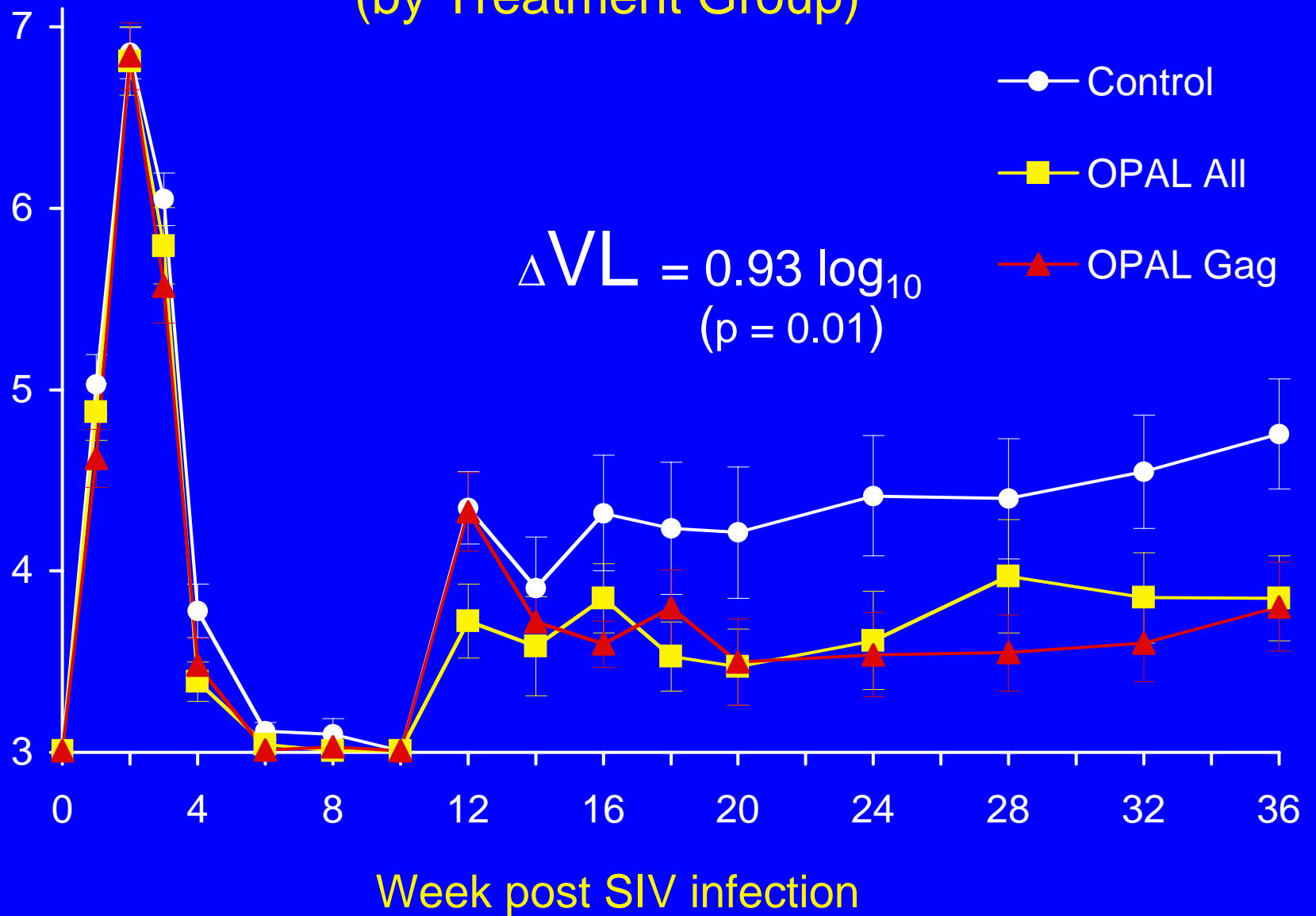


Experimental Design

- * 36 pigtail macaques
- * Infected with SIVmac251
- * Treated with antiretrovirals (Tenofovir, FTC)
- * Immunised with
 - Gag peptide
 - All SIV peptides (including Gag)
 - Controls
- * Recrudescence of VL studied

