DNA-Based Malaria Vaccines: USMMVP Experience

WHO/NIH Workshop: Heterologous Prime-Boost Vaccine Strategies for HIV, Malaria and TB
Rockville, MD, 17 Apr 2012

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DNA Prime / Vector Boost Needed for Protection in *P. knowlesi* rhesus challenge model

**Multistage Vaccine**: *PkCSP + PkSSP2/TRAP + PkAMA1 + PkMSP1*$_{19}$

**Regimen**: 3 DNA wks 0, 4, 16 + 1 copak wk 60

**Dose**: DNA: 1 mg/construct; Pox: 2x10$^8$ pu/construct

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Parasitemia (%) vs. Days after Challenge

- Copak only
- DNA prime Copak boost

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Clinical Development HuAd5 Vaccine
CSP + AMA1

Four Trials Conducted:

1. Low dose* (n=6)
   - AdCA – 2x10^{10} pu
   - AdCA – 1x10^{11} pu
   - Dose escalation: vaccine is safe
     - Low dose better tolerated
     - Low dose > high dose for ELISpot
     - High dose > low dose for ELISA

2. CSP x 2 (n=15)
   - AdC – 1x10^{10} pu
   - Challenge
   - CSP alone: 0/12 protected
     - second dose did not improve immunogenicity

3. DNA/Ad (n=20)
   - AdCA – 2x10^{10} pu
   - Challenge
   - DNA/Ad: 4/15 protected
     - only seronegatives protected

4. Ad alone* (n=18)
   - AdCA – 2x10^{10} pu
   - Challenge
   - Ad alone: 0/18 protected
     - Strong IFN-γ responses

* all volunteers Ad5 seronegative

Summary – Lessons Learned

- Gene-based vaccines are safe
- Dose trade-off between Ab, CMI (Ad)
- Constructs can be mixed on injection
- Prime/boost required for protection
- Protection associated with IFN-γ secreting CD8+ T cells
  » More precise definition of protective phenotype needed
- Pre-existing immunity to Ad5 may interfere
- Future
  » Collect more data on the effects of pre-existing immunity
  » Add antigens to improve protection
  » Compare platforms (DNA/Ad, Ad/MVA)
  » Test electroporation, adjuvants
  » Identify mechanisms of protection
Product Concept

• After establishing high grade protection in humans, multivalent constructs will be manufactured as the final product
• Clinical grade vectors showing good expression of up to three transgenes have been made (HuAd5)
• Pentavalent vaccine example:
  ➢ Construct 1: CSP, CelTOS/Ag2, LSA1
  ➢ Construct 2: MSP1, AMA1
Conference Points

- Do we know the optimum route/schedule for each platform? - No

- Is there agreement of optimal heterologous prime-boost regimens to induce specified immune responses? – Ad induces CD8+ T cells

- How to determine if optimal immune responses are due to the technology platform, or attributed to the construct? – Both platform and antigen are critical

- Can a particular heterologous prime-boost regimen success observed for one disease suggest promising strategies for the other 2 diseases? – Yes

- Do optimum heterologous prime-boost schedules fit with logistical deployment for where they will be needed most? - Yes

- Are there concerns about anticipated regulatory hurdles? - No

- Other long-term views on commercialization and deployment? - $ from outside pharmaceutical industry will be required (RTS,S paradigm)
### DNA-Ad is Congruent with EPI Schedule

<table>
<thead>
<tr>
<th>EPI Schedule</th>
<th>+ Malaria</th>
<th>% with Neutralizing Antibody</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>Vaccine</strong></td>
<td><strong>&lt; 16</strong></td>
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<tr>
<td>Birth</td>
<td>BCG OPV</td>
<td>7.14</td>
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<tr>
<td>6 weeks</td>
<td>DPT OPV</td>
<td>DNA</td>
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<tr>
<td>10 weeks</td>
<td>DPT OPV</td>
<td>DNA</td>
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<td>14 weeks</td>
<td>DPT OPV</td>
<td>DNA</td>
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<tr>
<td>9 months</td>
<td>Measles</td>
<td>Adeno</td>
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<tr>
<td>15 months</td>
<td>MMR</td>
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<tr>
<td>1\textsuperscript{st} booster (18 months)</td>
<td>DPT OPV</td>
<td>Adeno</td>
</tr>
<tr>
<td>2\textsuperscript{nd} booster (5 years)</td>
<td>DPT OPV</td>
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<tr>
<th>Age</th>
<th>% with Neutralizing Antibody</th>
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<tbody>
<tr>
<td>0.5 – 1 year</td>
<td>86.64 13.36</td>
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<td>1 – 2 years</td>
<td>71.79 28.21</td>
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<td>2 – 7 years</td>
<td>46.15 53.85</td>
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<td>7 – 12 years</td>
<td>26.81 73.19</td>
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<td>12 – 18 years</td>
<td>20.69 79.31</td>
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Thorner et al, J Clin Microbiol 2006 44:3781
Development Partners

● Recombinant virus
  » GenVec, Inc (Gaithersburg)
    – Joe Bruder, Jason Gall, Doug Brough
  » Vaccine Research Center, NIH (Bethesda)
    – Barney Graham, Bob Seder, Richard Koup, Robert Bailer
  » Aaron Diamond AIDS Research Center / Rockefeller University
    – Moriya Tsuji, Sandya Vasan, Neil Padte
  » Oxford University
    – Adrian Hill

● DNA
  » Vical Inc. (San Diego)
    – David Kaslow
  » Bioject Inc. (Tualatin, OR)
    – Richard Stoute

● PCR
  » Radbound U Nijmegen Medical Center
    – Robert Sauerwein
    – Rob Hermsen
Funding Partners

- **Military Infectious Diseases Research Program (Frederick)**
  - Michael Kozar, Frank Klotz

- **USAID (Washington, DC)**
  - Carter Diggs, Lorraine Soisson

- **Malaria Vaccine Initiative (BMGF) (Washington, DC)**
  - Christian Loucq, David Kaslow, Ashley Birkett, Ulrike Wille-Reece

- **Navy Bureau of Medicine and Surgery (Washington, DC)**
  - Keith Prusaczyk, Elizabeth Montcalm-Smith

- **Congressionally Directed Medical Research Program**
## Acknowledgements – USMMVP (NMRC & WRAIR)

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<tr>
<th>Vaccine</th>
<th>ELISpot / IFA</th>
<th>PCR:</th>
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<td>D Carucci</td>
<td>M Sedegah</td>
<td>A McCoy</td>
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<td>F Farooq</td>
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<td>M Guerrero</td>
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- The study protocols were approved by the National Naval Medical Center, Naval Medical Research Center and/or the Walter Reed Army Institute of Research Institutional Review Boards in compliance with all applicable Federal regulations governing the protection of human subjects.

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