**Herpes simplex vaccine development: Pipeline and possibilities**

STI vaccines: Advancing the global agenda
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**Impact of genital herpes: The case for a vaccine**

Leading cause of genital ulcer disease worldwide

Neonatal Herpes

311,600 years lived with disability (YLD) in 2013

Rare, high morbidity and mortality

Impact of HSV-2 on HIV epidemic

HSV-2 increases the risk of HIV-1 acquisition 2-3 fold
Genital ulcer disease increases risk of HIV-1 transmission 25%-50% of HIV infections attributable to HSV-2 in high prevalence settings
Modeling studies: a prophylactic vaccine that reduced HSV-2 acquisition by 75% would also decrease HIV incidence by 30-40% after 20 years

Genital HSV-1: a new epidemic

- Now most common cause of first episode genital herpes in women and MSM < 25 years old in USA, Australia, Europe
- May be due to decreasing HSV-1 seroprevalence
  - First exposure to decreasing HSV-1 at initiation of sexual activity
- Estimated 140 million cases genital HSV-1 worldwide
- Leading cause of neonatal herpes

HSV-2 prevention strategies

- Antiviral agents
  - Acyclovir, valacyclovir, famciclovir
    - Suppressive: Decreases risk of transmission (50%) among HIV-negative, HSV-2 discordant heterosexual couples in North America
- Male circumcision
  - Decreased risk of HSV-2 acquisition in men
  - Decreased risk of GUD in men and female partners
- Condoms
  - 30% decreased risk of transmission if used all of the time
  - These strategies are not highly efficacious, are not widely available, and are unlikely to interrupt HSV-2 epidemic

HSV-2 and genital tract inflammation

CD4+/CCR5+ and CXCR4+ cells and resident CD8+ T cells persist for 24 weeks
HSV-2 infection associated with increase in stromal inflammation in foreskin in both HIV+ and HIV- men
Oligoclonal, activated CD8+ tissue resident memory T cells persist at sites of genital herpes recurrences

These responses may be required to prevent HSV-2 infection ("Prime-pull" strategy in mice)

HSV Pathogenesis

Successful pathogen has evolved with us
- Many immune evasion strategies
- Wide clinical spectrum of infection
- Most acquisition and transmission is asymptomatic
- Genital HSV-2 shedding is frequent and often subclinical
- HSV is detected from genital tract on 20% of days in persons with symptomatic infection
- Shedding measured by HSV PCR from genital secretions is a sensitive marker of clinical disease and risk of transmission

Vaccine strategies: Prophylactic vs. Therapeutic

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Population</td>
<td>High risk HSV-2 seronegative</td>
<td>HSV-2 seropositive</td>
</tr>
<tr>
<td>Goal</td>
<td>Prevent infection –or- Reduce severity of disease</td>
<td>Reduce severity of disease and risk of transmission</td>
</tr>
<tr>
<td>Preferred endpoint</td>
<td>Infection (seroconversion) Incidence of genital herpes</td>
<td>Genital shedding and recurrences</td>
</tr>
</tbody>
</table>

Adapted from Johnston et al, JCI 2011
Clinical Trials of Prophylactic Vaccines

- Over 20,000 participants enrolled in prophylactic vaccine trials
- Most prophylactic vaccines have targeted glycoproteins (gD, gB)
  - Subunit vaccines
  - Elicit neutralizing antibody

Prophylactic vaccine

- gD2t subunit vaccine with alum/MPL adjuvant
- Enrolled >8000 HSV seronegative women aged 18-30 in North America
  - Vaccine given at months 0, 1 and 6
  - Control vaccine: hepatitis A
- Primary endpoint: genital herpes disease
  - 70 cases of genital herpes observed
  - 32 HSV-1 and 38 HSV-2
- 286 seroconversions observed:
  - 179 HSV-1 and 108 HSV-2

Belshe et al, NEJM 2012

Immune Correlates

- Magnitude of CD4+ T cell responses to gD2 not associated with prevention of infection
- CD8+ T cells responses were not detected

