

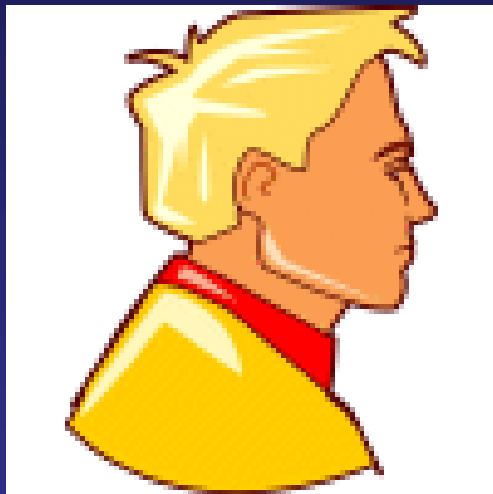
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HIV-1 escape from a HLA-B*13 epitope in p1 Gag: fitness cost and functional consequences

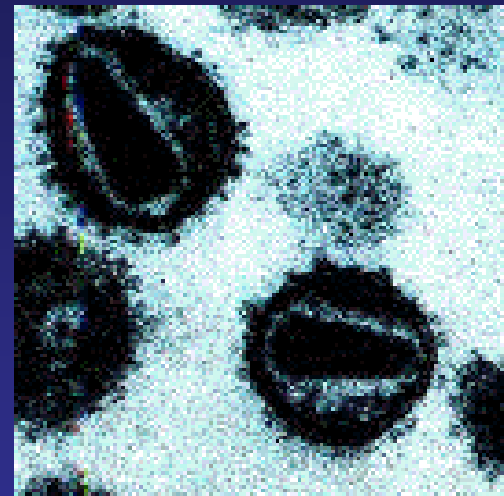
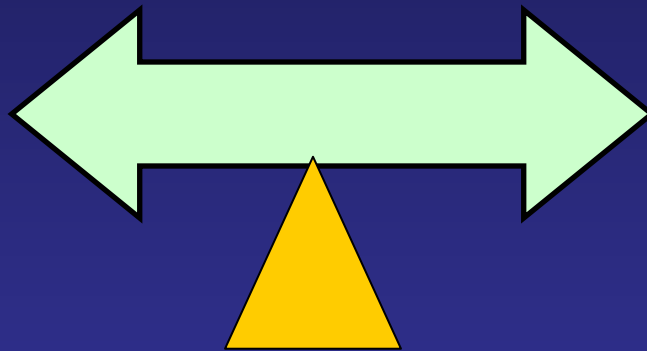
Julia G. Prado

University of Oxford

HIV-1 infection and host



HLA



CTL escape

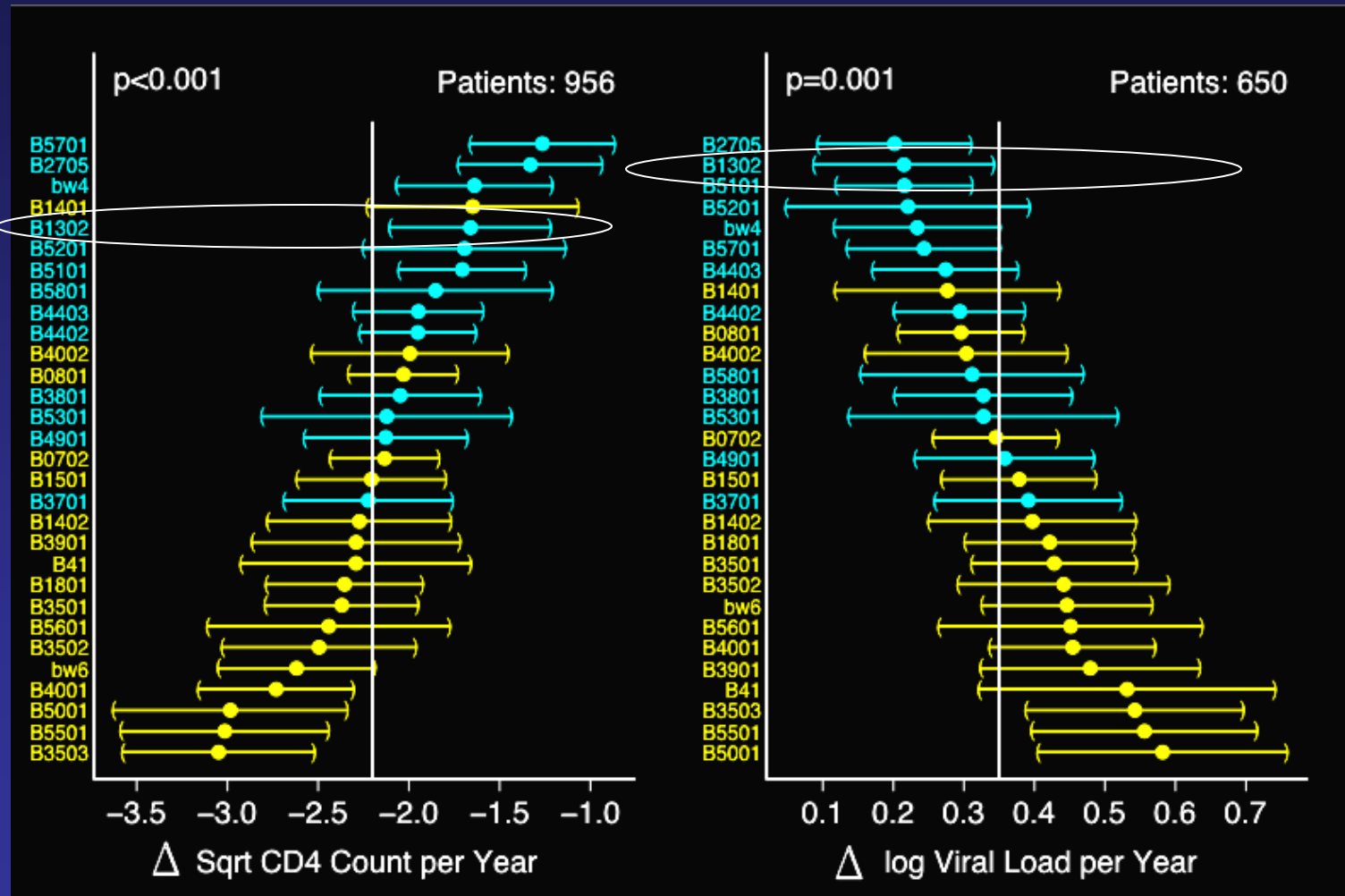
Some evidence...

