

AIDS Vaccine 2007 Roundtable Discussion:

“New Primate Models: Will They Help HIV Vaccine Development?”

1. Overview of Models of SIVmac Attenuation
2. New Model of SIVmac attenuation:
Targeting the Envelope Cytoplasmic Tail

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Holy Grails in HIV Vaccine Research

- Immunogens or viruses that elicit broadly neutralizing antibodies.
- Models for protection from pathogenic heterologous challenges.
- Identifying immune correlates:
 - For protection from infection
 - For protection from disease

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Attenuated Viruses in Studies of HIV/SIV Pathogenesis and Vaccines: 1991-2007

- Potentially powerful probes to delineate viral and host determinants of pathogenesis and immunopathogenesis
 - Effects of the attenuating mutation
 - Compensatory mutations
- Potentially useful in understanding correlates of protection
- Provide a source of continuing antigen exposure BUT ongoing replication creates opportunities for viral evolution to increasingly pathogenic variants
- Efficacy issues
- Safety concerns

Live Attenuated SIV

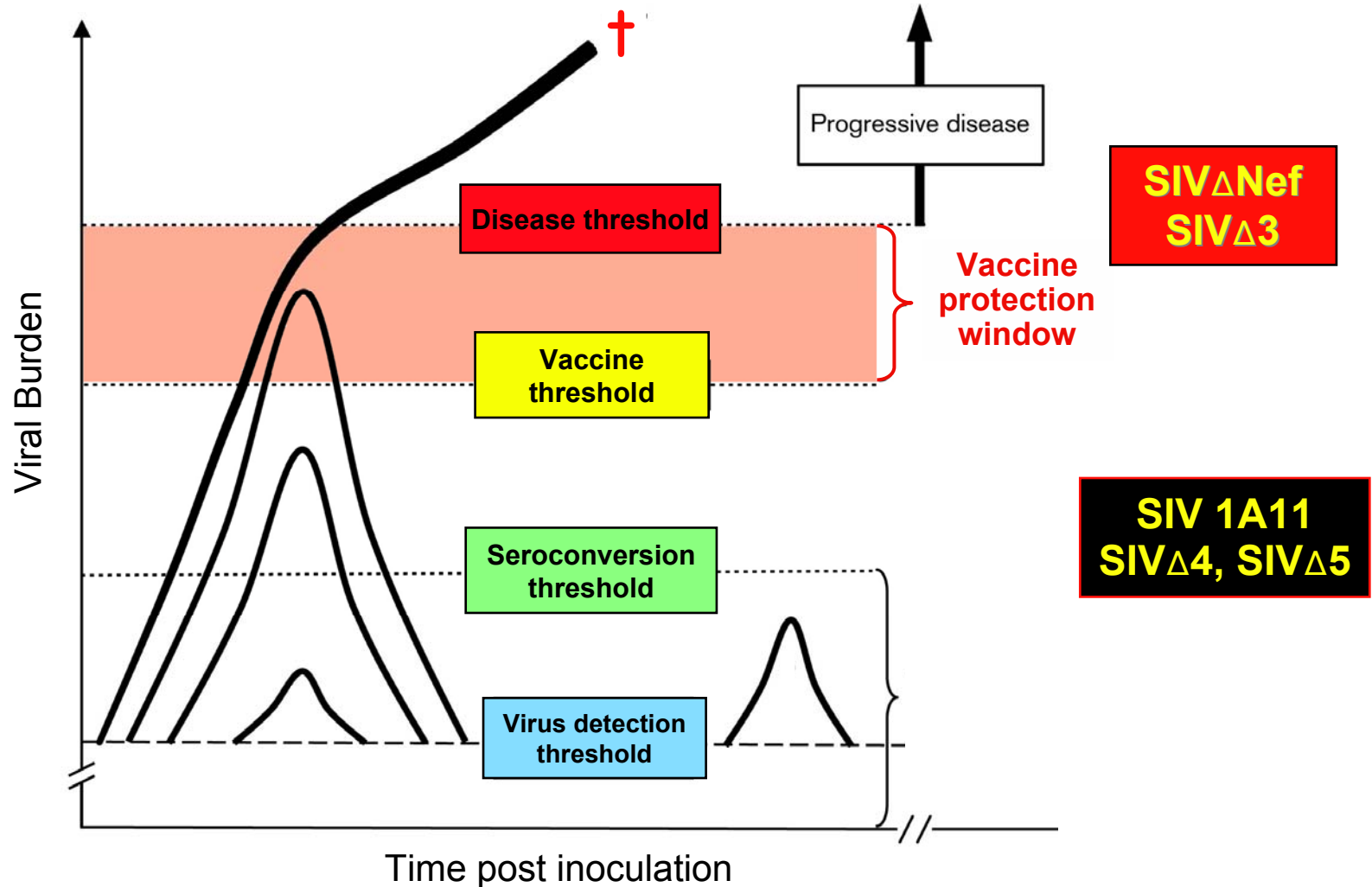
“ Δ Nef; Δ 3”

- Acute Peak Viral Loads: < SIVmac239
Viral Set Point: < SIVmac239 to undetectable
- Protection for homologous virus (SIVmac239, SIVmac251)
- Correlates of protection for SIVmac239 infection?
 - Increase plasma vRNA after CD8-depletion
 - CD4 late effector memory cells (CD27⁻, CD28⁻, CCR7⁻, CCR5⁻, CD45RA^{lo})
 - Subpopulation of CD4 effector cells (CD107a⁺, \uparrow perforin)
 - Neutralizing antibodies???
 - Non-immune mechanisms? (e.g. viral interference; target cell depletion)
- Limited protection for heterologous virus (E660) *
 - Wyand et al, JV '98: 3 of 4 Δ 3-infected animals died after E660 challenge
 - * Watkins, D (Keystone '07): Lower viral load in *Mamu* B*08 or B*17
- Pathogenic in neonates and long term-infected adults
- Mechanism of attenuation?