Lessons from Herpevac

- Goal: Vaccine to prevent HSV-1 and HSV-2?
  - Timing of vaccine series
  - Use in HSV-1 seropositive persons
- Immune Correlates
  - Neutralizing antibody is a correlate of protection against HSV-1 infection
    - Is this relevant for HSV-2?
- Efficiency
  - Phase III trial required large number of participants due to low attack rate
    - Cohorts with higher incidence are needed
- Endpoints:
  - Infection vs. Disease
Testing therapeutic HSV-2 vaccines: A new paradigm

- Endpoint: Shedding rate pre/post vaccine
- Participant is compared to themselves

**HSV vaccines currently in clinical trials: The Pipeline**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Platform</th>
<th>Adjuvant</th>
<th>Current Phase</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admedus</td>
<td>DNA, gD2 codon optimized</td>
<td>Ubiquitin tagged</td>
<td>I/B, therapeutic</td>
<td>Elicited cellular responses in Phase 1</td>
</tr>
<tr>
<td>VCL-HB01</td>
<td>DNA gD2 +/- UL46</td>
<td>Vaxfectin</td>
<td>I/B POC</td>
<td>Prelim results: Did not meet primary endpoint (decreased shedding)</td>
</tr>
<tr>
<td>GEN-003</td>
<td>Subunit gD2/Cp4</td>
<td>Matrix M2</td>
<td>II, therapeutic</td>
<td>55% reduction in shedding</td>
</tr>
<tr>
<td>HerpV</td>
<td>32-36-mer peptides, complexed with heat shock protein</td>
<td>QS-21</td>
<td>II, therapeutic</td>
<td>15% reduction in shedding</td>
</tr>
<tr>
<td>HSV529</td>
<td>Replication deficient HSV-2 (deletion UL5/UL29)</td>
<td>NA</td>
<td>I, therapeutic</td>
<td>Pending</td>
</tr>
</tbody>
</table>

**HSV Vaccines: Preclinical Pipeline**

<table>
<thead>
<tr>
<th>Candidate Name/Identifier</th>
<th>Replication competent</th>
<th>Replication deficient</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2 gDNL5-ICP0</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gD2-deletion</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-10</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A207/2 (HSV-2 mutated for g34.5, UL43.5, UL55-56, US10-12)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gD2</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gD2-gD2 HSV-2 gD dominant negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prime-pull strategy</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated HSV-2 in MPL/alum</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV-1 glycoprotein B lentiviral vector</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant HSV-1 gB intranasal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gD/gC/gE (Trivalent glycoprotein)</td>
<td></td>
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<td></td>
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**HSV Vaccines: Cause for optimism**

- Success of HPV and VZV vaccines
- Rich pipeline with novel candidates
  - Several platforms
  - Therapeutic vaccines rapidly moving forward
- New insights into importance of neutralizing antibody and cellular immune response
- Increased knowledge about lack of geographic diversity of virus
  - 0.4% maximum genetic divergence
- Extensive experience with optimizing clinical trials design (prophylactic and therapeutic)
  - Endpoints
  - Populations

**HSV Vaccines: Challenges**

- Need additional data about immune correlates and what responses need to be stimulated
  - May be different for therapeutic and prophylactic vaccines
- Available animal models do not mimic human disease or immune system
- Lack of standardized assays
- Efficiency: Use of smaller, iterative clinical trials
- Must continue to pursue prophylactic vaccines
- Manufacture of select vaccines
- Improved public-private partnership

**Therapeutic vaccine example: GEN-003 Phase 1B results**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>Mean Baseline Rate</th>
<th>Mean Post Treatment Rate</th>
<th>Mean Relative Change from Baseline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28</td>
<td>11.8</td>
<td>13.2</td>
<td>12%</td>
<td>0.8</td>
</tr>
<tr>
<td>GEN003 (10 µg)</td>
<td>31</td>
<td>11.5</td>
<td>11.3</td>
<td>-2%</td>
<td>0.75</td>
</tr>
<tr>
<td>GEN003 (30 µg)</td>
<td>29</td>
<td>13.5</td>
<td>6.6</td>
<td>-51%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GEN003 (100 µg)</td>
<td>27</td>
<td>14.8</td>
<td>10.4</td>
<td>-30%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Preliminary results: Phase II - 55% reduction in shedding (10µg + 75µg adjuvant dose)