- The breadth of Gag CTL responses is associated with control of HIV-1 replication. (*Kiepiela et al 2008, Edwards et al 2002...*).
- Low viral fitness p24 Gag CTL escape mutants (TW10, KF11, KK10) can contribute to control HIV replication. (*Martinez-Picado et al 2006, Crawford et al 2007, Brockman et al 2007, Schneidewind et al 2008...*).

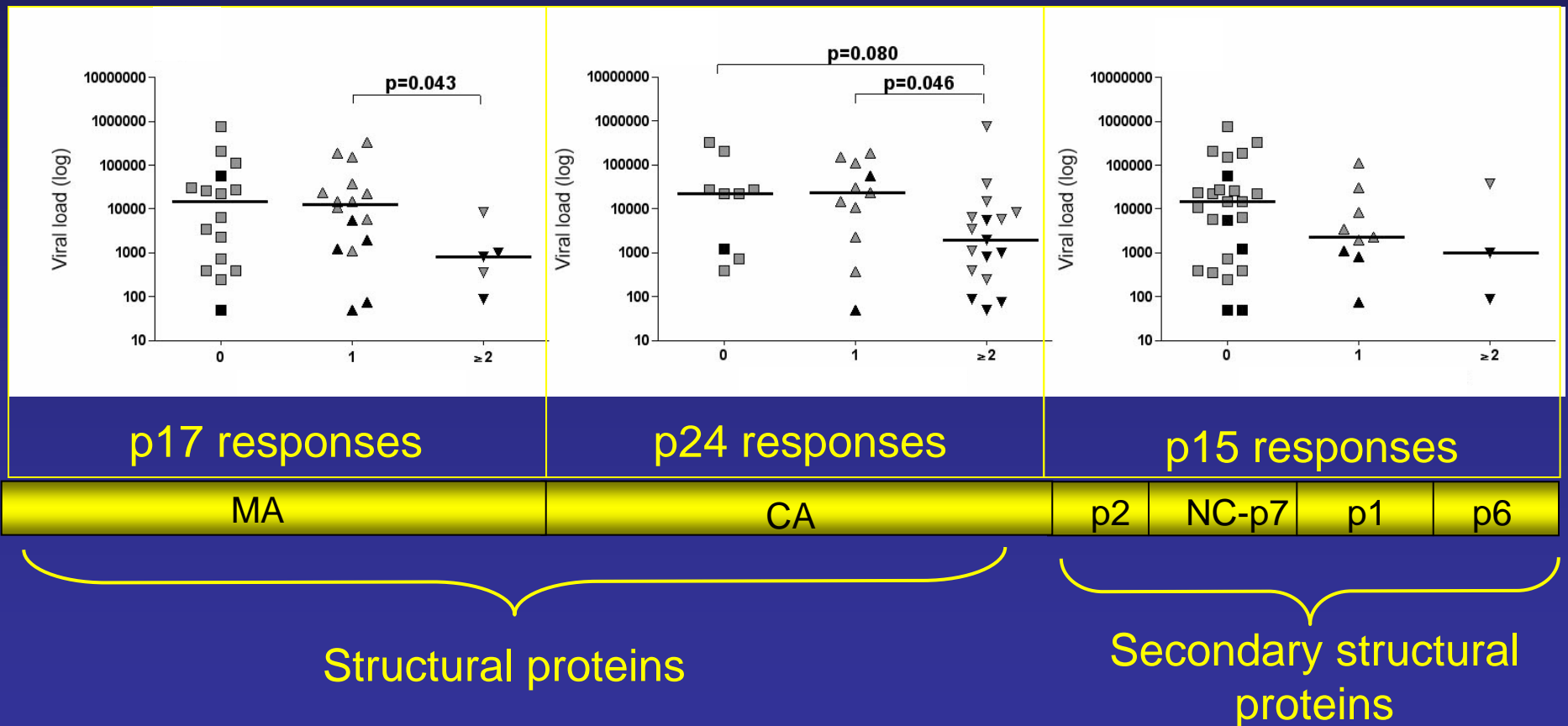
AIM

- HLA-B*13 - characterization of CD8+ T cell escape mutants in a secondary Gag structural region of the HIV genome.

