



*Envelope Variation as a Primary Determinant of Lentiviral Vaccine Efficacy**

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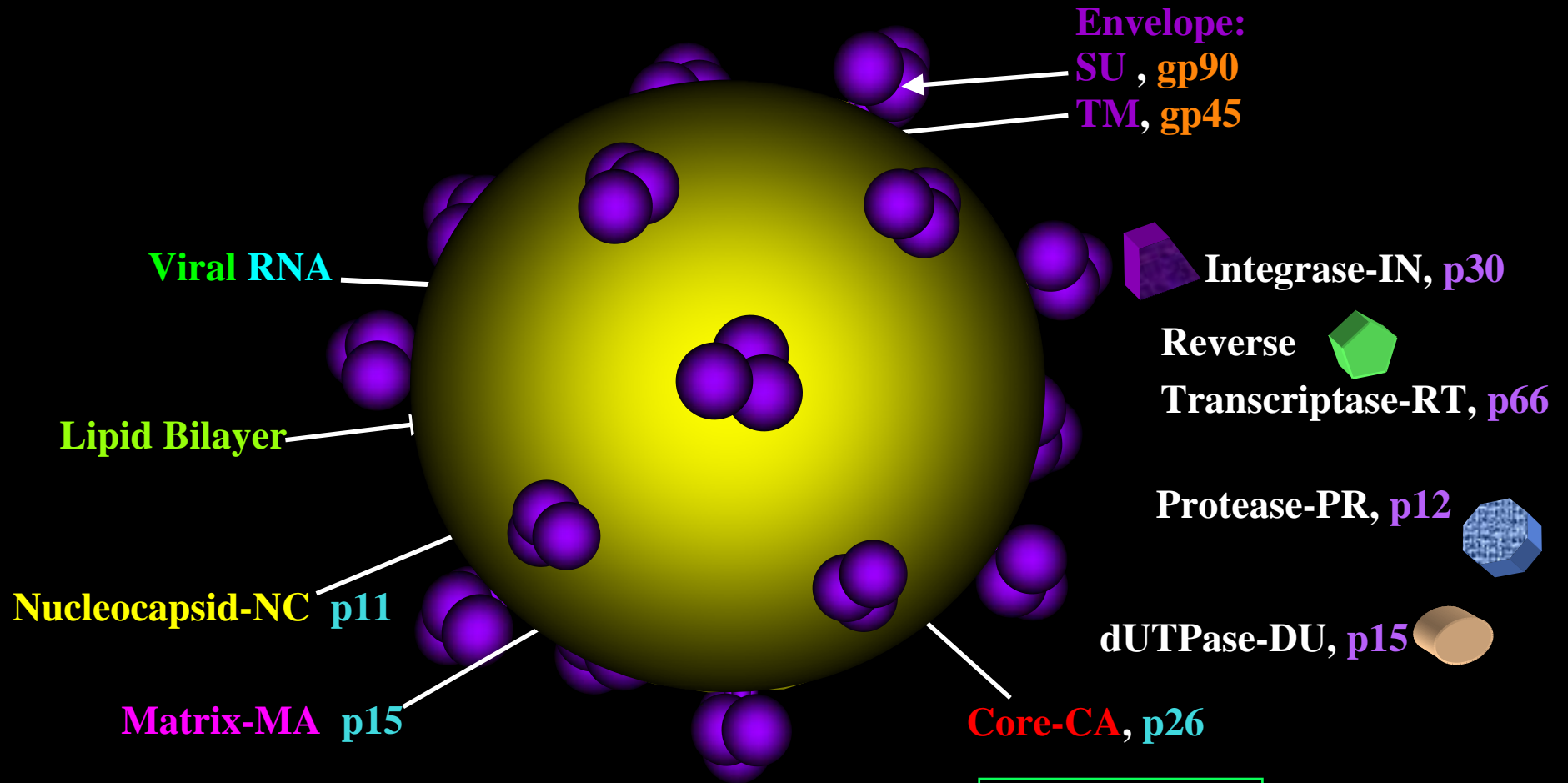
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**Craigo et.al., (2007) PNAS (in press)*



