Comparative efficacy of Gag/Pol/Env vaccines derived from temporal isolates of SIVmne against cognate virus challenge

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Differential Phenotypes of Temporal Isolates of HIV

• Viruses isolated early during the asymptomatic phase, are typically macrophage-tropic, slow replicating, minimally cytopathic, and non-syncytium inducing: M-tropic, slow-low/NSI phenotype

• Viruses emerge later are often able to infect CD4⁺ T-cell lines, and replicate rapidly, cytopathic, and syncytium inducing: T-tropic, rapid-high/SI phenotype
Questions

• Do vaccines derived from early or late isolates induce qualitatively different immune responses?
• Do these responses show differential protection against early or late virus isolates?
Temporal Isolates of SIVmne

- Inoculum: SIVmne CL8 (molecular clone of E11S)
  - Slow replication kinetics
  - Macrophage tropic
  - Low cytopathicity
- Late (Wk 170) isolate: SIVmne 170
  - Rapid replication kinetics
  - Syncytium-forming
  - Highly cytopathic

Differential In Vivo Pathogenicity of Temporal Isolates of SIVmne

Kimata et al. Nat Med. 5:535-541, 1999
Preferential Transmission or Amplification of E11S-like Viruses After Intrarectal Inoculation

Inoculum

A

SIvMne uncloned virus

Inoculum

Intrarectal challenge (n=6)

93204

93205

93206

93191

93080

92175

Intravenous challenge (n=10)

91319

91320

91323

91324

92170

93032

92179

91064

91070

92168

PBMC cDNA isolated 2 wks after inoculation of naïve animals

Polacino et al. J. Virol. 73:3134-3146, 1999
Study Design

• Recombinant vaccinia virus priming (wk 0 and 8)
  – Each vaccinee receives two recombinants: one expressing Gag-Pol; the other, Env gp160
  – Two isolates: SIVmne CL8, or SIVmne 170
• A single booster immunization 10 or 12 mo later with the cognate recombinant proteins: Gag-Pol and Env
• N=16 vaccinees per arm; 16 naïve controls
• Four weeks after the booster immunization, animals were challenged intravenously with CL8, 170 or chimeric viruses between CL8 and 170, all at 20 50% animal-infectious doses (AID$_{50}$)
CL8 Vaccines Protected Against Homologous CL8 Virus Challenge

Mean Plasma Viral Load (vRNA eq/ml)

Challenge Virus: CL8

Weeks after Challenge

- CL8 Imm
- Cont CL8

p<0.004
CL8 Vaccines Failed to Protect Against SIVmne170 Challenge

**Challenge Virus:** CL8

![Graph showing mean plasma viral load (vRNA eq/ml) over weeks after challenge.](image)

Weeks after Challenge

p<0.004
170 Vaccines Failed to Protect Against Late Virus Challenge

Challenge Virus:  CL8

Challenge Virus:  170 Wk

Weeks after Challenge

Mean Plasma Viral Load (vRNA eq/ml)

p<0.004
170 Vaccine Also Failed to Protect Against CL8 Challenge

**Challenge Virus: CL8**

**Challenge Virus: 170 Wk**

![Graph showing mean plasma viral load (vRNA eq/ml) across weeks after challenge.](image-url)

- **CL8 Imm**
- **170w Imm**
- **Cont CL8**

Weeks after Challenge:

- 0
- 4
- 8
- 12
- 16
- 20
- 24

Mean Plasma Viral Load (vRNA eq/ml): p<0.004
Chimeric Viruses Derived from Temporal Isolates of SIVmne

Persistent and High Viral Load Following Infection with CL8 and 170 Chimeras

- Challenge Virus: 170/8
- Challenge Virus: 8/170

Weeks after Challenge

Mean Plasma Viral Load (vRNA eq/ml)

- Cont CL8/170
- Cont 170/CL8
Chimeric Viruses Are Pathogenic In Vivo

Weeks after challenge

Mean CD4⁺ T cells/ul of blood
CL8 Vaccines Control Infection by Chimeric Viruses 170/8 and 8/170

Challenge Virus: 170/8

Challenge Virus: 8/170

Weeks after Challenge

Mean Plasma Viral Load (vRNA eq/ml)

p<0.001

p<0.001
170 Vaccine Failed to Protect Against Chimera with Env from the Late 170 Isolate

Challenge Virus: 170/8

Challenge Virus: 8/170

Weeks after Challenge

Mean Plasma Viral Load (vRNA eq/ml)
Partial Control of CL8 Env Chimera (170/8)
Infection by 170 Vaccines

Challenge Virus: 170/8

Challenge Virus: 8/170

Mean Plasma Viral Load (vRNA eq/ml)

Weeks after Challenge
SIV-Specific Antibody Response* to Prime-Boost Immunization with SIVmne CL8 or 170 Vaccines

*ELISA Antigen: SIVmne E11S
SIV-Specific IFN-γ⁺ T-cell Response* to SIVmne CL8 or 170 Vaccines on Day-of-Challenge

*Stimulating Antigen: AT-2 inactivated SIVmne E11S
Summary

• CL8 vaccines protected against CL8 challenge
• Not entirely because CL8 is “wimpy”: CL8 vaccines protected against 170/8 and 8/170 chimera, infection by which resulted in high and persistent plasma viral load
• Env-specific responses played a major role in protective immunity elicited by this vaccine regimen
• Neither CL8 nor 170 vaccine protected against the late isolate 170, possibly it represents escape variants
• Vaccines based on the late isolate 170 failed to protect against the homologous virus170, or even the “wimpy” virus CL8
Questions

• Vaccines: Are vaccines based on late HIV isolates relevant for protection against transmitted viruses?

• Model: Are challenge models based on late viral isolates relevant for vaccine evaluation?
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