Why look at individuals with HLA-B*13?



Number of Gag responses in individuals B*13 is associated with reduction in VL



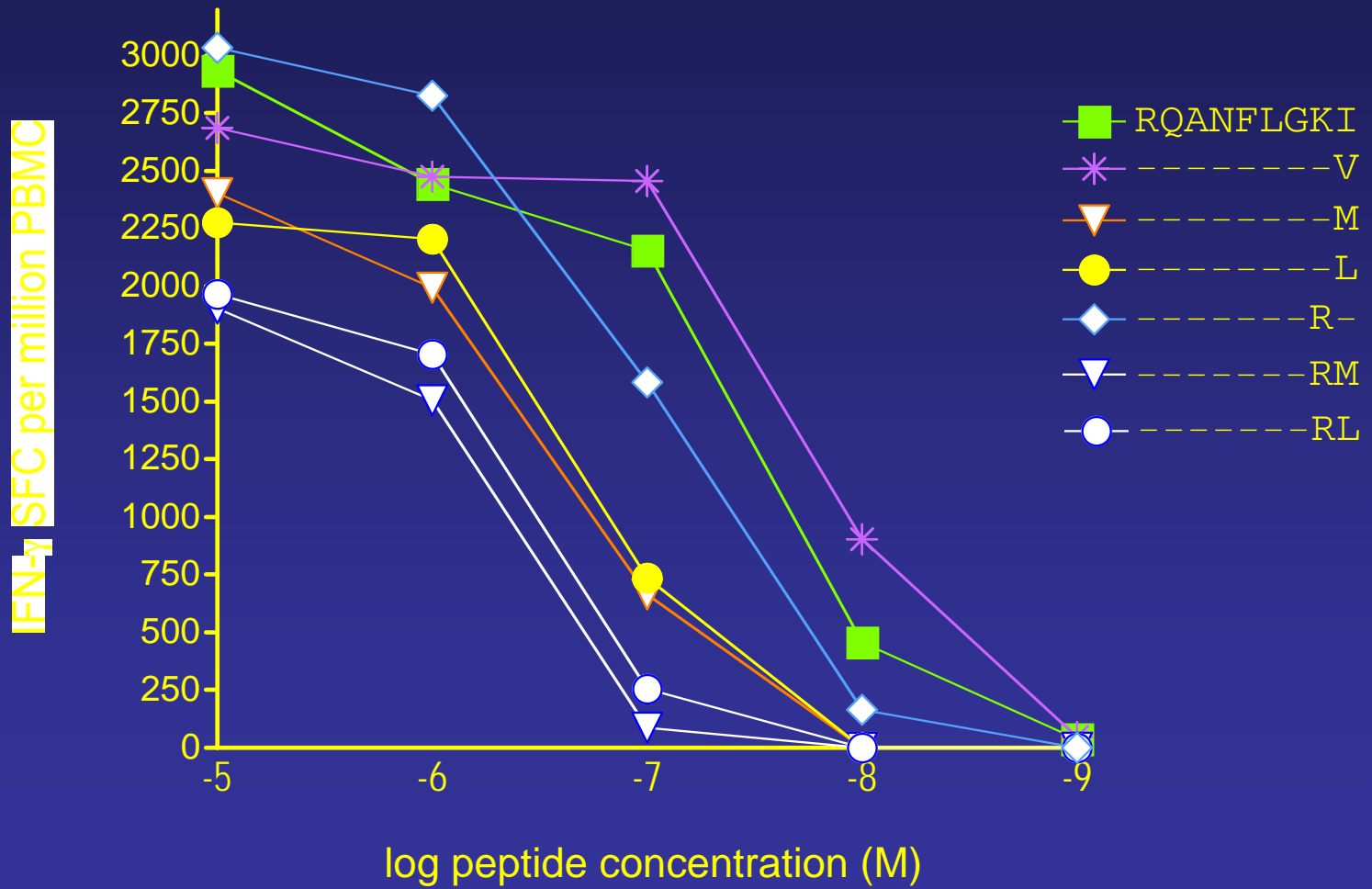
Polymorphisms in Gag RI9 epitope are associated with B*13 expression



