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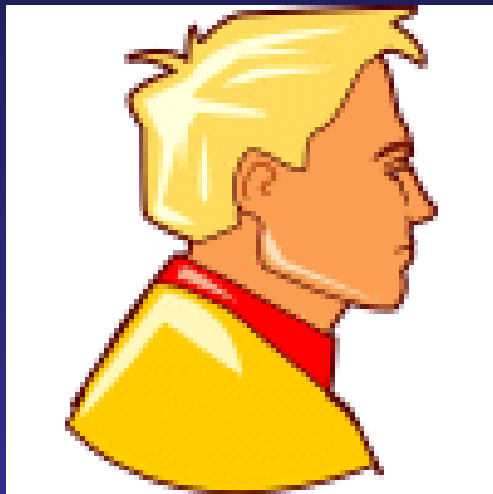
# HIV-1 escape from a HLA-B\*13 epitope in p1 Gag: fitness cost and functional consequences

Julia G. Prado

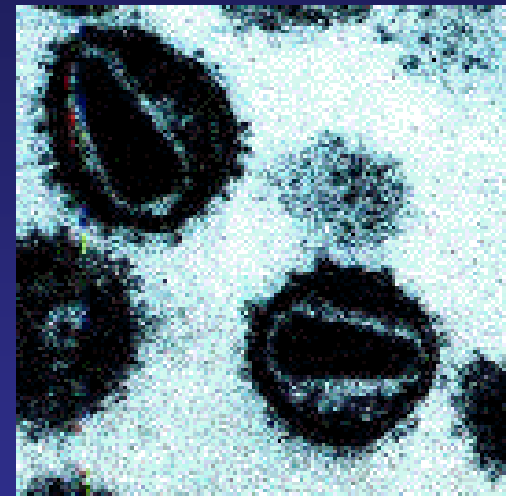
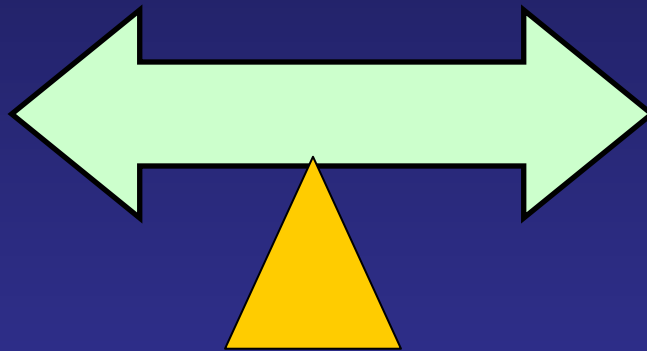
*University of Oxford*

# HIV-1 infection and host

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HLA



CTL escape

## Some evidence...

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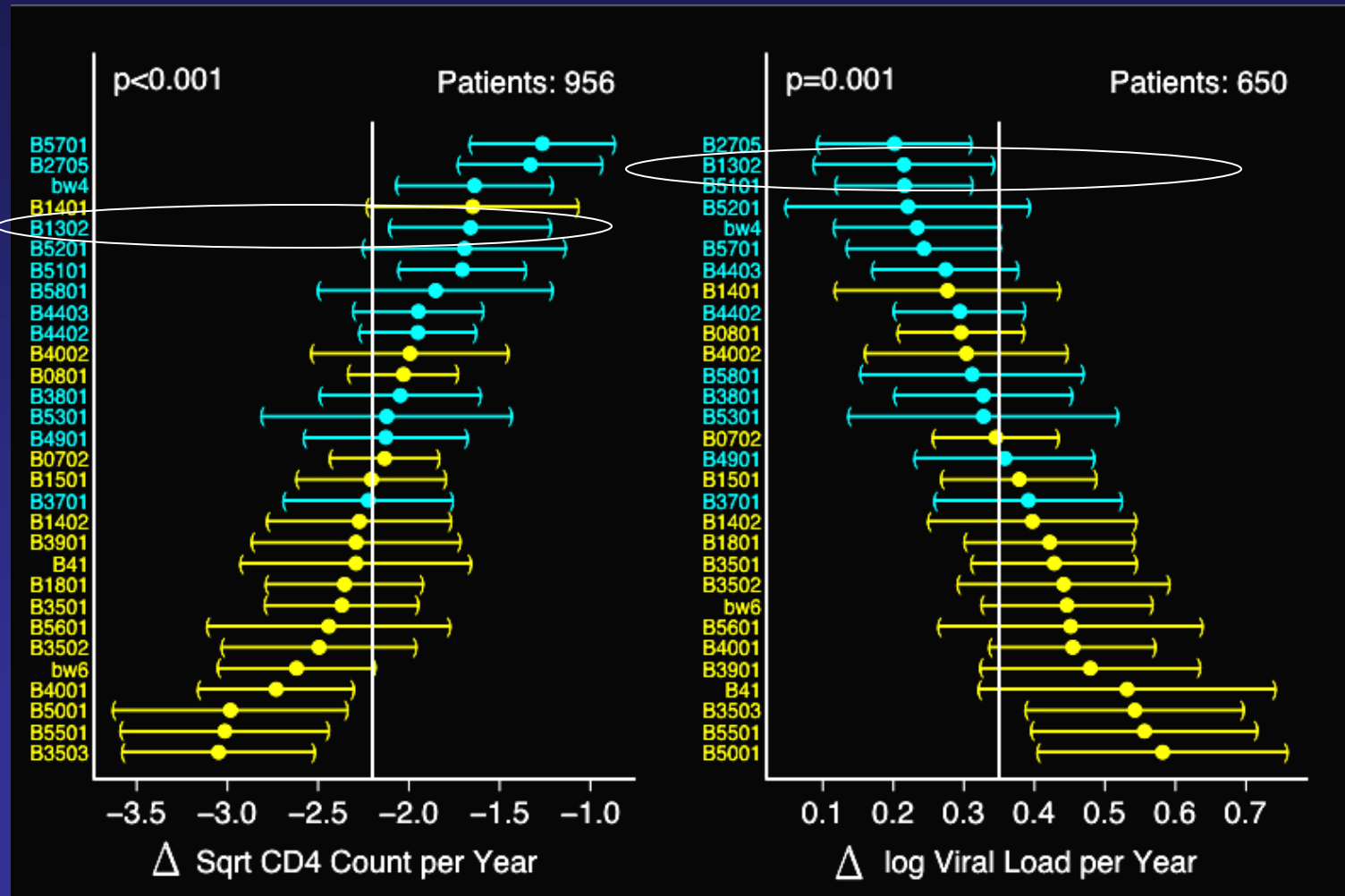
- The breadth of Gag CTL responses is associated with control of HIV-1 replication. (*Kiepiela et al 2008, Edwards et al 2002...*).
- Low viral fitness p24 Gag CTL escape mutants (TW10, KF11, KK10) can contribute to control HIV replication. (*Martinez-Picado et al 2006, Crawford et al 2007, Brockman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