The EIAV Virus



Pol

$\Delta S2 \Rightarrow EIAV_{D9}$

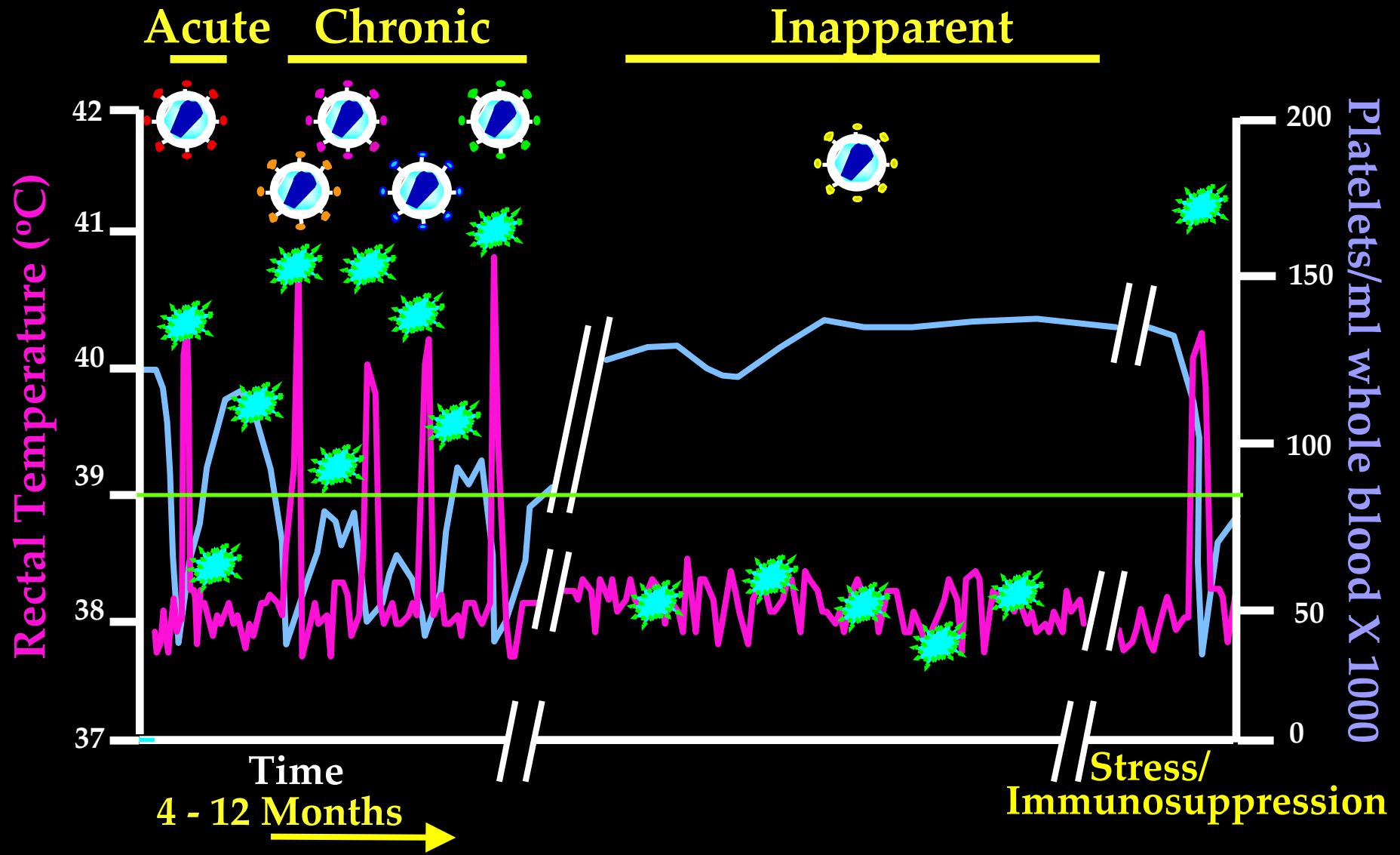


Gag



Env

Typical Clinical Course of EIAV Infections



Similarities Between EIAV & HIV

- Transmitted via blood
- Macrophage/monocyte tropism
- Diverse Env quasispecies & antigenic heterogeneity
- Envelope architectural characteristics
 - Extensive glycosylation
 - Immune decoys
- Similarities ➡ significant to initial virus exposure:
 - Key factors most relevant to vaccine efficacy