Live Attenuated Viruses

- Inverse correlation between level of attenuation and protection

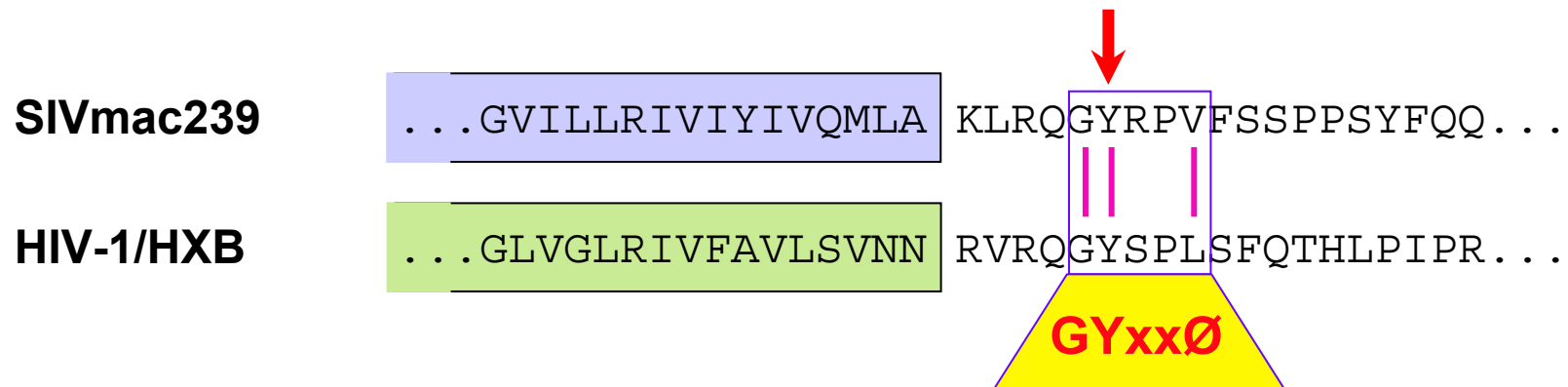
The Threshold Hypothesis



Adapted from Whitney et al *Curr Opin Infect Dis* 17: 17-26 '04

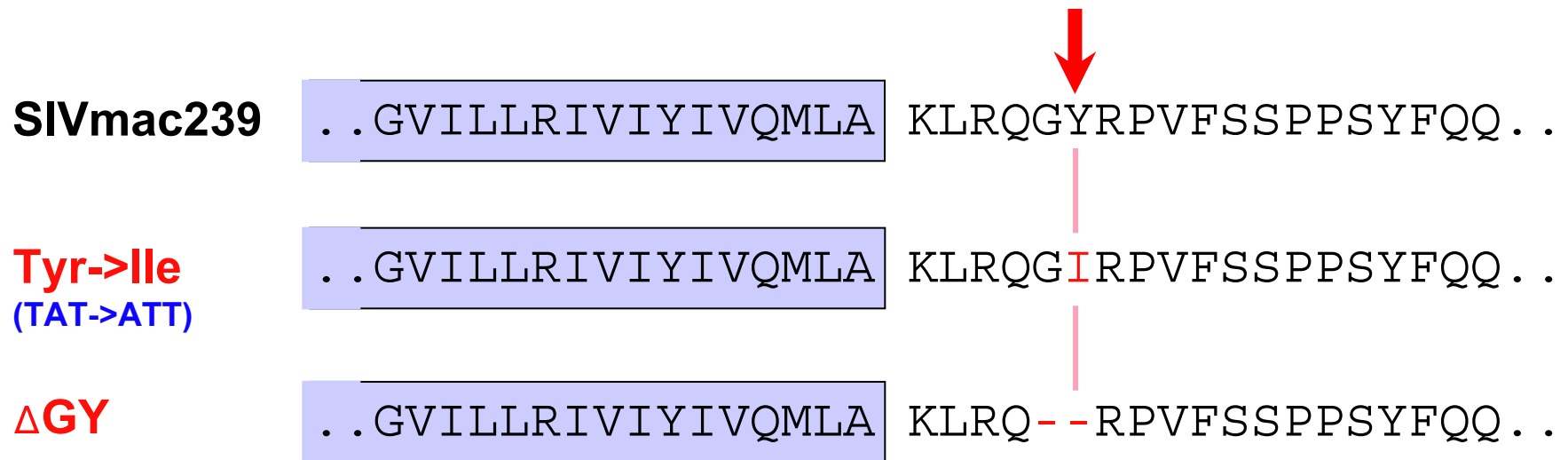
Targeting the SIVmac cytoplasmic tail: A new model for SIV attenuation

- Ablation of a trafficking signal “GYxxØ” in the SIVmac Env



-
- Present in all HIV/SIV Env sequences.
 - Signal for endocytosis via clathrin coated pits
Binds μ 2 chains of AP2.
 - Modulate Env surface expression on cells.
 - Mediates basolateral sorting of Env and viral budding in polarized cells.