# AIM

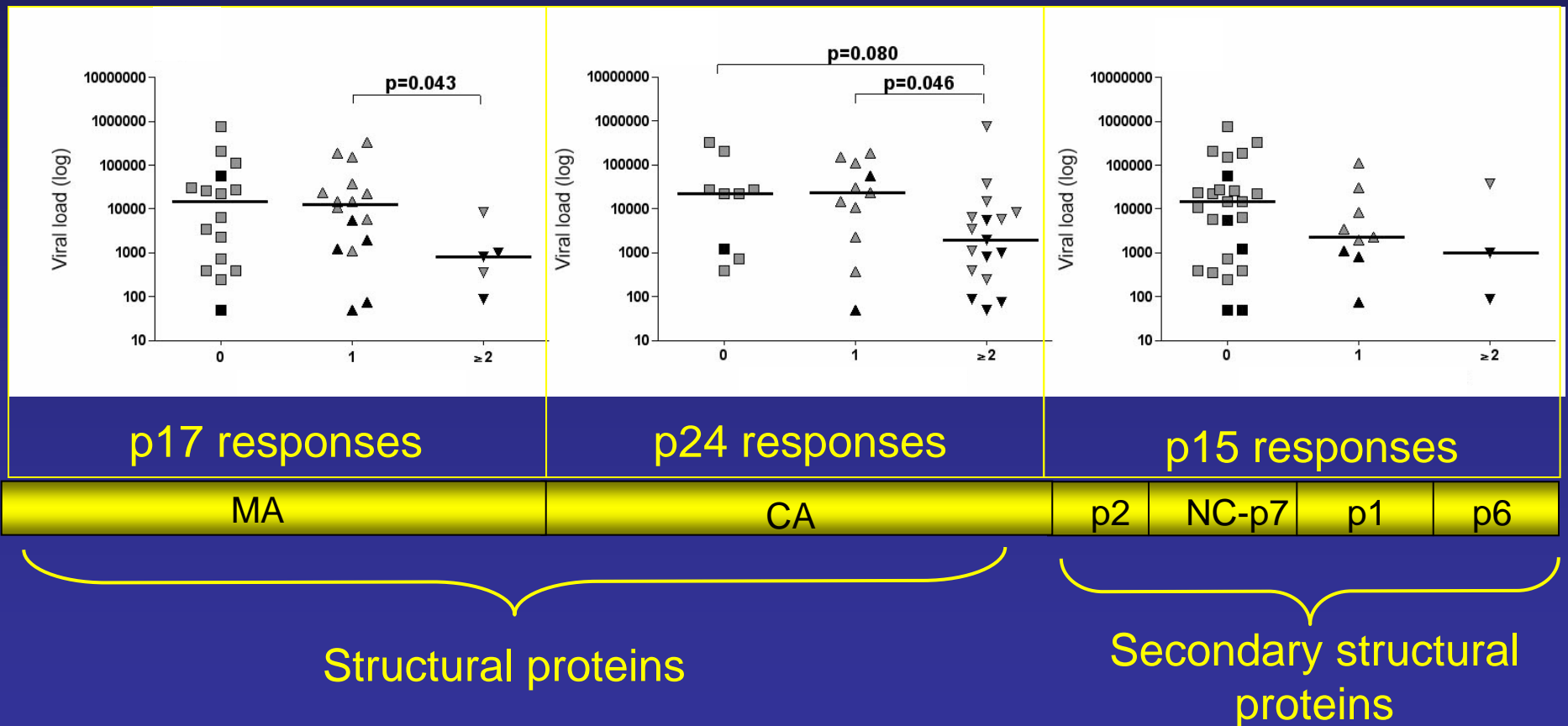
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- HLA-B\*13 - characterization of CD8+ T cell escape mutants in a secondary Gag structural region of the HIV genome.

