From the Bench to the Bedside & Back Again…

Lessons from HPTN035

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How well did preclinical **efficacy** models predict outcomes?

How well did preclinical **safety** models predict outcomes?

How should we modify the models to provide more predictive biomarkers of efficacy & safety?
## Pre-Clinical Evaluation Score Card: HIV

<table>
<thead>
<tr>
<th></th>
<th>PRO 2000</th>
<th>BufferGel</th>
<th>Cellulose sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple clades</td>
<td>Yes</td>
<td>Variable; some enhancement⁴</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell-associated vector transmission</td>
<td>Yes</td>
<td>Yes; ↓ motility &amp; viability of immune cells pH 5.0²</td>
<td>Yes</td>
</tr>
<tr>
<td>Activity in seminal plasma</td>
<td>↓4-fold(R5)¹</td>
<td>Semen:Gel 1:1→pH 4.5-5.0²</td>
<td>↓↓57-fold (R5)¹</td>
</tr>
<tr>
<td>Half-life</td>
<td>? Hours</td>
<td>Short acting</td>
<td>??</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Mild/↓SLPI</td>
<td>Tested with diaphragm/↓SLPI³</td>
<td>moderate</td>
</tr>
<tr>
<td>Epithelial barrier</td>
<td>Minimal</td>
<td>Not done</td>
<td>moderate</td>
</tr>
</tbody>
</table>

¹*BMC Infect Dis.* 2006; 6: 150  
²*BMC Infect Dis.* 2005 30;5:79  
⁴*J Acquir Immune Defic Syndr.* 2006;43(4):499
Anti-HIV Activity in CVL Pre & Post Gel: Spiking Strategy

HeLaCD4-CCR5 cells & JRFL

p < 0.001

HeLaCD4-CCR5 cells & JRFL
CVL Post-Application Inhibits HSV

PRO 2000 Gel

Placebo Gel

p < 0.001
Anti-HSV Activity Reduced if Virus Introduced Diluted in Seminal Plasma

The PRO 2000 in CVL samples were 97 and 166 μg/ml.

J Infect Dis. 2007;196(9):1394
Interference Translates to Interference Translates to Murine HSV Model

Days Post Infection

Percent survival

N = 20

Placebo; vPBS
Placebo; vSeminal
2% PRO; vPBS
2% PRO; vSeminal

P = 0.0007
P = 0.0001
# Post-Coital PRO 2000 Gel Study

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug</td>
<td>No drug</td>
<td>Drug</td>
<td>Drug</td>
</tr>
<tr>
<td>No coitus</td>
<td>Coitus</td>
<td>Coitus</td>
<td>No coitus</td>
</tr>
<tr>
<td>Intrinsic anti-viral activity in CVL</td>
<td>Impact of semen on intrinsic anti-viral activity</td>
<td>Impact of semen on drug &amp; anti-viral activity following spiking</td>
<td>Anti-viral activity following spiking</td>
</tr>
</tbody>
</table>
Why no efficacy against HSV?

- Greater interference by semen

- **Anatomy**
  - Drug needs to be at the introitus & labia to prevent HSV; applicators designed to deliver drug to the posterior vagina/cervix
  - MRI studies demonstrate ↑ bare spots in the lower vagina (3 cm above the introitus)*

- Higher attack rate

*Contraception. 2009 Apr;79(4):297-303
Safety models

- Dual chamber model
- Murine model
- Expanded Phase I safety model
Intact mucosal epithelium is impervious to HIV-1

Disrupted epithelium allows HIV-1 across to infect target cells

Mucosal epithelium

T-cells

Disruptive agent
Dual Chamber Model

- Impact on epithelial integrity
  - Cell architecture (confocal)
  - Transepithelial Electric Resistance (TER)

- Inflammatory response
- Impact on HIV-1 translocation
  - p24 detection
  - Confocal microscopy
Summary of Findings

- N-9 and cellulose sulfate, but not PRO 2000 or tenofovir, triggered drop in TER.
- Drop in TER associated with increased migration of HIV across epithelial barrier & infection of immune cells in basal compartment.
- Cellulose sulfate, but not PRO 2000 or tenofovir, activated NF-κB pathways and enhanced HIV replication in U1 cells.

Mesquita et al JID, 2009 in press.
Moving forward…

- Clades important
- Cell-free vs. cell-associated
  - Data inconclusive… ? both transmit
  - How do IC50’s translate; which assays?
- Rapid onset of action & sustained effect critical
- Postcoital studies
- Modify HSV models
  - HSV & HIV infect different sites?
  - Male-female transmission models (? cotton rat)
- Modify Phase I studies