Development of Vaxfectin®-formulated HSV-2 Plasmid DNA Vaccines for Prophylactic and Therapeutic Applications

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14 July 2011 - DNA Vaccines 2011 - San Diego, CA
Herpes Simples Virus (HSV-2)

- Herpes virus family (dsDNA enveloped virus)
- Leading cause of genital herpes worldwide (STD)
- 1 in 6 infected in U.S. (40-60MM)
- 1 in 4 worldwide by age 50 (500M)
- Latent infection (nerves/ganglia)
  - 20% symptomatic patients with recurrences
- No licensed vaccine, only antiviral treatment
- HSV-2 costs in the US estimated >$1B
- Unmet medical need
  - Prevention of infection (prophylactic vaccine)
  - Prevention of recurrence of lesions and transmission (therapeutic vaccine)
DNA Vaccine Composition

- Codon optimized HSV-2 consensus sequences
- Antigen candidates
  - gD full-length (FL) vs secreted (S)
  - VP11/12 (UL46) full-length
  - VP13/14 (UL47) full-length
- Vaxfectin® adjuvant
  - Well-tolerated and good safety profile in human clinical trials
- Single vial formulation stored at 2-8°C
Mice received 100 μg of plasmid encoding UL46, UL47, or gD at 0, 2, 4 weeks; IFN-γ ELISPOT assay performed 2-3 weeks later.

Muller J Gen Virol 2009
Vaxfectin® Adjuvant

Cationic Lipid

\((\pm)-N-(3\text{-}aminopropyl)\text{-}N,N\text{-}dimethyl\text{-}2,3\text{-}bis(cis\text{-}9\text{-}tetradecenyloxy)\text{-}1\text{-}propanaminium\ bromine\)

GAP-DMORIE

DPyPE

Cationic Liposomes

\(1,2\text{-}diphytanoyl\text{-}sn\text{-}glycero\text{-}3\text{-}phosphoethanolamine\)

Co-Lipid

Vaxfectin® Profile

- Two-lipid mixture
- Forms microparticles
- Increases immune responses and protection in animal models
- Dose sparing
- Scaleable cGMP manufacturing
- Simple formulation
- Patented technology

\(\frac{\text{pDNA}}{\text{lipid}}\) Complex
Mouse Challenge Model

**Vaccination**
- Route: Intramuscular +/- Vaxfectin®
  (N = 10/group)

**Challenge**
- Route: Vaginal
  HSV-2 strain 186
  50 x LD₅₀ (1.5 x 10⁴ PFU)
- Three week survival assessment

**Ganglia Dissection**

**Serum for antibody by ELISA**

**Daily vaginal swab for HSV-2 qPCR**
Impact of HSV-2 Vaccine on Antibody Titers, Primary Infection and Latency

**Anti-gD Antibody Titers**

- PBS-S
- Vax-S
- PBS-FL
- Vax-FL

*p = 0.034  p = 0.026

**Vaginal HSV-2 DNA Copy Number**

- Day 5 vaginal qPCR copies
- Wilcoxon rank sum test

*p = 0.024  *p = 0.019

**DRG HSV-2 DNA Copy Number**

- Day 90 DRG qPCR copies
- Wilcoxon rank sum test

*p = 0.007

Week 8 gD ELISA GMT 2 weeks after 3rd vaccination t-test

Day 5 vaginal qPCR copies Wilcoxon rank sum test

Day 90 DRG qPCR copies Wilcoxon rank sum test

100 μg pDNA dose
Summary of Murine Studies

- **Vaxfectin®** increased immunogenicity of gD pDNA
  - 5-6 fold increase in antibody titers compared to pDNA alone

- **Vaxfectin®-formulated** plasmid DNA decreased vaginal HSV-2 copy number following viral challenge
  - 80-100% survival at 0.1 mg pDNA dose following 50 x and 500 x LD$_{50}$ HSV-2 challenge
  - 2 log reduction in vaginal HSV-2 copy number for Vaxfectin® formulated full length gD pDNA compared to full length gD pDNA alone

- **Vaxfectin® formulated** gD pDNA reduced viral latency
  - 60% of mice had undetectable HSV-2 viral genomes in Vaxfectin® formulated full length gD pDNA compared to full length gD pDNA alone
### Guinea Pig Therapeutic Study Design

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Vaccine</th>
<th>pDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>gD/UL46/UL47 + Vaxfectin®</td>
<td>14</td>
<td>FL-gD in the right leg</td>
<td>300 µg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UL46/UL47 in the left leg</td>
<td>150 µg/150 µg</td>
</tr>
<tr>
<td>UL46/UL47 + Vaxfectin®</td>
<td>14</td>
<td>UL46/UL47 in the left leg</td>
<td>150 µg/150 µg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irrelevant pDNA in the right leg</td>
<td>300 µg</td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>PBS</td>
<td>NA</td>
</tr>
</tbody>
</table>

#### Timeline

**Primary Infection**
- Days 0
- HSV-2 Strain MS (10⁶ PFU)

**Lesion Recurrence**
- Days 15
- DNA Vaccine
- Days 28
- DNA Vaccine
- Days 42
- DNA Vaccine
- Days 63
- DNA Vaccine
Reduction in Frequency of Recurrent Lesions in Vaccinated Guinea Pigs

Mean (± SE) number of shedding days/animal over the last 14 day period

Mean (± SE) HSV-2 genome copies

p < 0.05 compared to control by t-test

<table>
<thead>
<tr>
<th>Group</th>
<th>Animals Shedding Virus</th>
<th>Days of Virus Shedding</th>
<th>Virus Shed (Log₁₀ HSV-2 Genomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gD/UL46/47</td>
<td>9/14 (64%)</td>
<td>1.07 ± 0.27</td>
<td>2.45 ± 0.20</td>
</tr>
<tr>
<td>Control</td>
<td>12/14 (86%)</td>
<td>2.29 ± 0.41</td>
<td>2.91 ± 0.19</td>
</tr>
</tbody>
</table>

a Mean (± SE) number of shedding days/animal over the last 14 day period

b Mean (± SE) HSV-2 genome copies

c p < 0.05 compared to control by t-test
Conclusions from Therapeutic Guinea Pig Studies

- UL46/UL47 pDNAs formulated with Vaxfectin® reduced lesion recurrence compared to naïve control group.
- The combination of gD pDNA with UL46 and UL47 pDNAs formulated with Vaxfectin® further decreased lesion recurrence compared to naïve control.
- Trivalent vaccine reduced days of viral shedding by 50%.
Next Steps

• Complete product definition
  • Guinea pig therapeutic and prophylactic models
• Seek funding for preclinical safety and clinical studies
  • Grants; partnerships
• Initiate toxicology and biodistribution studies
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