# 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

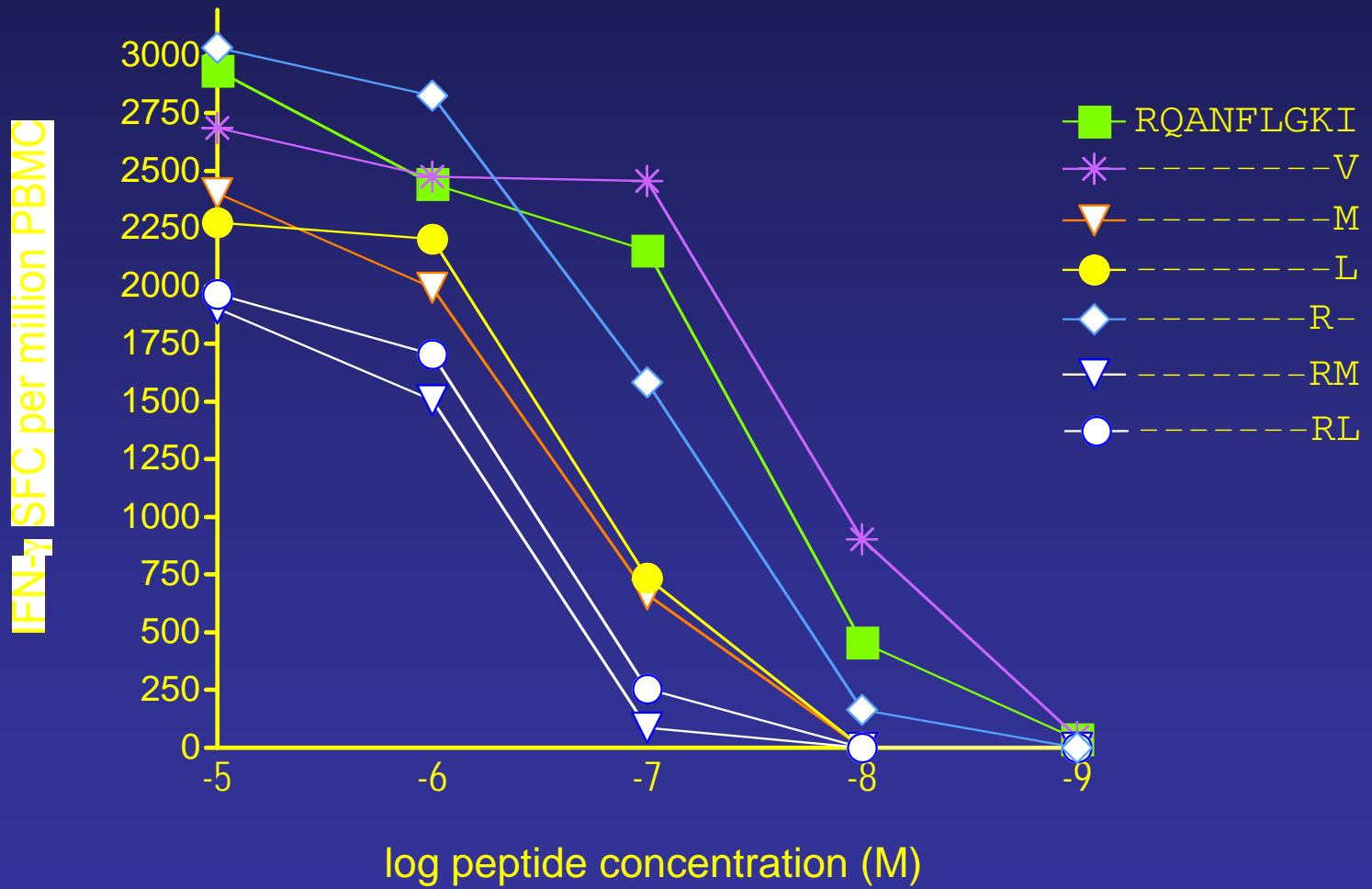


RI9  
429 R Q A N F L G K I 437

R<sub>P=0.002</sub>

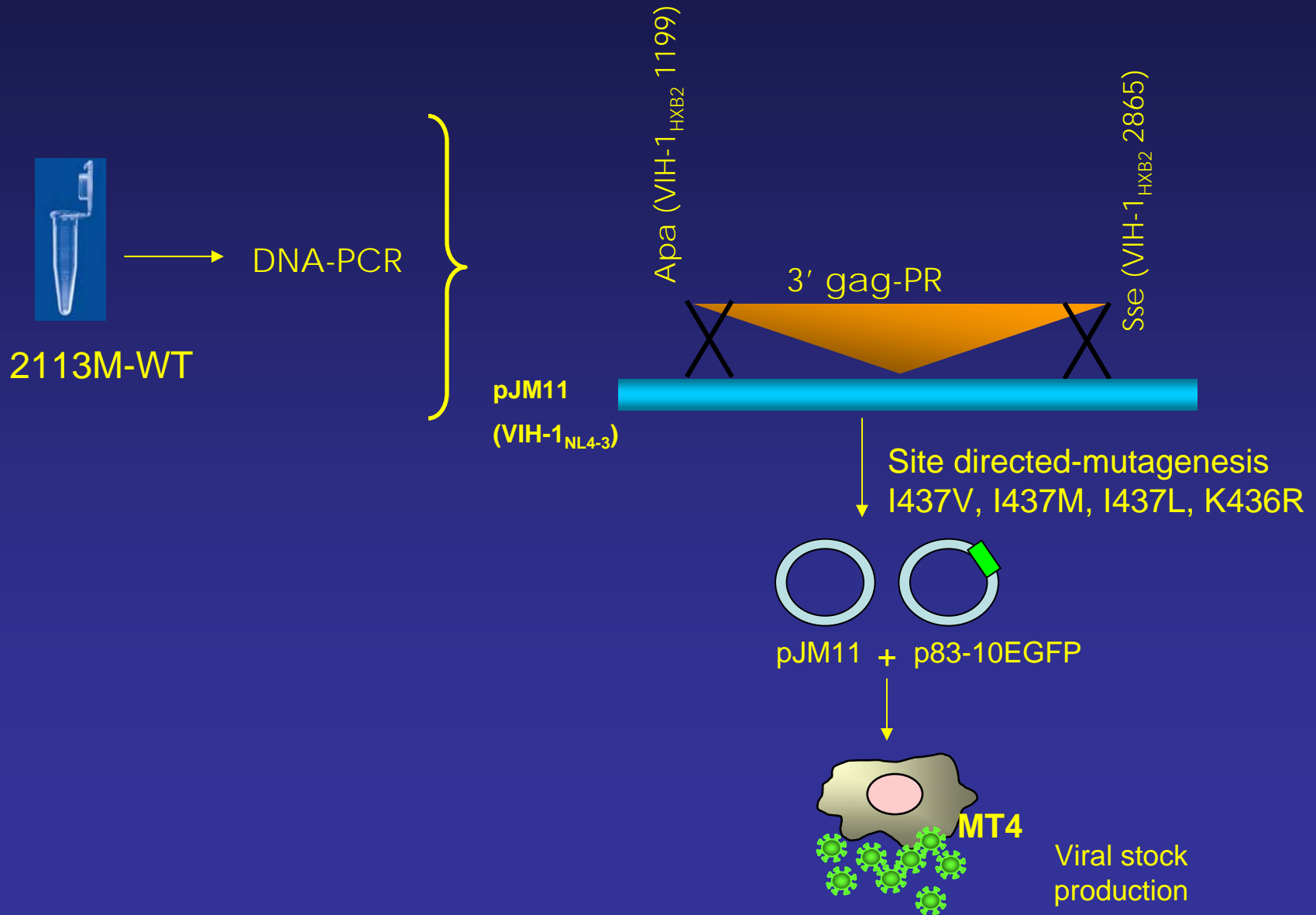
P=2.41 10<sup>-7</sup> V/L/M

# Viral escape to CD8+ R19 responses

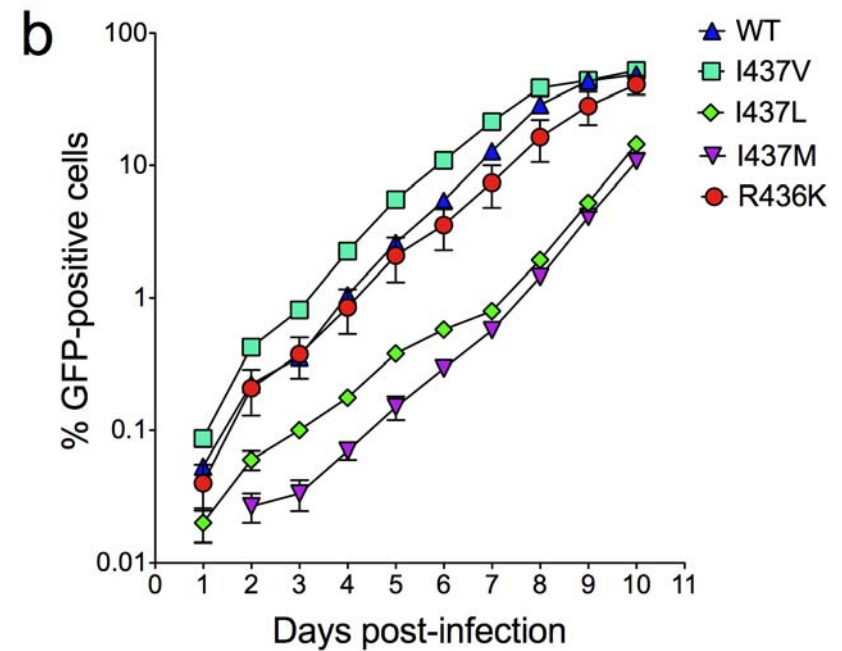