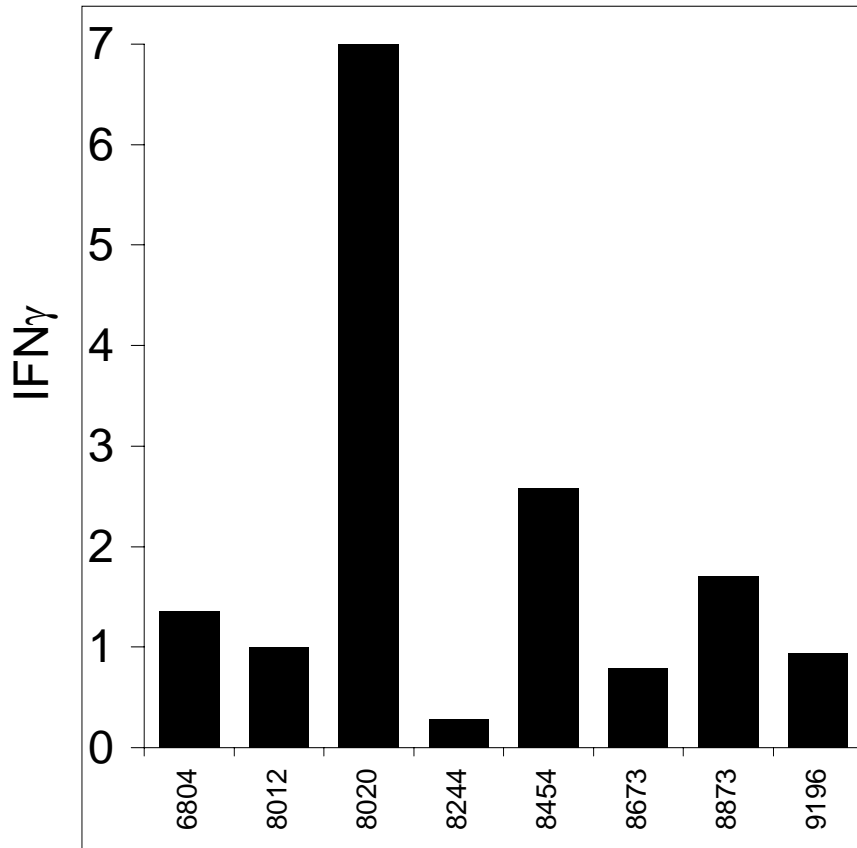
Viral Load

(by Treatment Group)

