Heterologous Prime-Boost & Adjuvanted Env Protein HIV Vaccine Approaches

Susan W. Barnett
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Background & vision of HIV vaccine

- Phase III Thai trial (RV144) was “tipping point” for HIV vaccines (ALVAC prime-Env protein boost)
- Primary goal of an effective HIV vaccine is to prevent infection/virus dissemination
- Vaccine candidates might include:
  - Vector/nucleic acid prime plus adjuvanted protein boost
  - Proteins with safe & potent adjuvants
  - Combined prevention strategy using anti-retrovirals, microbicides, and vaccine interventions
Clinical efficacy of RV144 HIV vaccine trial waned over time

- Env Ab-mediated protection
- V2 Abs associated with protection
- Abs waned over time

Vaccine Efficacy 60% at 6-12 months

B. Haynes, et al., NEJM, 2012
Key components of effective vaccines

- Nucleic Acid & Viral Vectors
- Delivery System
- Immune Potentiator
- Antigen
- Long-lived B & T cell memory
- MF59 or Alum
- HIV Env

e.g., TLR agonist
MF59®: a safe & potent adjuvant

An oil-in-water emulsion used in licensed product (Fluad)

Composition:
- 0.5% Polysorbate 80 water-soluble surfactant
- 0.5% Sorbitan Triolate oil-soluble surfactant
- 4.3% Squalene oil
- Water for injection
- 10 mM Na-citrate buffer

Density: 0.9963 g/ml
Size: 160nm

- MF59 increases antigen uptake and activates local immune cells
- Dose sparing, improved vaccine immunogenicity & efficacy
- 150 million doses of MF59® vaccines distributed with no safety signals
Enhancing, dose-sparing effects of MF59 on pandemic flu vaccine (H5N1) in humans

- Higher frequencies of H5 CD4 T cells
- Higher frequencies of H5N1 memory B cells
- Protective antibody titers after two doses, broadly neutralizing drifted H5 clades

Galli et al. PNAS 2009
MF59® adjuvanted influenza vaccine, Fluad, was 75% more efficacious than non-adjuvanted vaccines in young children.

* Statistically significant; ‡ Post-hoc analysis

1 Vesikari T et al., NEJM, 2011.
Modulation and enhancement of MF59 potency

- Antibodies
  - MF59 alone
  - MF59 + TLR agonist

- Th1 T cells
  - IFNγ positive CD4 T cells (per 10^5)

Geometric Mean ELISA Titer (IgG)
MF59 + CpG enhances neutralizing antibody responses against SF162 in rabbits

B. Burke, et al., Virology, 2009
Evaluation in NHP of alum and MF59-based formulations using TLR4 and TLR7 SMIPs

Groups:
1. ENV
2. ENV + Alum
3. ENV + Alum + TLR4
4. ENV + Alum + TLR7
5. ENV + MF59
6. ENV + ANE/TLR4
7. ENV + ANE/TLR7
8. ENV + pIC:LC
9. ENV + ISCOM

From Bob Seder et al. unpub.
Preclinical POC for prime-boost & adjuvanted Env
Protection by active immunization in SHIV macaque model

- Protection in macaques against mucosal or systemic virus challenge using:
  - DNA prime-Env protein boost (Cherpelis, 2001; Buckner, 2004)
  - Alphavirus prime-Env protein boost (Xu, 2006; Barnett, 2010)
  - Adenovirus prime-Env protein boost (Lubeck, 1997; Bogers, 2008)
  - Vaccinia prime-Env protein boost (Hu, 1992; Hu, in prep)
  - Adjuvanted Env protein alone (Barnett, 2008; Verschoor, 1999)

- Antibody-mediated protection observed
  - High titer & high avidity binding Abs
  - Virus neutralizing Abs
  - ADCC

- CD4+ T helper responses
Summary

- Active immunization with HIV Env vaccines conferred antibody-mediated protection in SHIV-macaque model
  - Protection vs. homologous or closely related heterologous challenges
  - High dose intravaginal, intrarectal, and intravenous challenges
  - Gag-specific CTL not required for protection in these studies
  - Antibody-mediated protection (high titer, high avidity, neutralizing, ADCC)
  - Proof-of-concept established for Env-based vaccines with or without V2 loops