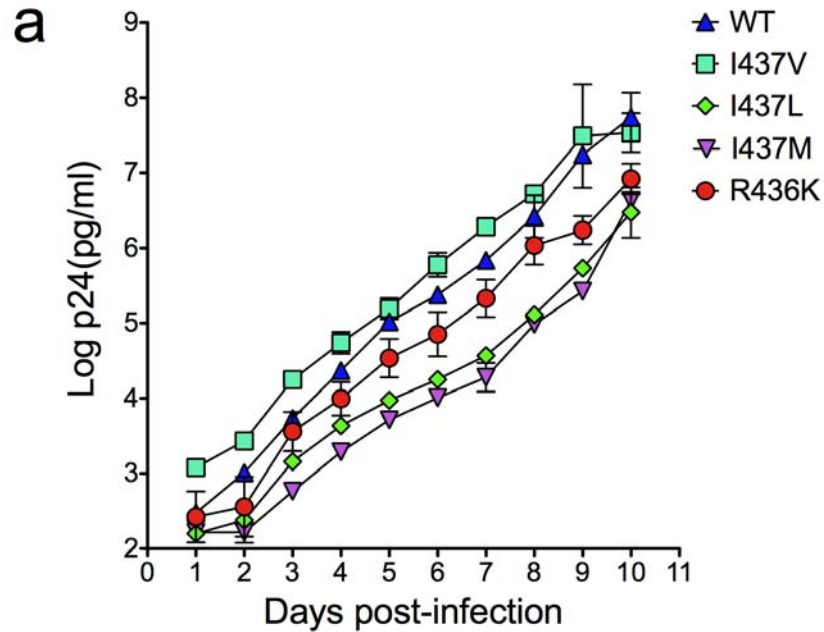




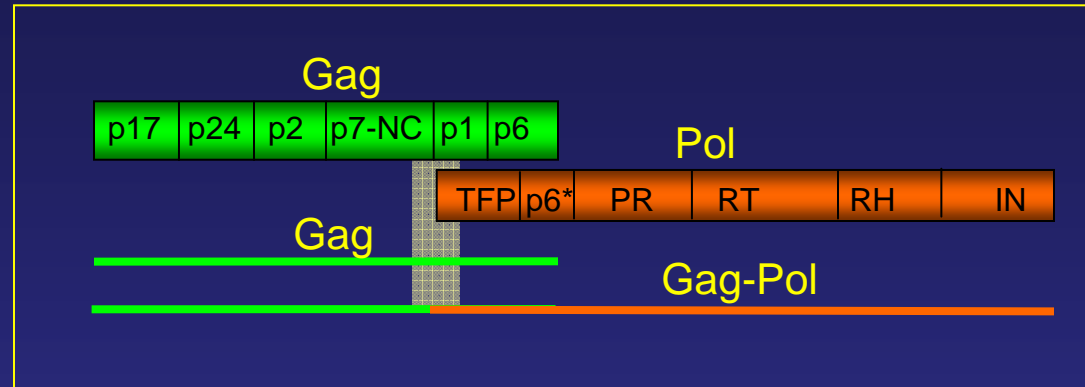
# Construction of recombinant HIV virus



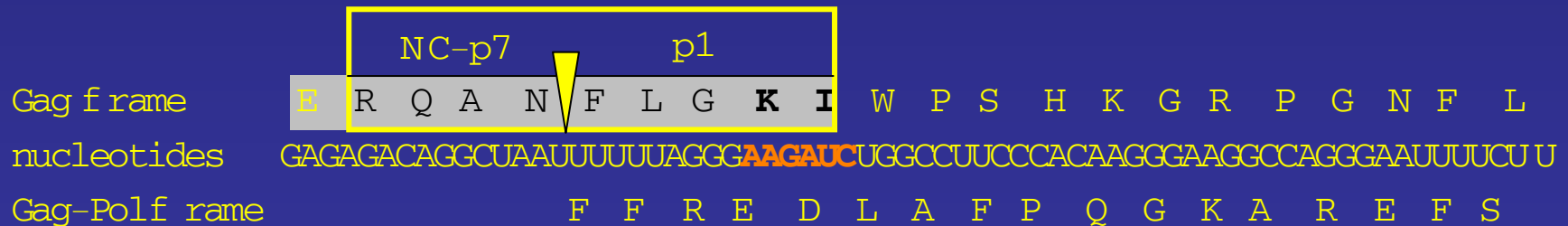
# Viral escape in R19 affects in vitro viral replication