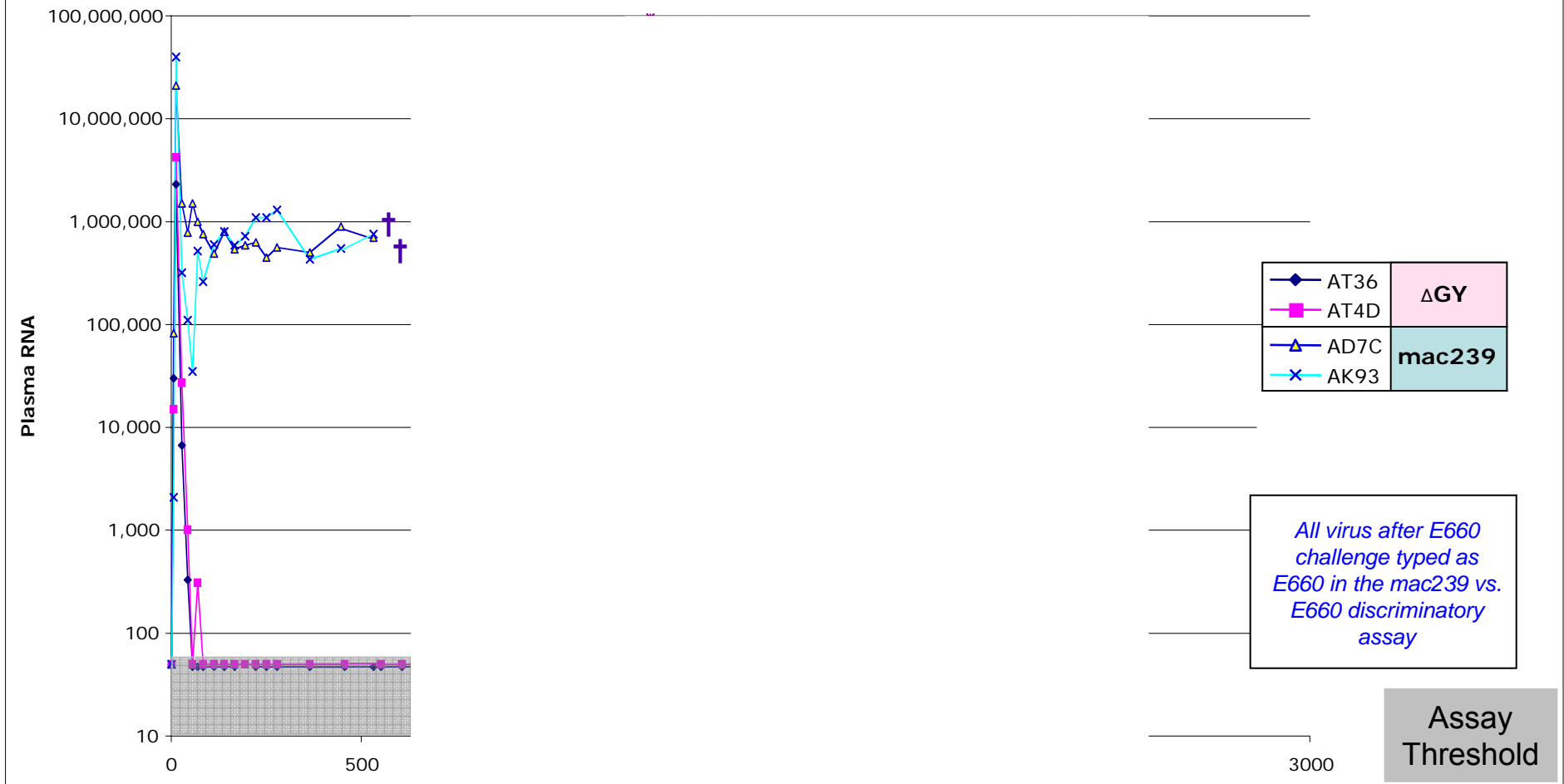
Env Cytoplasmic Tail mutants of SIVmac239
for *in vivo* evaluation in **pigtailed macaques**