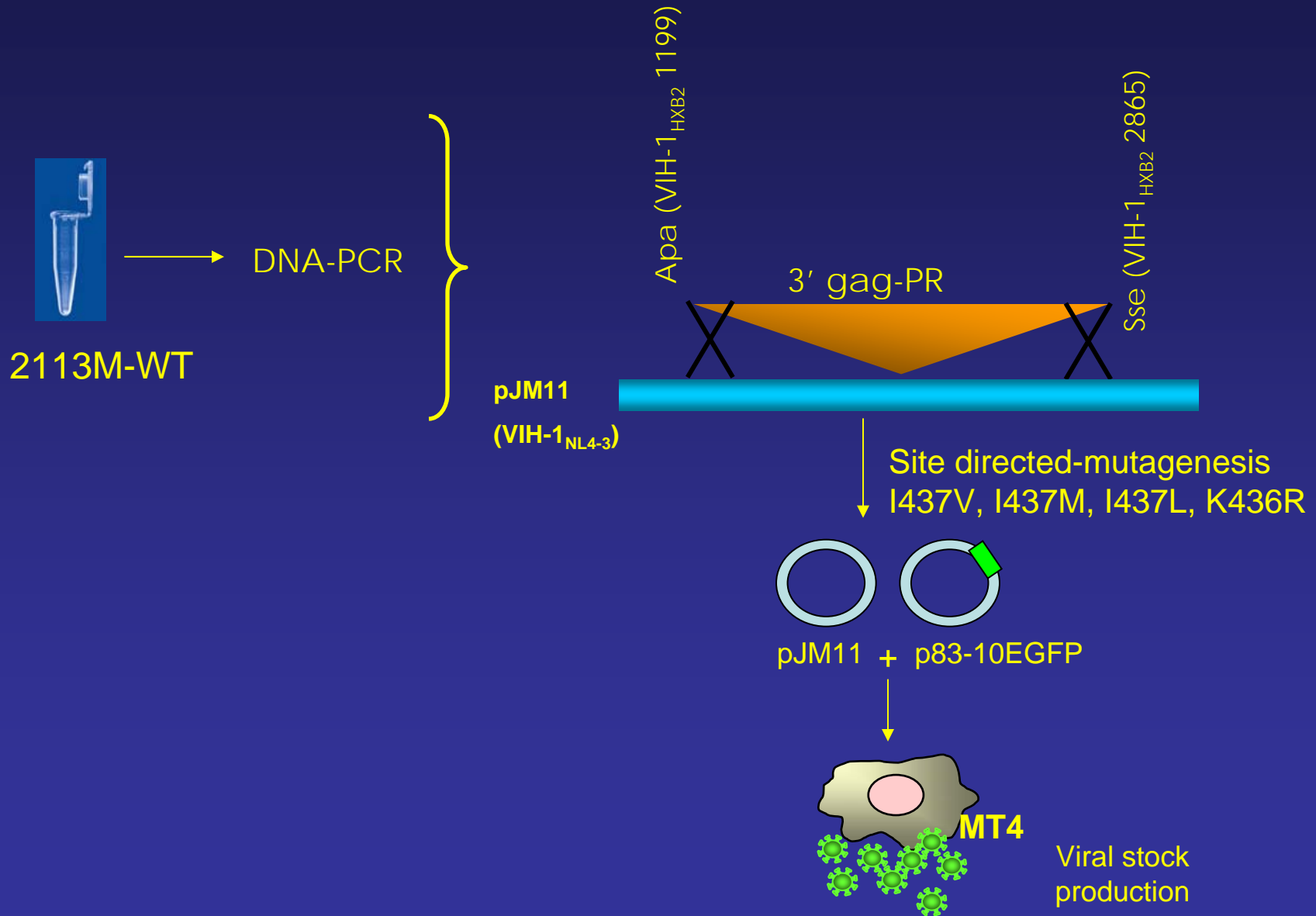
$R_{P=0.002}$

$P=2.41 \cdot 10^{-7}$ V/L/M

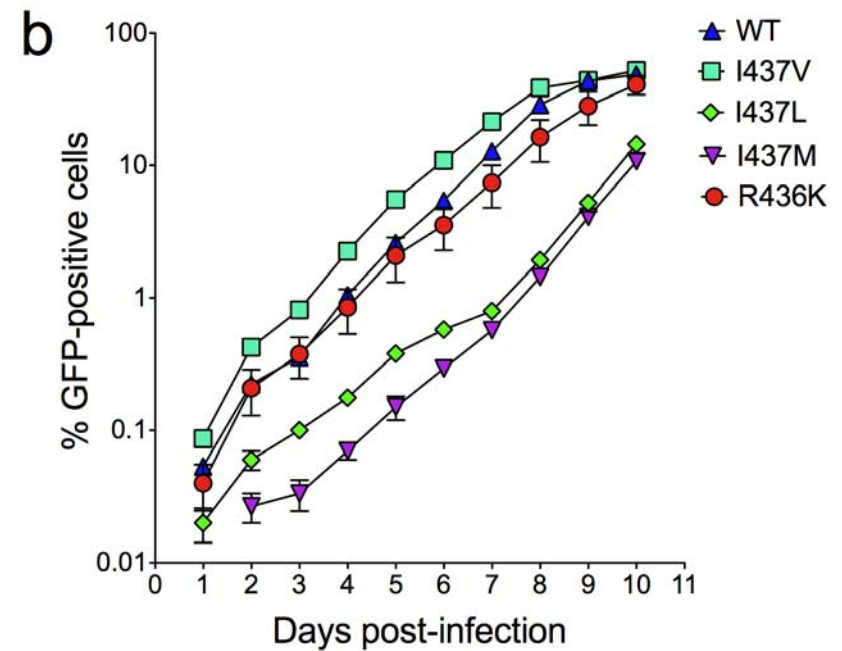
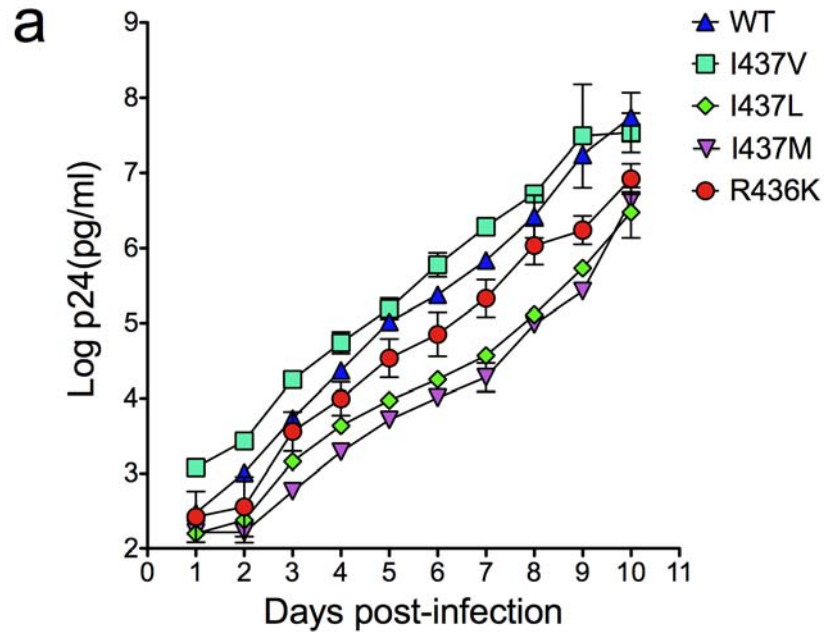
Viral escape to CD8+ R19 responses