# What mechanisms underlie the fitness constraint?

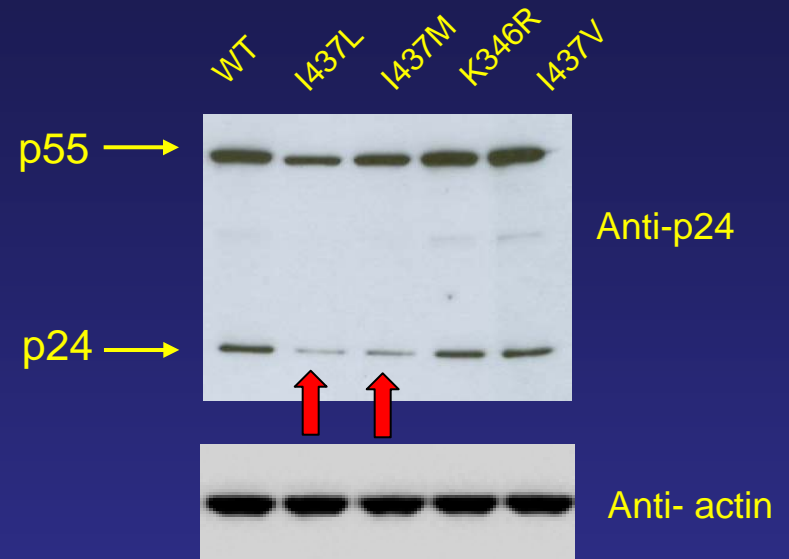
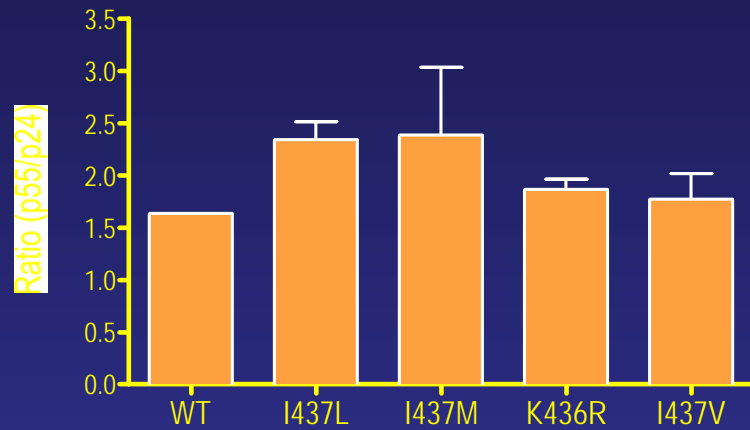


## R19

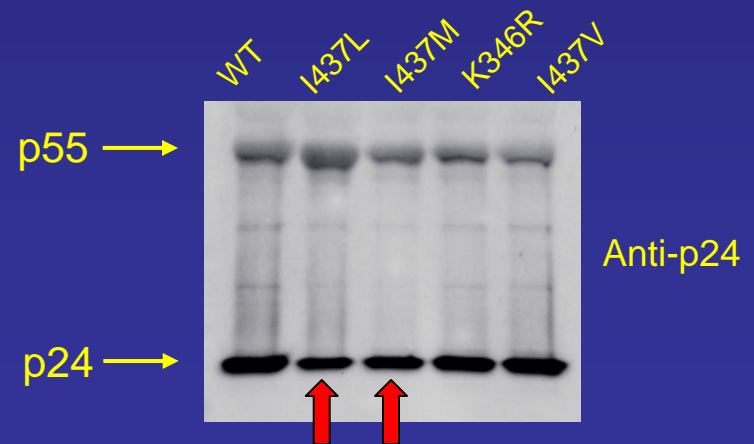
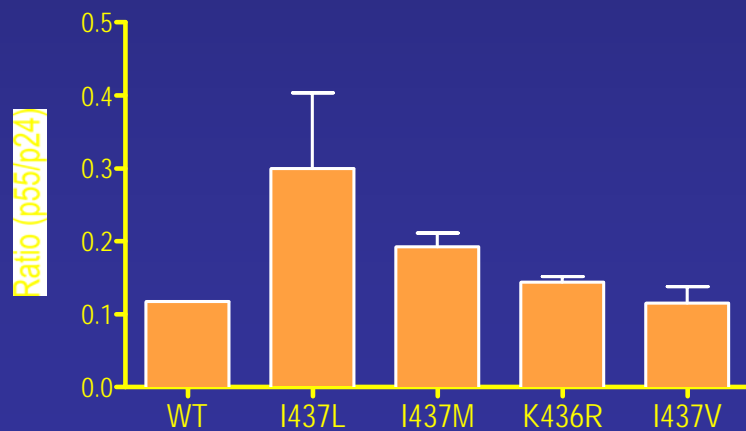