Group #1: Δ GY vs mac239

mac239 Δ GY
 { RQGYRPV -> RQ--RPV }

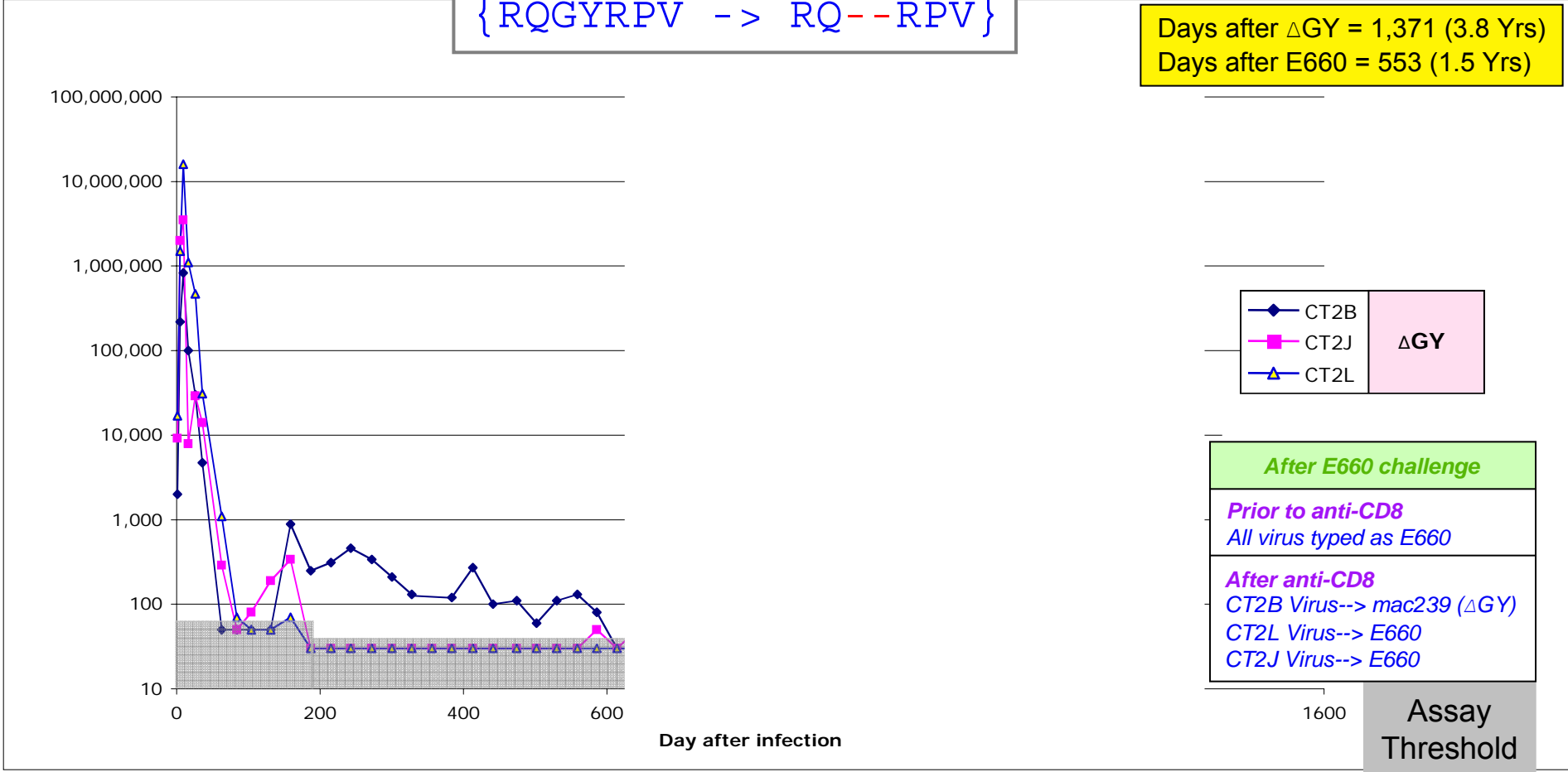
Days after Δ GY = 2,499 (6.6 Yrs)
 Days after E660 = 1,043 (2.6 Yrs)



Group #2: Δ GY

mac239 Δ GY
 {RQGYRPV -> RQ--RPV}

Days after Δ GY = 1,371 (3.8 Yrs)
 Days after E660 = 553 (1.5 Yrs)