- SIV-based vaccine – low dose repeated mucosal challenge studies in progress for several of these approaches to confirm results

- These results are consistent with the observed efficacy of the prime-boost approach employed in RV144
### Phase 1 trial of DNA/PLG prime Env protein boost

#### HVTN049 clinical trial design (SF162 gp140ΔV1 Env)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number Active (Control)</th>
<th>Dose DNA / gp140 µg (per plasmid)</th>
<th>Part A: Dose Escalation</th>
<th>Part B: Explore Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Month</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>T1</td>
<td>10 (2)</td>
<td>250 / 100</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>T2</td>
<td>10 (2)</td>
<td>500 / 100</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>T3</td>
<td>10 (2)</td>
<td>1000 / 100</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>T4</td>
<td>20 (4)</td>
<td>1000 / 100</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>T5</td>
<td>30 (6)</td>
<td>None / 100</td>
<td>gp140</td>
<td>gp140</td>
</tr>
<tr>
<td>Total</td>
<td>80 (16)</td>
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</table>

Neutralizing Ab responses in HVTN 049 Phase 1

Elicitation of high titer Tier 1 neutralizing Abs

From David Montefiori.
HVTN 049 ICS magnitude of positive responses to Env or Gag (Pool 1)

**CD4+ T Cells**

- Positive response
- Negative response

<table>
<thead>
<tr>
<th></th>
<th>2 weeks post VAC5</th>
<th>2 weeks post VAC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1/13</td>
<td>0/29</td>
</tr>
<tr>
<td>Any Pool 1</td>
<td>6/9</td>
<td>0/9</td>
</tr>
<tr>
<td>gp140</td>
<td>8/9</td>
<td>0/9</td>
</tr>
<tr>
<td>250 mcg DNA/PLG + gp140</td>
<td>20/26</td>
<td>0/9</td>
</tr>
<tr>
<td>500 mcg DNA/PLG + gp140</td>
<td>17/29</td>
<td>0/9</td>
</tr>
<tr>
<td>1000 mcg DNA/PLG + gp140</td>
<td>0/9</td>
<td>1/26</td>
</tr>
<tr>
<td>gp140</td>
<td>20/26</td>
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</tr>
</tbody>
</table>

**HVTN 049 ICS magnitude of positive responses to Env or Gag (Pool 1)**

- Placebo
- Any Pool 1
- gp140
- 250 mcg DNA/PLG + gp140
- 500 mcg DNA/PLG + gp140
- 1000 mcg DNA/PLG + gp140
- 2 weeks post VAC5
- 2 weeks post VAC3
- Env
- Gag
HVTN 049: DNA priming of gp140 protein* does not influence the proportion of polyfunctional CD4+ T cells

*with MF59 adjuvant
HVTN 049: DNA priming of gp140 protein* shifts CD4\(^+\) T-cell response toward Th\(_1\)


*with MF59 adjuvant
Clinical findings from HVTN049 Phase 1
SF162 gp140 protein in MF59 adjuvant with or without DNA priming

• All vaccinees (Env alone or DNA prime-Env)
  - High frequency of Env-specific CD4+ T cells
  - High titer Tier 1, low Tier 1b & Tier 2 neutralizing Abs (D. Montefiori)
  - High titer & cross-subtype binding Abs, IgA and IgGs (G. Tomaras)

• DNA-prime-Env vaccinees
  - TH1 phenotype of multifunctional Env-specific CD4+ T cells
  - High frequency of Env-specific memory B cells (N. Frahm)
  - Higher titers of neutralizing Abs & ADCC (G. Ferrari)
Lessons learned

- **Regimen**
  - DNA or vector prime plus adjuvanted Env protein boosts provide vaccine protection against high dose SHIV challenge in NHP
  - Adjuvanted Env protein also provided protection
  - Env protein boosts provide the highest Ab titers and greatest protection
  - Priming vaccines and adjuvants can augment Ab responses and push CD4 T cell responses toward a polyfunctional TH1 response that may be desirable

- **Antigens**
  - Both V2 deleted and native forms of Env gp140 provided protection

- Vaccine antigens & regimens are yet be found to optimally present virus neutralizing epitopes to the human immune system
  - The role of other antibody effector functions in vaccine protection should also be investigated
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