Efficacy of Attenuated EIAV Vaccine Trials

EIAV vaccine strain/dose	Route	Plasma viral RNA levels (DOC)	Interval to Challenge (months)/ dose	Protection from clinical disease (%)	Protection from detectable infection (%)
<i>EIAV_{D9}/10⁵</i>	IM	10 ³	6/LDME	8/8 (100%)	8/8 (100%)
<i>EIAV_{D9}/10⁵</i>	IV	10 ³	6/LDME	8/8 (100%)	8/8 (100%)
<i>EIAV_{D9}/10⁵ & 10³</i>	IM	10 ³	6/LDME	12/12 (100%)	12/12 (100%)
<i>EIAV_{D9}/10⁶</i>	IV	10 ³	6/3000 HID	3/3 (100%)	3/3 (100%)*
Control	NA	NA	LDME/3000 HID	0/16 (0%)	0/16 (0%)

***Plasma & Tissues**

LDME, Low Dose Multiple Exposure

HID, Horse Infectious Doses

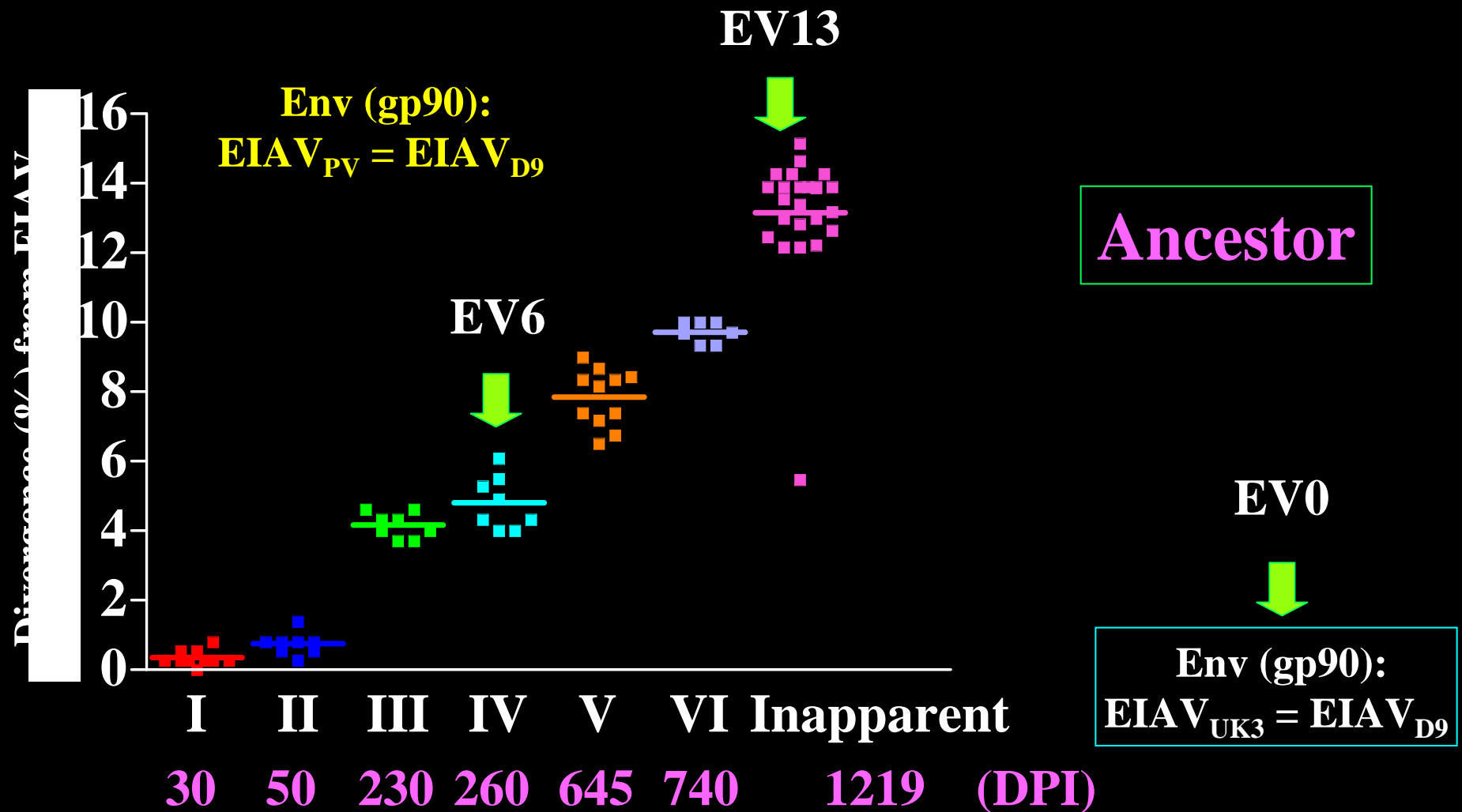
Working hypothesis:

Envelope is a primary determinant of viral pathogenesis & vaccine efficacy

Challenge Strains: Variant Envs in Identical Proviral Backbones

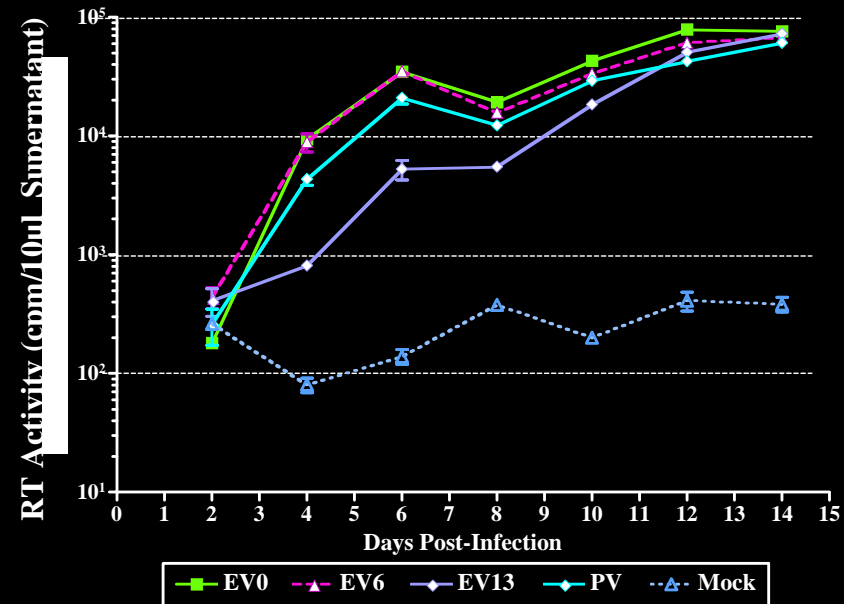


Development of Challenge Strains with Defined, Increasing Levels of Variation



In Vitro Analyses: Replication Kinetics

Fetal Equine Kidney cell infections:



In Vivo Analyses: Clinical Disease

(4 Ponies/EV strain)