CT2B Δ GY
 CT2J
 CT2L

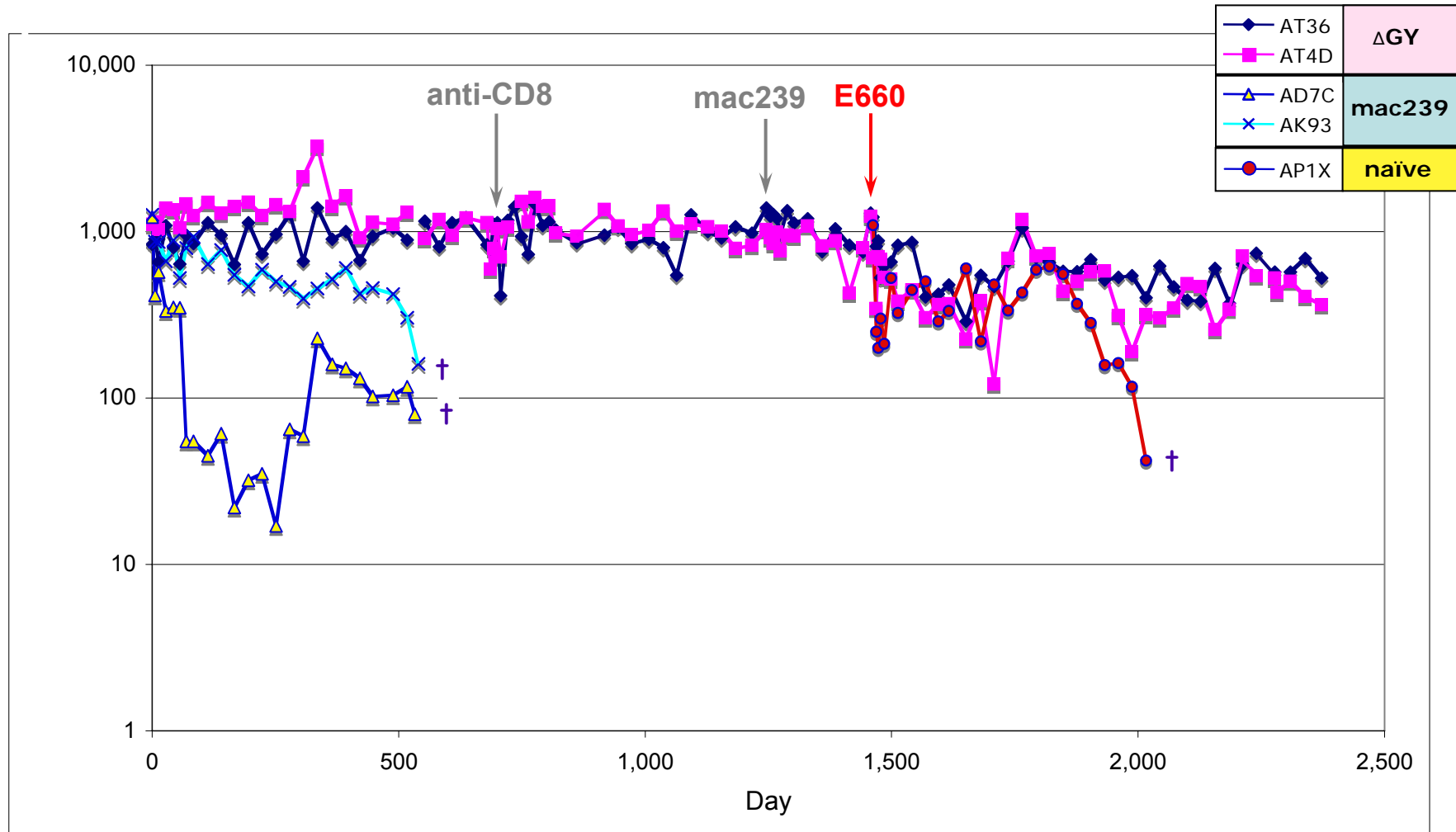
After E660 challenge
 Prior to anti-CD8
 All virus typed as E660
 After anti-CD8
 CT2B Virus--> mac239 (Δ GY)
 CT2L Virus--> E660
 CT2J Virus--> E660