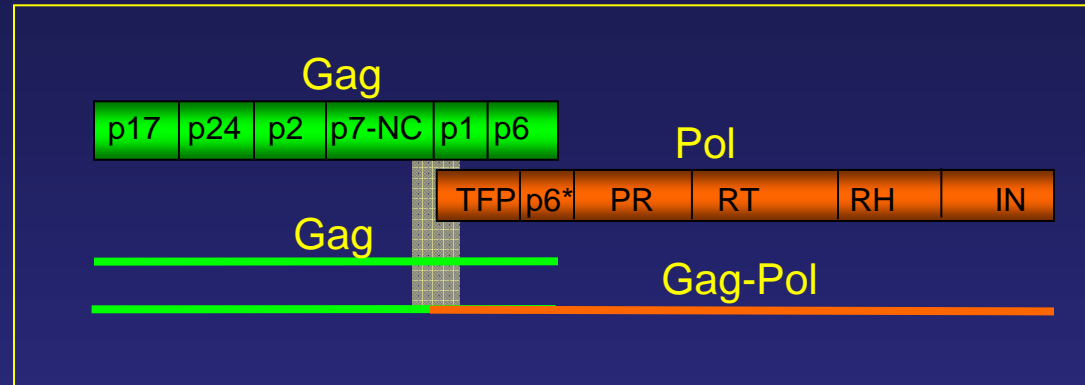
Construction of recombinant HIV virus



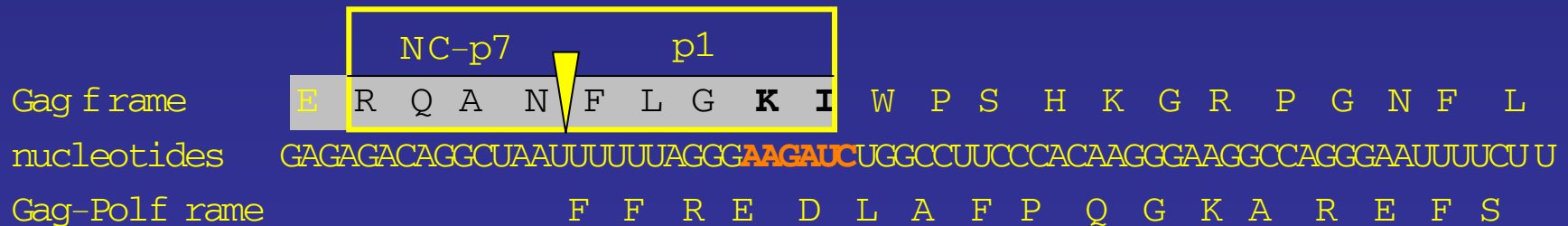
Viral escape in R19 affects in vitro viral replication



What mechanisms underlie the fitness constraint?