100%, Peak viral loads ~10⁵-10⁷ cp RNA/ml

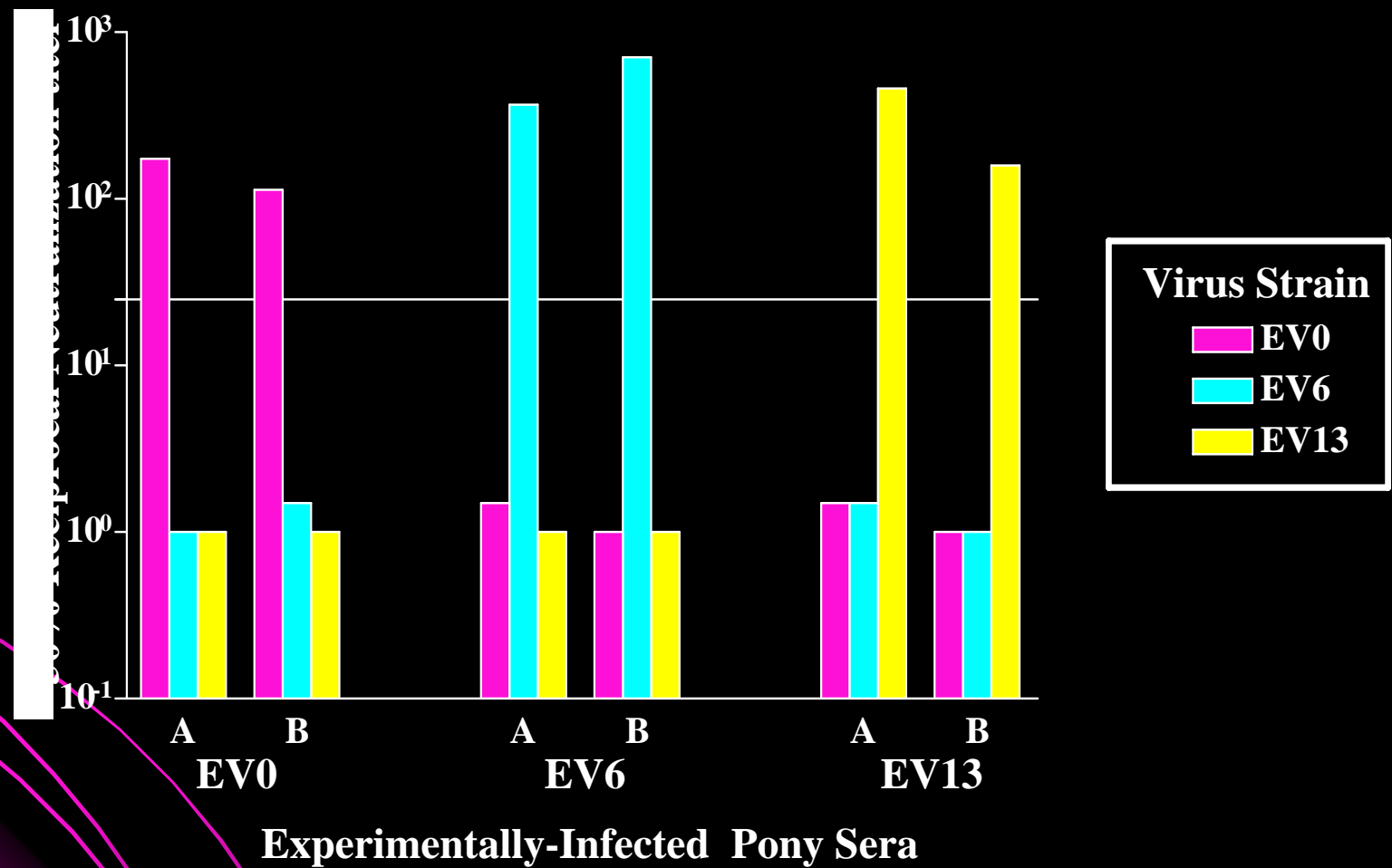
Replication Dynamics

Steady state viral loads ~ 10⁴ cp RNA/ml

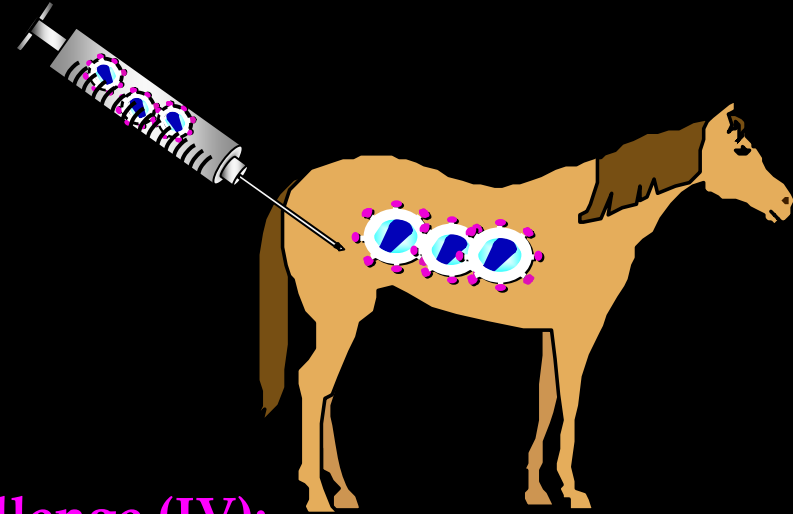
Immunogenicity/Serology (6MPI)

Env-Spec Titer ~ 10⁵
Avidity ~ 43%
Conformation Ratio ~ 1.1

Challenge Strains were Neutralization Distinct



Immunization & Challenge



Inoculation (IM) EIAV_{D9}:

24 EIAV naïve ponies

10^3 TCID₅₀ 10^3 TCID₅₀



0 1 2 3 4 5 6 7 8 9 10 11 12

MONTHS POST IMMUNIZATION

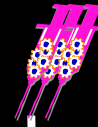
Monitor

- Clinical signs
- EIAV-specific antibody response
- EIAV-specific cellular response
- Plasma viral load

Challenge (IV):