1600
 Assay Threshold

Group #1

SIVmac Δ GY-infected -> E660 Challenge

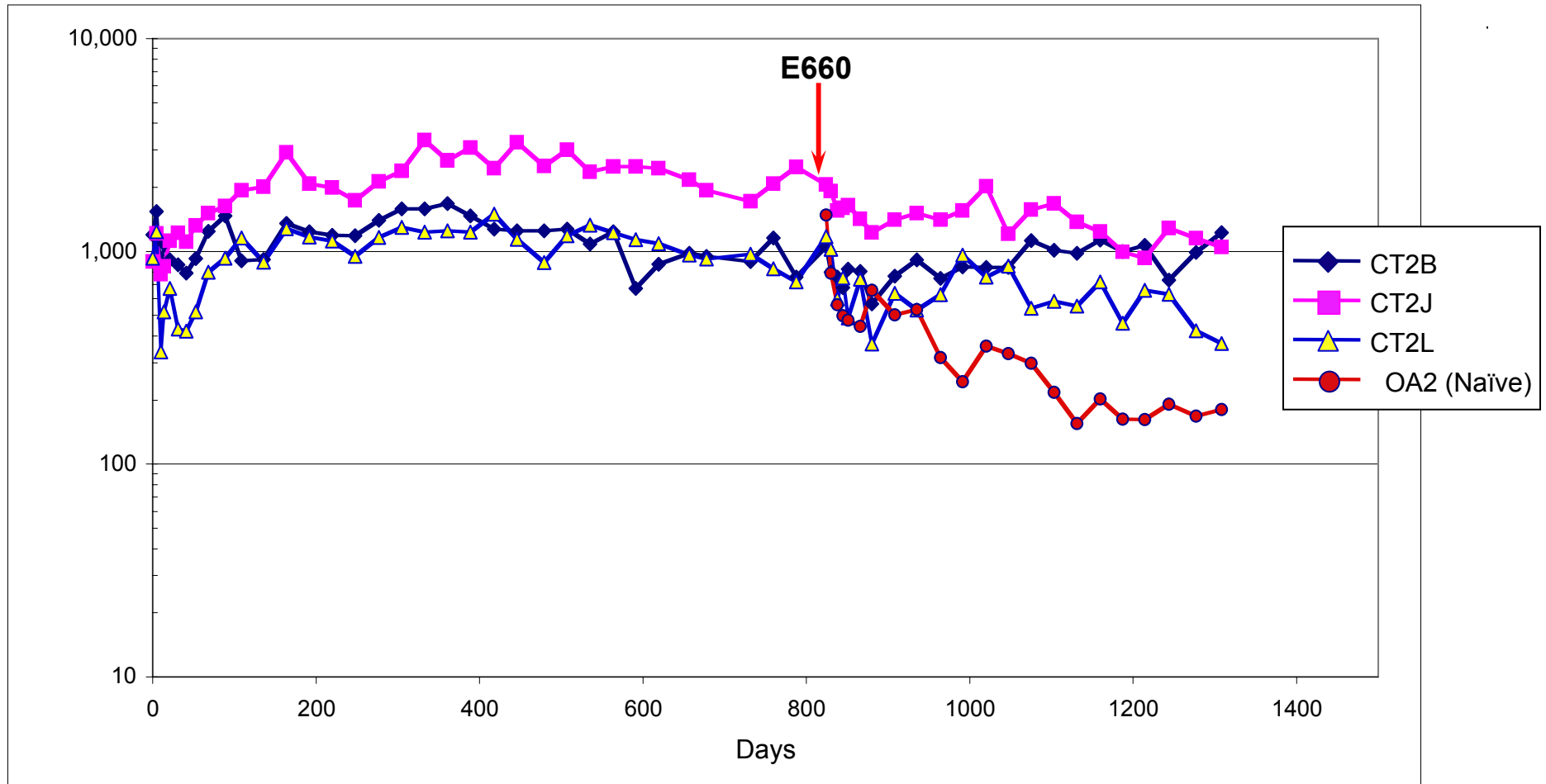
CD4 Cell



Group #2

SIVmac Δ GY \rightarrow E660 Challenge

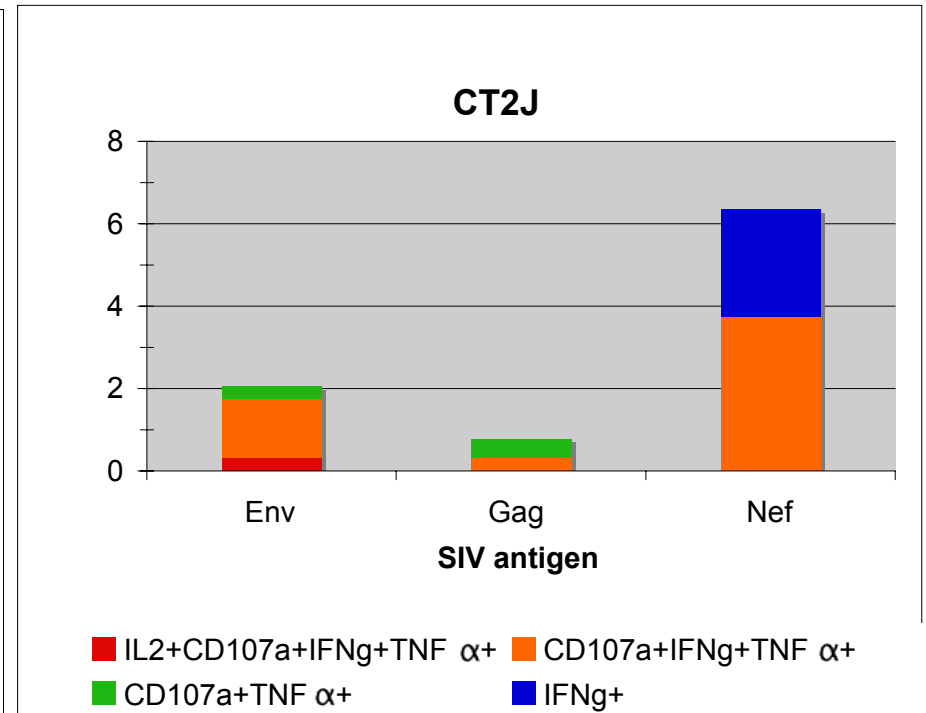
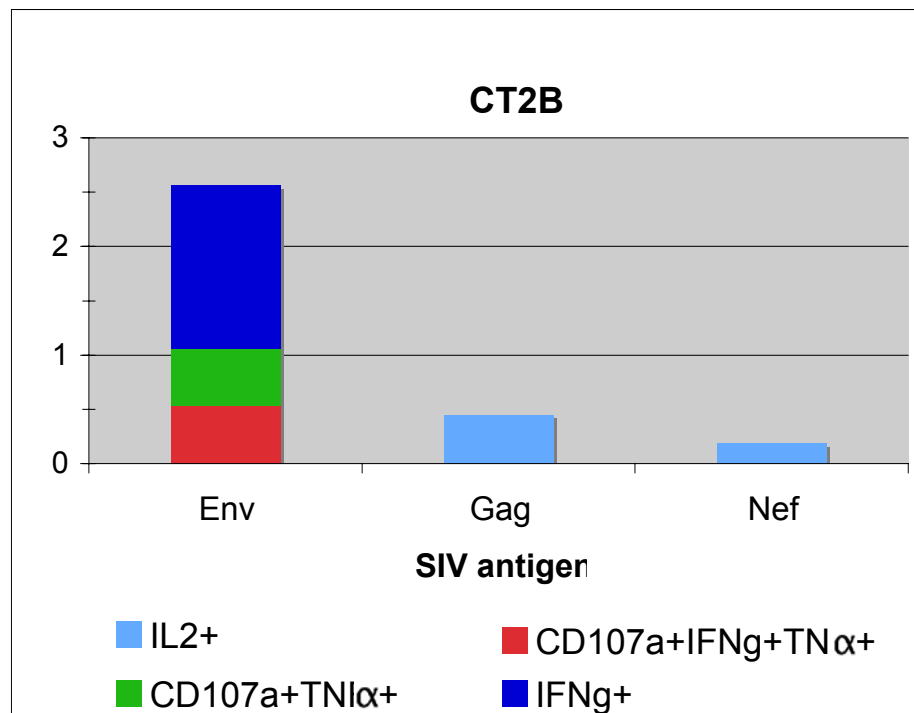
CD4 Cell