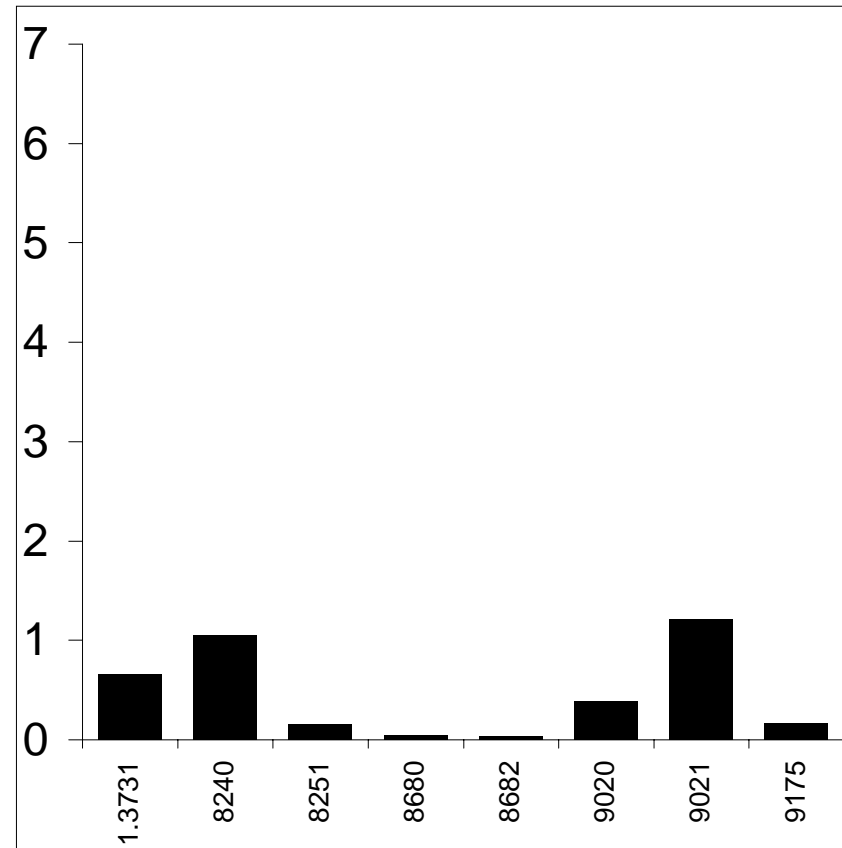


GAG-SPECIFIC CD8 T CELL REPNONSES

Gag responses - OPAL Gag



Gag responses - OPAL All

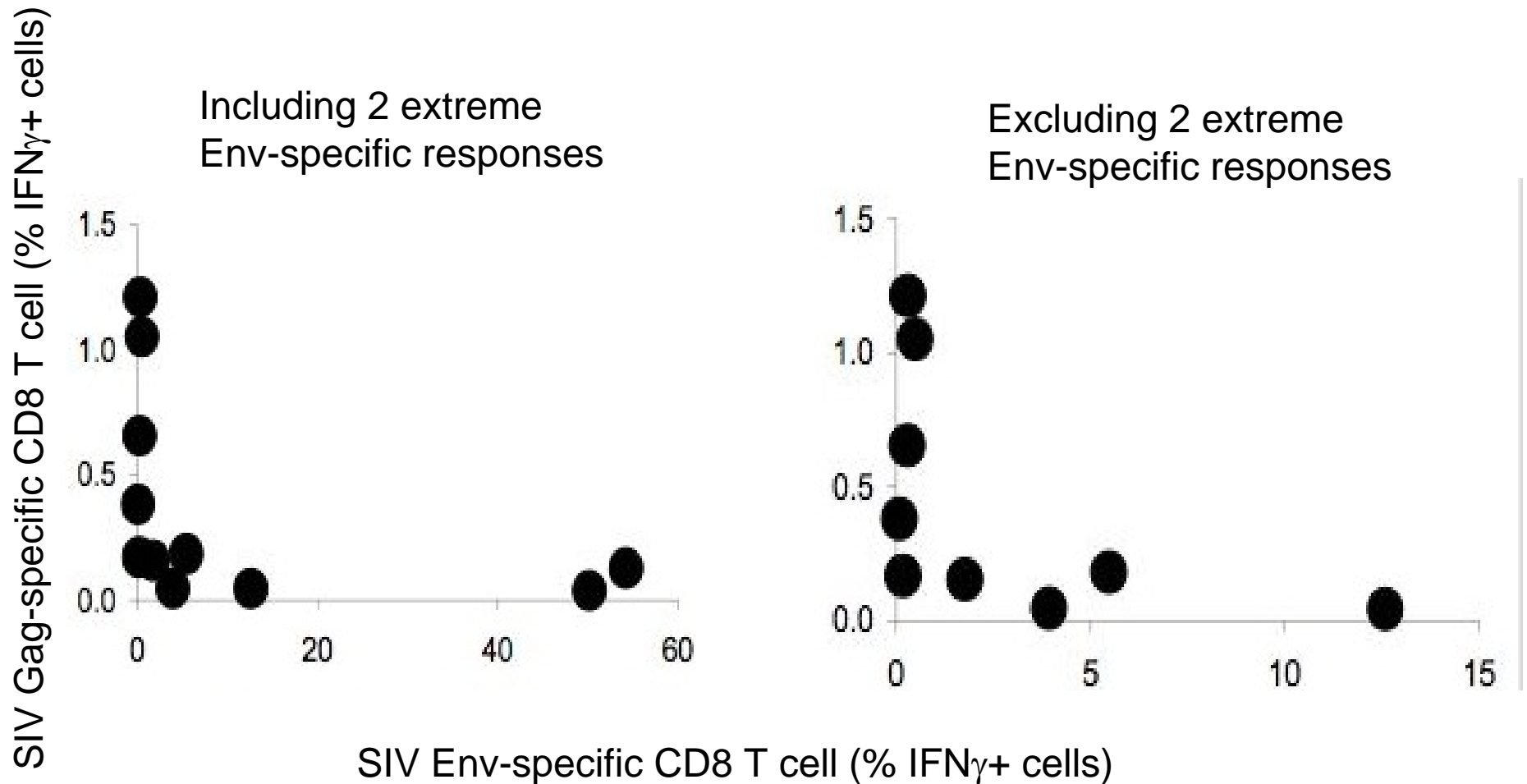


Animal ID

At same dose of Gag in both groups, why are Gag responses reduced in the OPAL All group???

NEVER THE TWAIN SHALL MEET - Gag \circledast Env but rarely both

Week 12 post infection in the ALL group



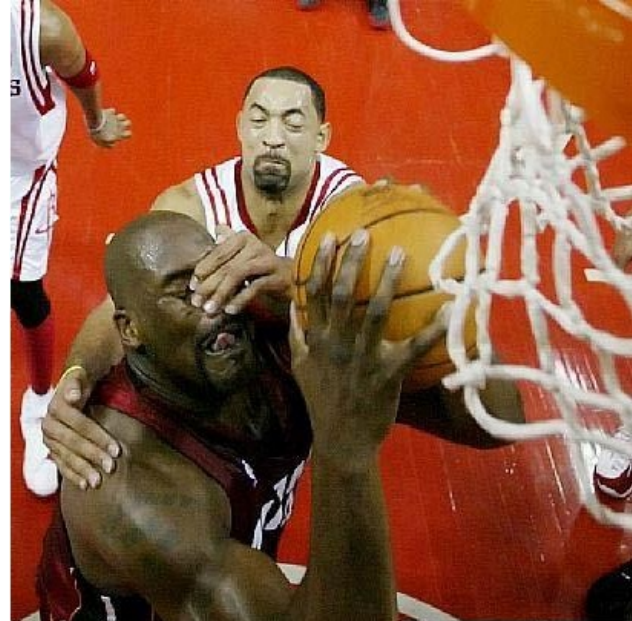
DOMINANCE?





DOMINANCE?







COMPETITION?









IN A NUT SHELL

Characteristics	Gag	Env
Maintain lower viremia		








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Early and rapid CD8 T cell escape (Gag-specific CTL exerts vigorous selection pressure)		

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Low diversity of escape mutants (Gag more constrained in its “mutational manoeuvres”)		

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Maintain lower viremia		
Early and rapid CD8 T cell escape (Gag-specific CTL exerts vigorous selection pressure)		
Low diversity of escape mutants (Gag more constrained in its “mutational manoeuvres”)		
Strong response regardless of other CD8 T cell responses (broadest multi-protein responses may not always be the most useful)		

FUTURE WORK

- Are a subset of HIV Env-specific T cell responses helpful?
- Prevent Env responses dominating Gag responses
- T cell mapping and escape studies in SIV Env
- Explore the relationships between CD8 T cell escape, NAb escape and N-linked glycosylation sites.

(Peut *et al.*, Poster #P03-06)

ACKNOWLEDGEMENTS

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AIDS Vaccine 07



NHMRC

NIH

Australian-Thai HIV Vaccine consortium

Viral Load Env Responders and Gag Responders OPAL SIVmac251 Trial

