Heterologous Tier 1 R5 SHIV-C Challenges: Correlates of Protection

Enterprise Meeting:
“The Appropriate Use of Tiered Virus Panels when Assessing HIV-1 Vaccine-elicited Neutralizing Antibodies"

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Topics

1. Paired tier 2 and tier 1 clade C SHIVs with exclusive R5 tropism

2. Orientation of V2 and access to the CD4 binding site

3. Correlates of protection:
   i. Anti-Env nAbs
   ii. Cell-mediated immunity
   iii. Protection-linked mimotopes
   iv. An unexpected humoral correlate of protection
Paired Tier 2 and Tier 1 R5-only SHIV-C Strains with HIV-1-like LTRs

- SHIV-1157i: parental infectious molecular clone (IMC); encodes env of Zambian infant 1157i; the parental SHIV-1157i was inoculated into a neonatal rhesus monkey (RM) that progressed to AIDS

- SHIV-1157ipd3N4, tier 2; pathogenic IMC\(^1,2\); encodes the “late” env cloned from this diseased RM 135 weeks post-infection\(^3\).

- SHIV-1157ipEL-p, tier 1, encodes the recently transmitted, “early” env version of the same env originally isolated from Zambian infant 1157i who became a long-term nonprogressor. The biological isolate, SHIV-1157ipEL-p, was generated after re-adaptation by rapid serial passage at peak viremia\(^4,5\).

Both SHIV-Cs have engineered LTRs with NF-kB site duplications (SIVmac239, the backbone for the SHIVs, has only 1 NF-kB site/LTR).

\(^1\)Song et al., J Virol 2006; \(^2\)Garcia et al., 2010; \(^3\)Humbert et al., Retrovirology 2008; \(^4\)Siddappa et al., PLoS One, 2010; \(^5\)Watkins et al., J Virol 2011
Flipping the V2 Position: Loss of Access to the CD4 Binding Site


Mauve early Env; Olive late Env
Recombinant Proteins as Immunogens

- In Incomplete Freund’s Adjuvant (IFA)

- Multigenic protein immunogens: SIV Gag-Pol (core) particles, HIV Tat, trimeric HIV1084i gp160 (tier 2)

  - **Group 1 (8 monkeys):**
    - Gag-Pol particles of SIVmne (differing from challenge virus)

  - **Group 2 (4 monkeys):**
    - Gag-Pol particles of SIVmac239 (identical to challenge virus)

- **Tier 1 challenge virus:** SHIV-1157ipEL-p (“early” env); 5x low-dose i.r. followed by 1X high-dose challenges

The primary HIV-Cs, HIV1084i and HIV1157i, were isolated from different infants of the same cohort of HIV+ mothers/infants in Lusaka, Zambia. Both viruses are recently transmitted isolates and represent HIV Env heterogeneity (22.1%) of different viruses circulating in the local community.

¹Lakhashe et al., *PLoS One*, 2011
SHIV-1157ipEL-p: env derived from long-term nonprogressor infant
SHIV-2873Nip: env derived from rapid progressor infant
Correlates of Protection

Neutralizing Ab titers ($IC_{90}$) as well as the sum of SIV Gag + HIV Tat IFN-γ ELISPOTs were significantly linked to lower tier 1 SHIV-C peak viremia.
Protection-linked mimotopopes
Protection-linked Biopanning to Identify Ab Epitopes Associated with Vaccine Success: No Bias

PL biopanning is independent of the mechanism(s) by which Abs protected the monkeys against virus challenges. There is also no \textit{a priori} bias toward any given Ab target.

\cite{Bachler2013}
An unexpected humoral correlate of protection
**Sequence Alignment and Mimotope Location on HIV-1 Tat**

### A

<table>
<thead>
<tr>
<th>Biopanning #</th>
<th>Yield of Ab epitopes</th>
<th>Yield of mimotopes</th>
<th>Mimotope name</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Induced by vaccination (PL-biopanning)</td>
<td>Tat mimotopes isolated using RGe-11 (PL-Tat mime)</td>
<td>r-12-A7</td>
<td>S N T T M L L E P W K V Y</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>r-12-B5</td>
<td>H S L S P L E A W K T T</td>
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<td></td>
<td></td>
<td></td>
<td>r-12-C11</td>
<td>N S W M W L E P W K Y T</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>r-12-D12</td>
<td>N M P Y M R M E P W K L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>r-12-F4</td>
<td>S N H Y Y F L E P W K A</td>
</tr>
<tr>
<td>II.</td>
<td>Induced by vaccination (conventional biopanning)</td>
<td>Tat mimotopes isolated using RA9 (RA9 Tat mime)</td>
<td>At1-2</td>
<td>W E P V D P R S Y - W N I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At1-A10</td>
<td>T S K L E P W K A W D H</td>
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<td></td>
<td></td>
<td>At1-D3</td>
<td>Y T G P L E P W K K Q R</td>
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<tr>
<td>III.</td>
<td>Induced by exposure to first challenge virus</td>
<td></td>
<td>At-2-9</td>
<td>T Q A R A T L E P W K H</td>
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<td></td>
<td></td>
<td></td>
<td>At-2-F7</td>
<td>A V - S L E P W K W N M S</td>
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<td></td>
<td>At-2-H4</td>
<td>E W P M W V L E P W K R</td>
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<td></td>
<td>At-2-D8</td>
<td>T S K L E P W K A W D H</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>At-2-E1</td>
<td>G T D M S Q M E P W K T</td>
</tr>
</tbody>
</table>

Shaded in grey: AA sequences identical to Tat immunogen (HIV-IIIB)

### B

Summary: Lessons Learned from Tier 1 SHIV-C Challenges

Passive immunization\(^1-^3\)

- Complete cross-clade protection with an anti-V3 loop crown human IgG1 nmAb (HGN194)
- Significantly better immune exclusion by the dimeric IgA1 (dIgA1) version of the same anti-V3 loop crown nmAb than with the dIgA2 form; the dIgAs were given mucosally
- Strong synergy between the IgG1 form of HGN194, given intravenously at a suboptimal dose, and the intrarectally administered dIgA2 form, against intrarectal SHIV-C challenge

Active immunization: correlates of protection (significant lowering of peak viremia)\(^4,5\)

- Cell-mediated immune responses
- nAb titers (TZM-bl and PBMC assays)
- Abs targeting the neutralizing N-terminus of HIV-1 Tat, but not those against the full-length Tat protein, were significantly linked to lower SHIV-C peak viremia
- Serum IgG isolated from vaccinees neutralized Tat transactivation \textit{in vitro}
- A panel of protection-linked Env mimotopes

\(^1\)Watkins et al., \textit{PLoS ONE} 2011; \(^2\)Watkins et al., \textit{AIDS} 2013; \(^3\)Sholukh et al., \textit{Retrovirology} 2015; \(^4\)Lakhase et al., \textit{PLoS ONE} 2011; \(^5\)Bachler et al., \textit{J Virol} 2013
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