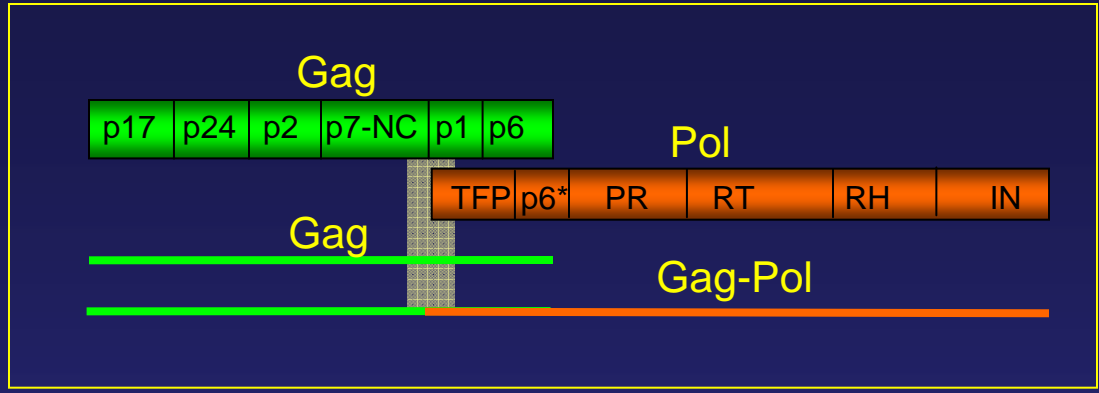
# I437M and I437L show an accumulation of p55