3 groups of 8 vaccinated 3 groups of 6 EIAV naïve (control) ponies

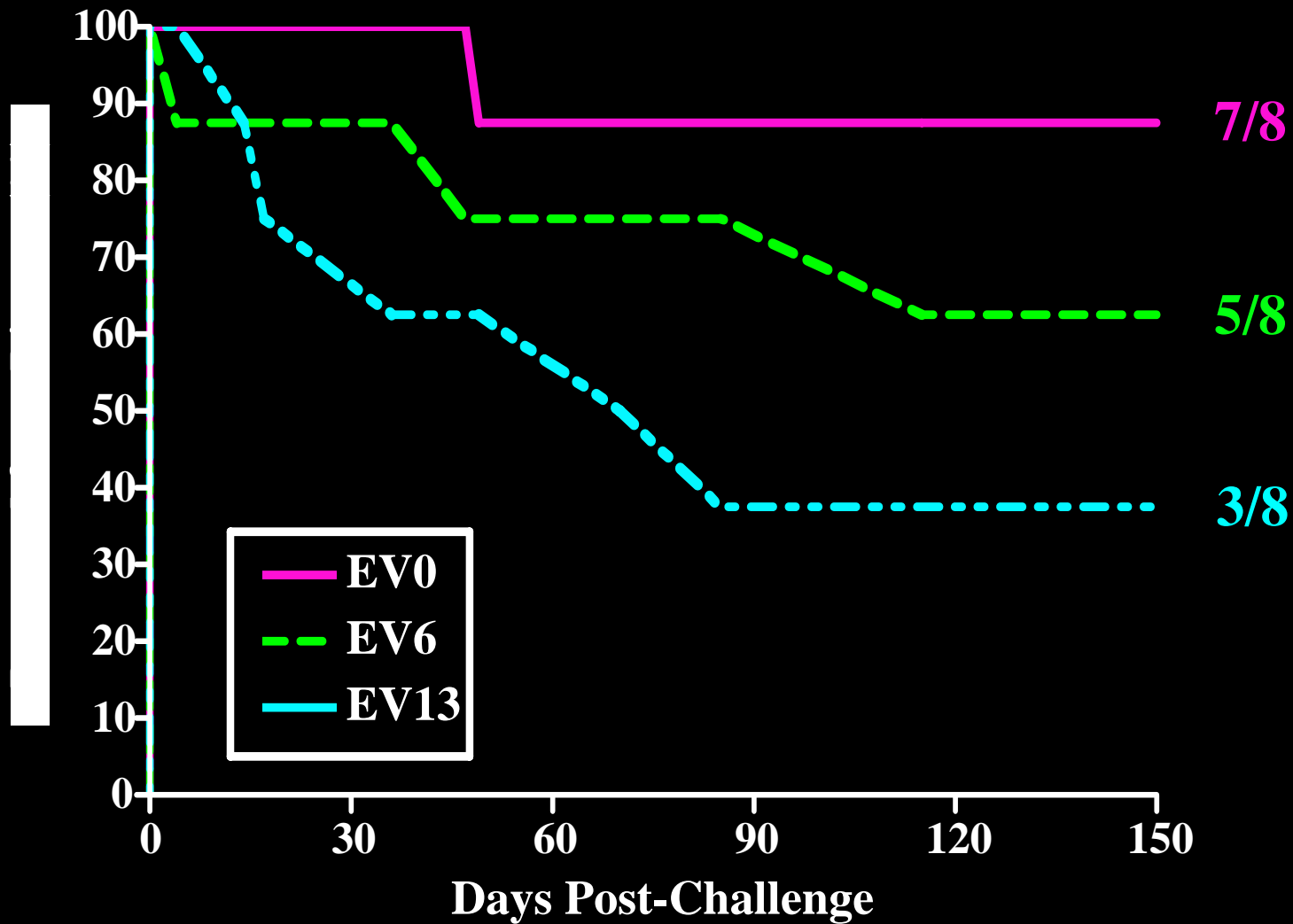
10^3 TCID₅₀ EV0, EV6 or EV13



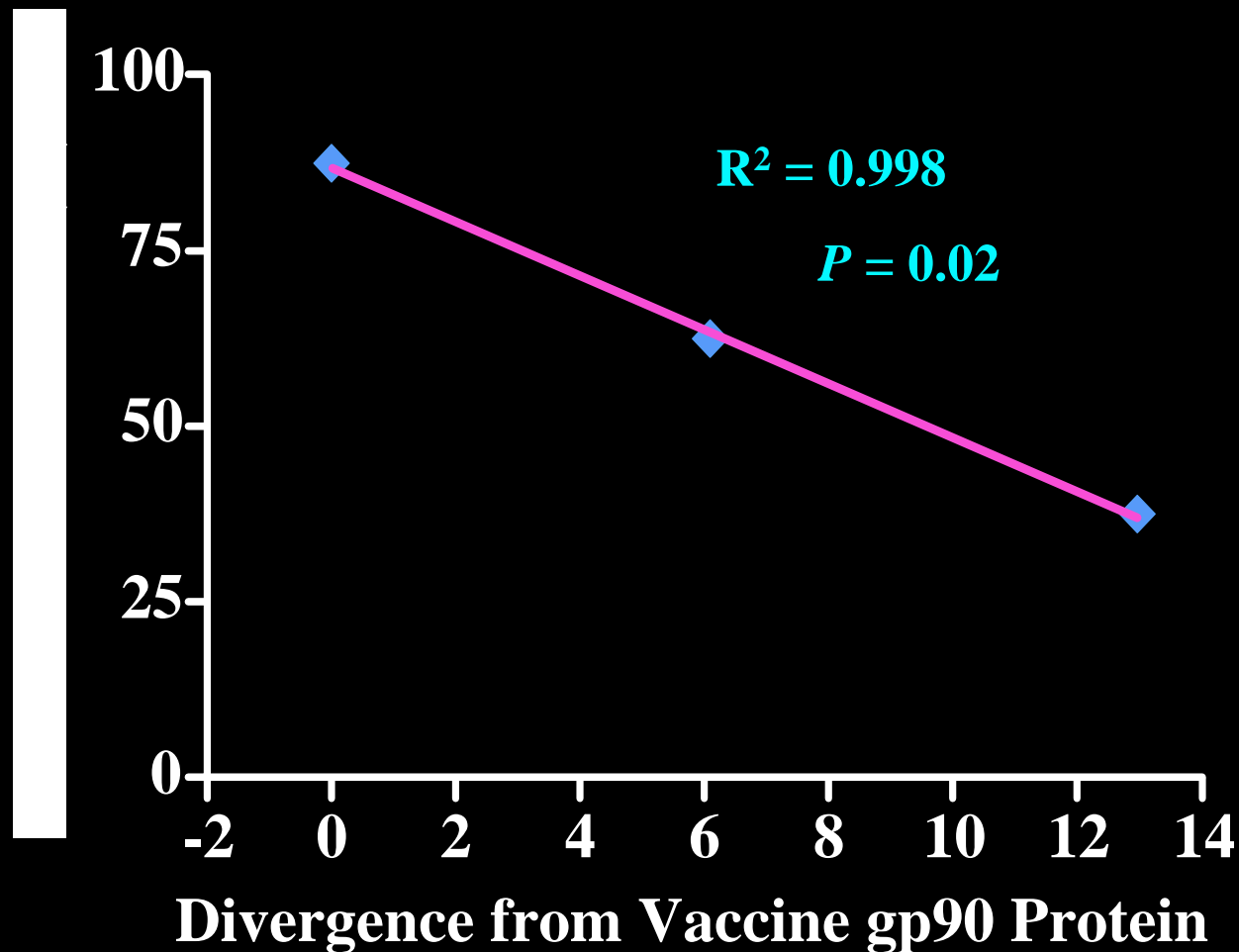
Monitor

- Clinical signs
- EIAV-specific antibody response
- EIAV-specific cellular response
- Plasma viral load
- RT PCR for WT Challenge

Protection from Clinical Disease



Inverse Correlation of Disease & Divergence



When Y (Protection) = 0 , X (Divergence) = 23

Conclusions

- Envelope variation alone dramatically affected protection from disease
- Envelope gp90 variation had a significant inverse linear association with protection from disease
- Envelope gp90 (SU) variation in the absence of gp45 (TM) variation is a critical determinant for vaccine efficacy
- Ancestral envelope did not confer broad levels of protection
 - 6% variation protection dropped by 25%
 - 13% variation, protection dropped by 50%

Implications

- Minimal envelope variation can pose a major obstacle to lentiviral vaccine efficacy
- Ancestral envelopes as individual immunogens in our system will not confer protection against lentiviral quasispecies
- Multivariant immunogens?
- Consensus immunogens?



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