Group #2

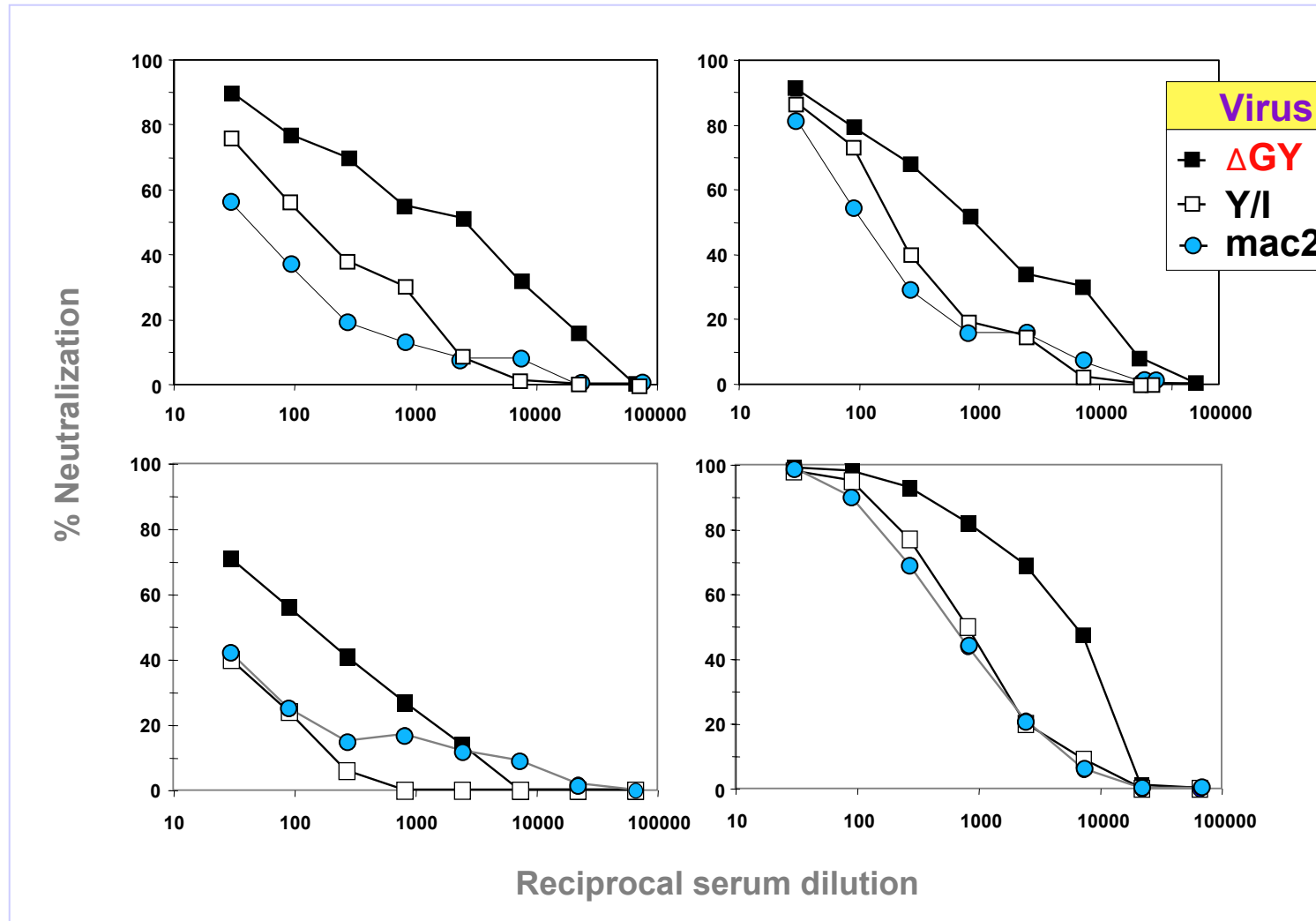
CD8 T cell responses to SIV antigens in Δ GY-infected animals