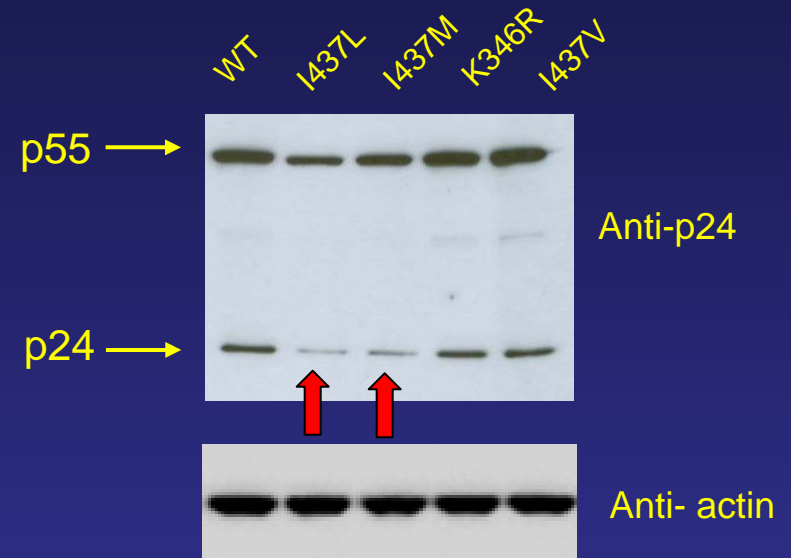
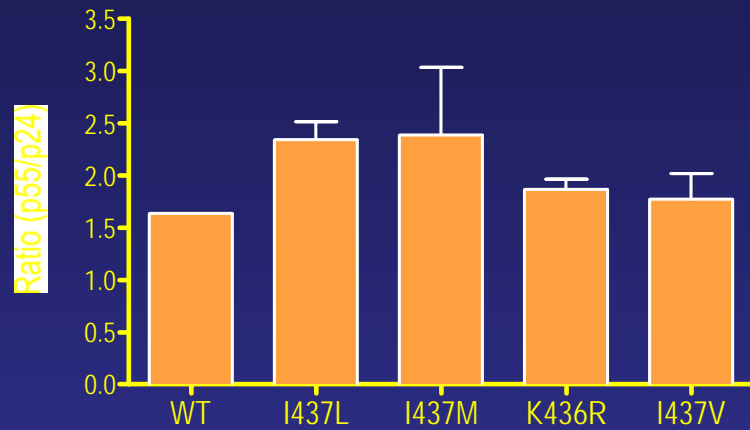


R19

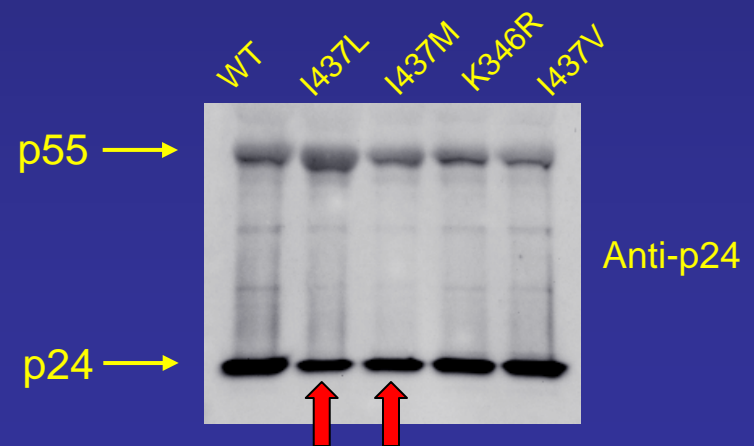
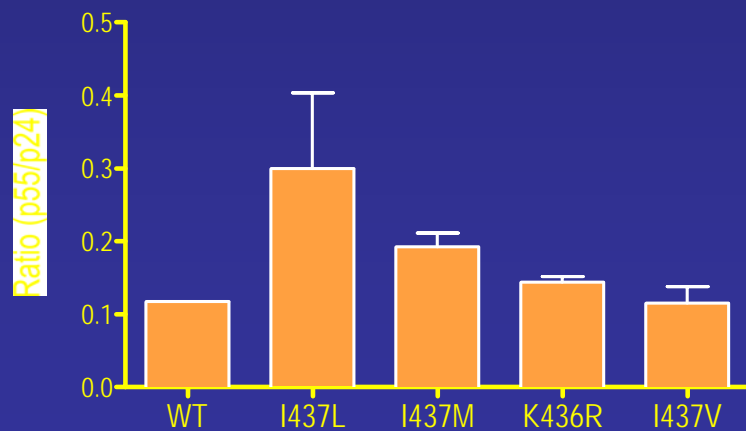


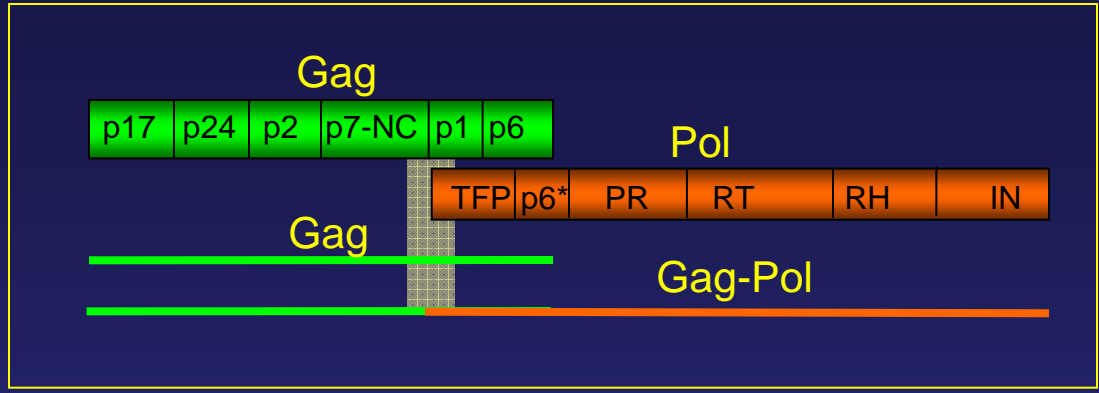
I437M and I437L show an accumulation of p55