## A. Cell lysates

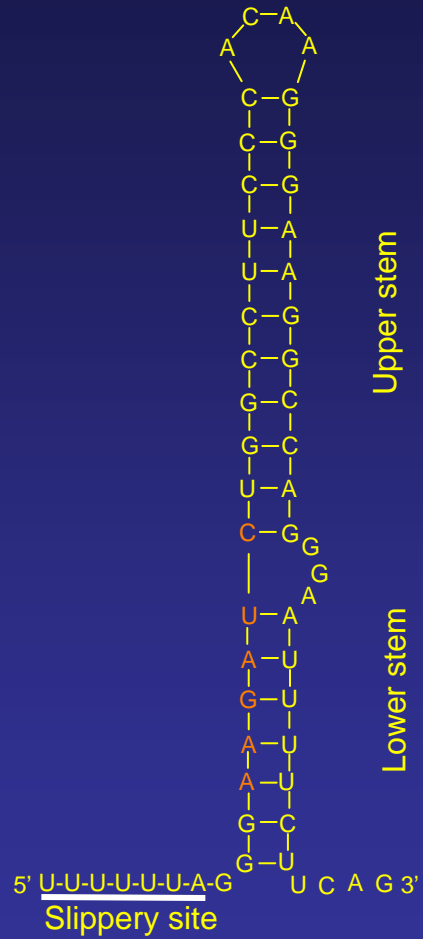


## B. Virions





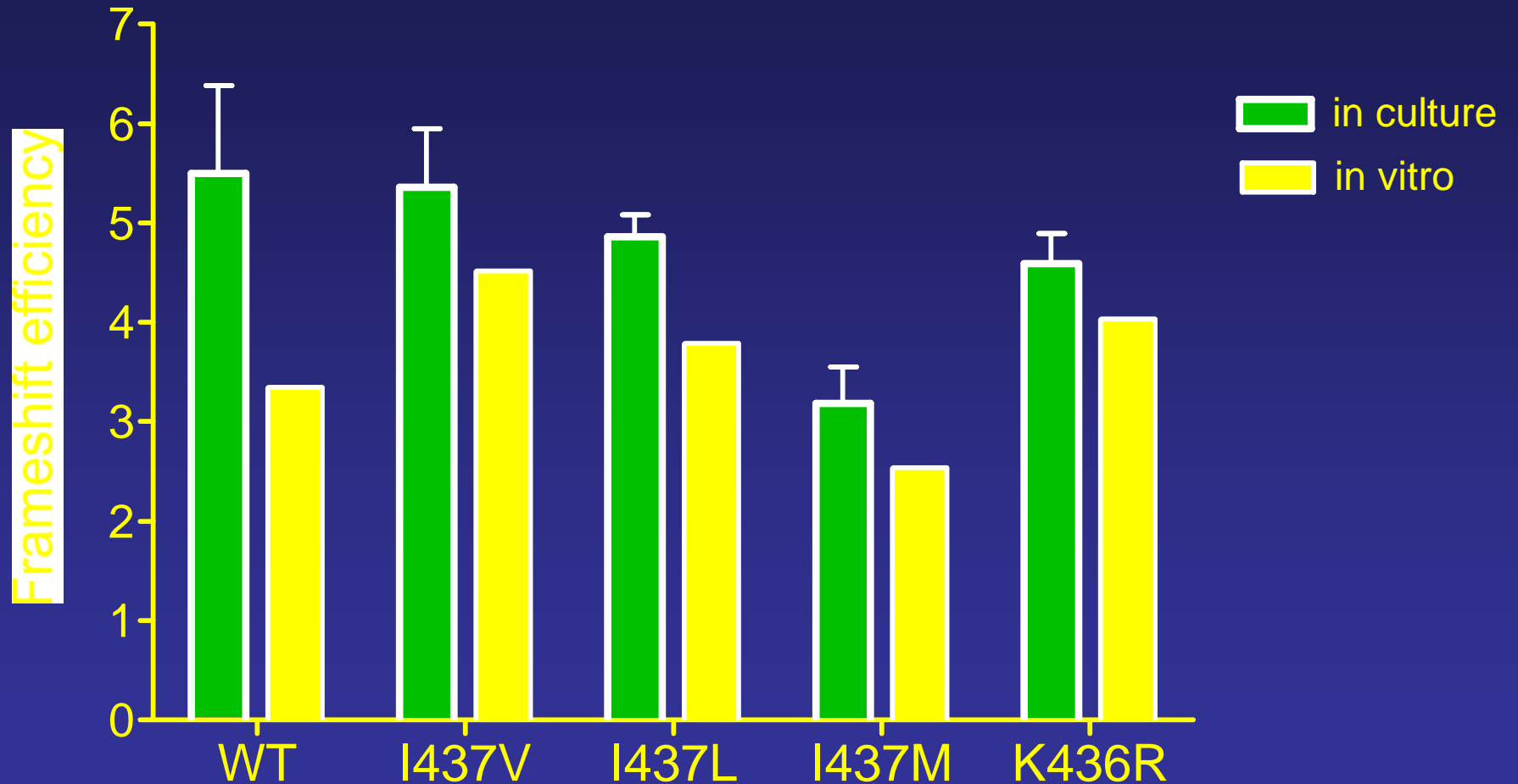
### Frameshift stem-loop



### 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 <b>AAGAUC</b> 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-----

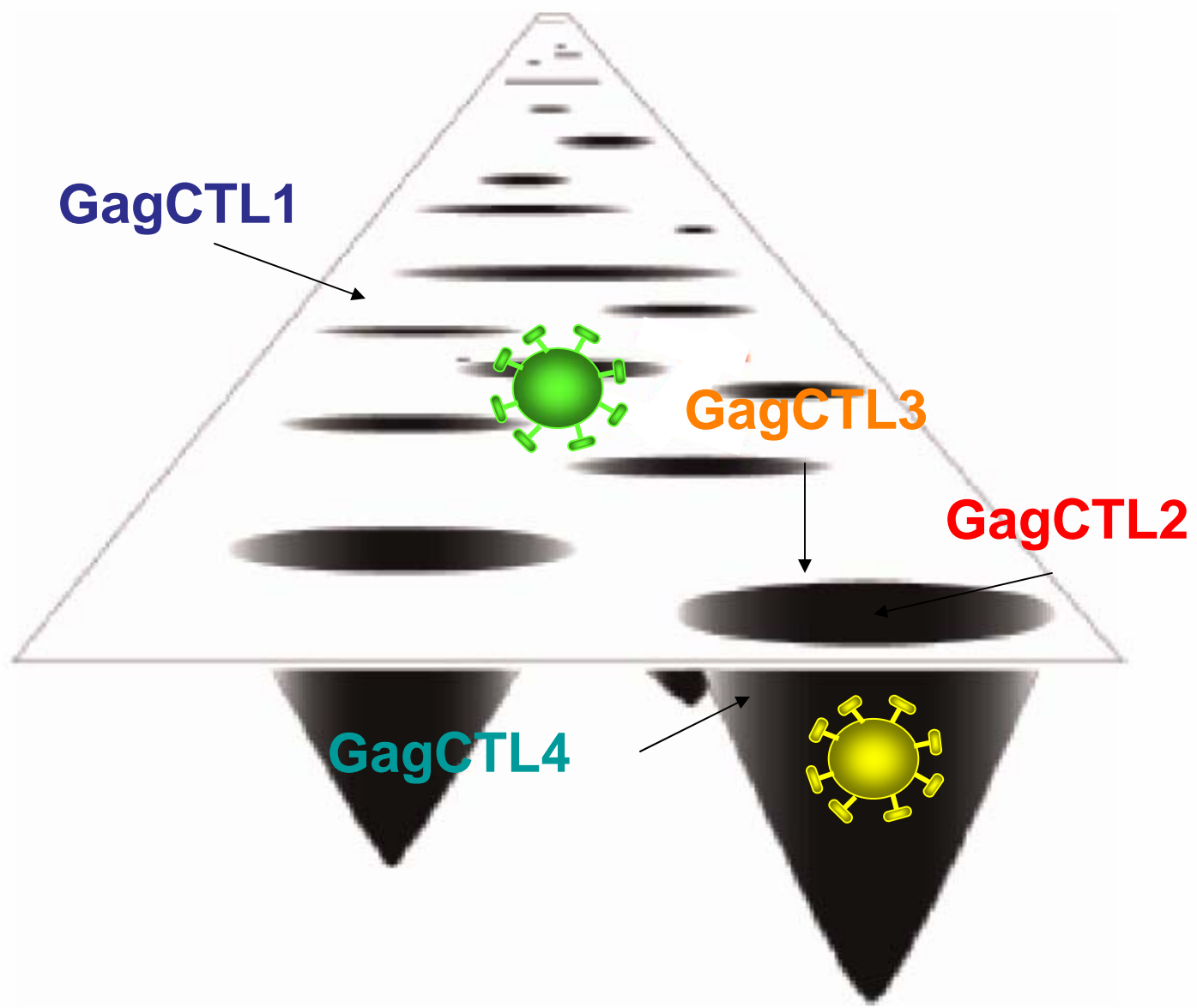
# I437M reduces ribosomal frameshift



# Summary

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- 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.





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**Javier Martinez-Picado**  
**Maria Carmen Puertas**

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**Ian Brierley**

# Durban team

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