Pre-E660 Challenge

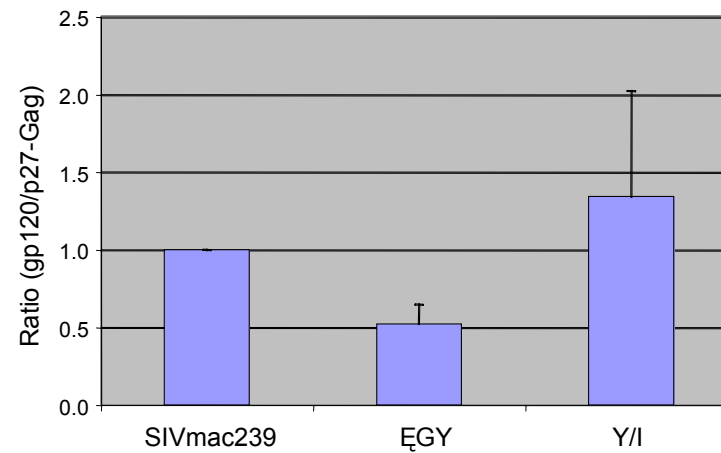
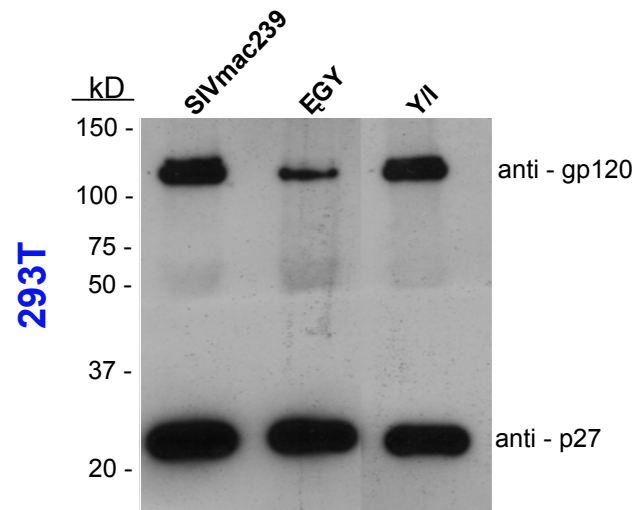
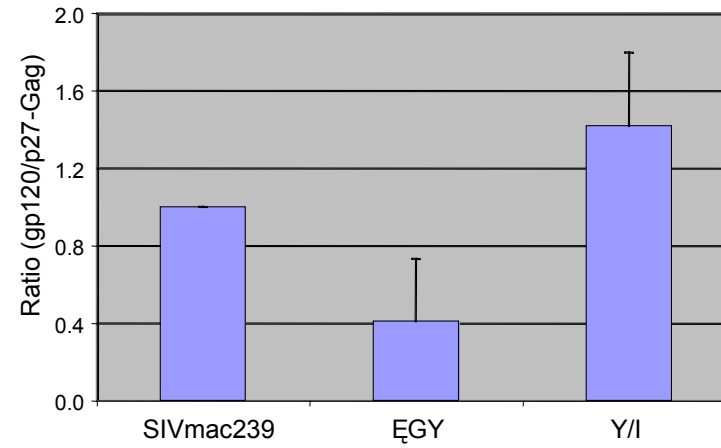
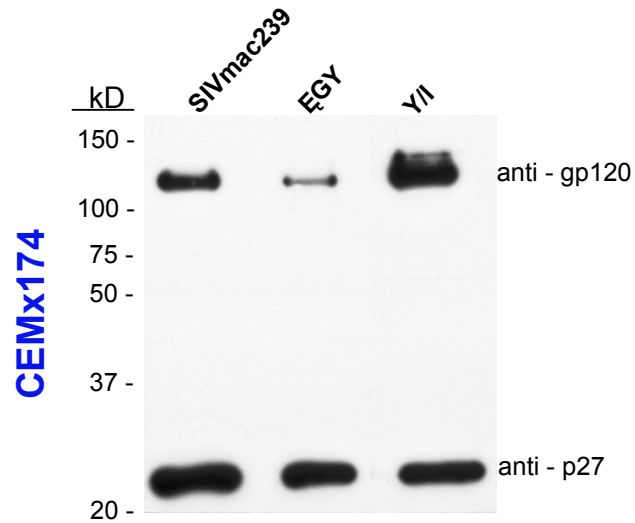


Δ GY infection = (818 days, 2.2 years)

Increased Neutralization Sensitivity of Δ GY to sera from SIVmac239-infected macaques



Decreased Env incorporation into Δ GY virions



Δ GY: Conclusions and Caveats

(**Caveats:** Small numbers of animals; rhesus vs. pigtailed)

n = 5 (pigtail)

2 (mac239 challenge)
5 (E660 challenge)

8.3×10^5
 2.3×10^6
 3.5×10^6
 4.2×10^6
 1.6×10^7

- Acute Viral Peak- (High)
- Viral Set Point- (Very low)
 - 5 of 5 animals- undetectable
 - Follow-up: 2 animals (6.6 years); 3 animals (3.8 years)
- Protection from SIVmac239 challenge
- Protection from E660 challenge
 - 5 of 5 animals with E660 viral set points <100
 - Follow-up: 2 animals (2.6 years); 3 animals (1.5 year)
- Immune correlates- (Unknown)
 - CD8 cells-> for both Δ GY control and E660 control
 - Antibodies-> increased neutralization sensitivity for Δ GY
- Possible mechanism for attenuation- (e.g.)
 - Virions with less Env
 - Increased susceptibility of infected cells to cellular control?
 - Less GALT Depletion?
 - Less chronic immune activation?

Where is the virus?
What cells is it infecting?
Cytotoxicity?
Inflammatory responses?

Host

Virus

Δ GY

Cell

Alterations in viral assembly
Qual./Quant. alterations Env
Mechanisms of neut. sensitivity

Transport pathways
Subcellular compartments
Cellular partners for TM tail
Cell-type specific differences

**Immune
Response**

Qualitative differences
Quantitative differences
Cellular & Humoral
Immune correlates

Acknowledgments

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Past

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Present

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