A. Cell lysates

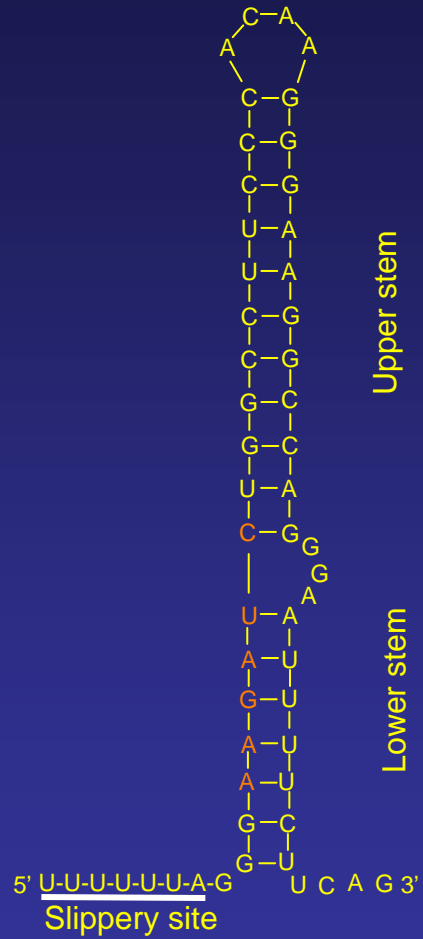


B. Virions





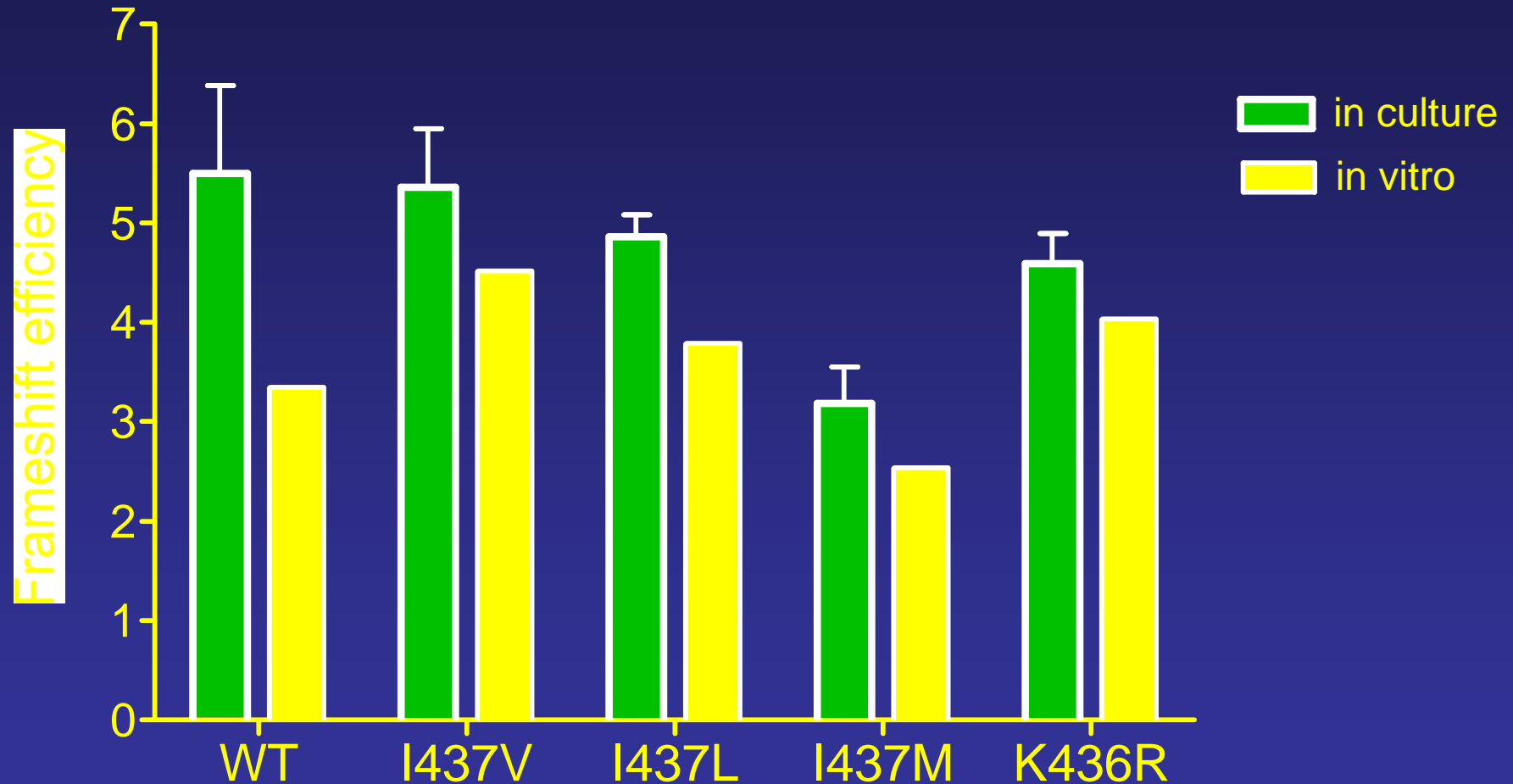
Frameshift stem-loop



R19

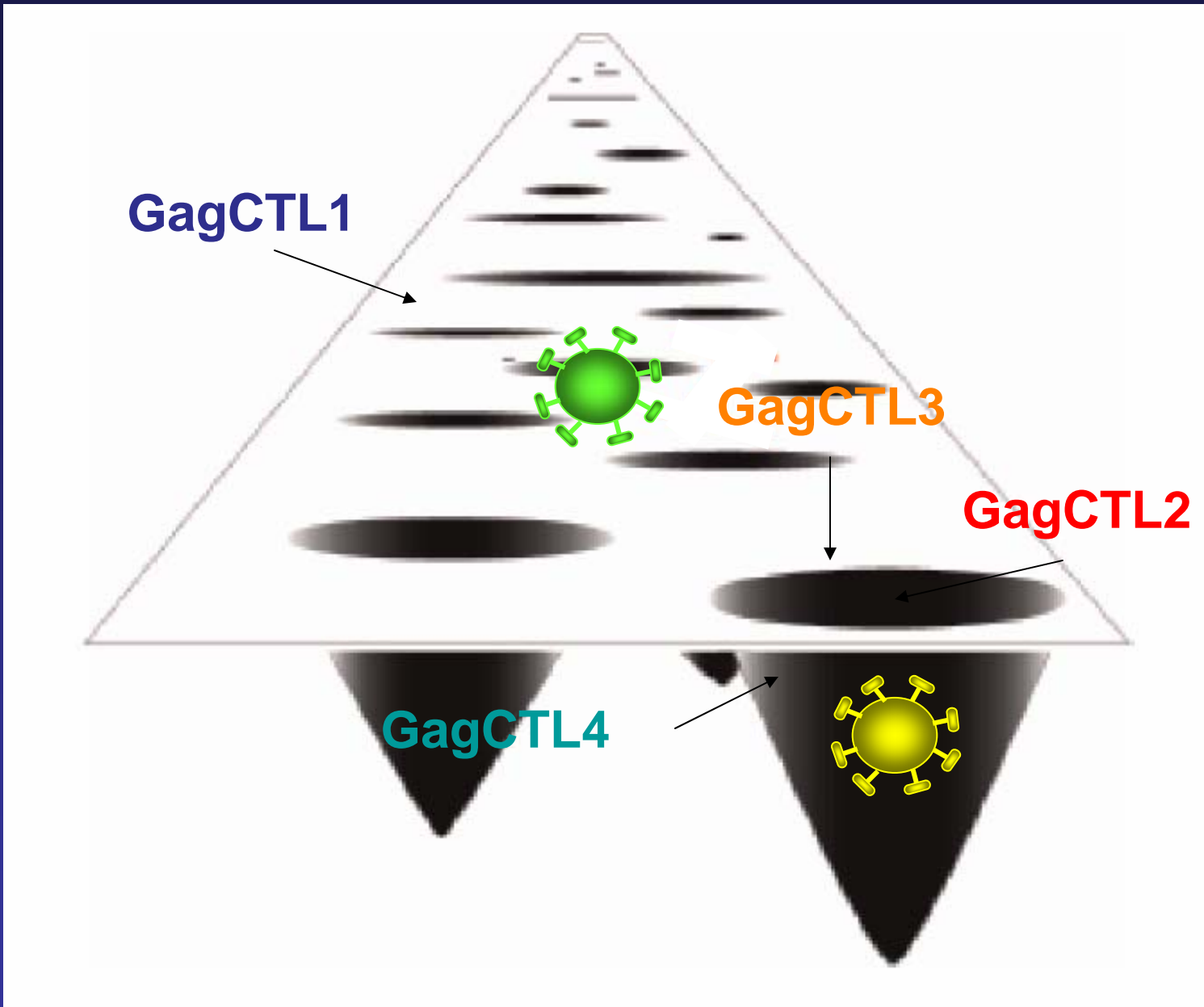
	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> NC-p7 p1 </div>	
Gag f rame	<div style="border: 1px solid black; padding: 2px; display: inline-block;"> E R O A N F L G K I </div>	W P S H K G R P G N F L
nucleotides	GAGAGACAGGCUAAUUUUUUAGGG AAGAUC UGGCCUCCACAAGGGAAGGCCAGGGAAUUUUUCUU	
Gag-Polf rame	F F R E D L A F P Q G K A R E F S	
2113M-WT	--A--G-----	A--U-----G-----C--
I437V	-----	-----G-----
I437L	-----	-----C-----
I437M	-----	-----G-----
K436R	-----	-----G-----

I437M reduces ribosomal frameshift



Summary

- HLA-B*13 RI9 mutants affect CTL recognition.
- Fitness cost of p1 escape mutants is associated with accumulation of unprocessed viral proteins and modification of the frameshift efficiency.
- Selection of low fitness escape mutants in HLA-B*13 individuals together with the breadth of Gag CTL responses may contribute to control HIV replication.



Modified from Berkhout et al Rev. Med. Virol, 2005

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Oxford team

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Javier Martinez-Picado
Maria Carmen Puertas

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Ian Brierley

Durban team

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