Clinical evaluation of universal influenza vaccines and pipelines for new influenza vaccines

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January 24, 2013
US Influenza Vaccines  
January 2004

• All licensed seasonal vaccines are egg based  
  — Most vaccine is split or subunit inactivated vaccine  
  — Live attenuated is the other option  
  — Virus replication is required for production  
• Vaccine is produced in a six month production window (January-June each year)  
  — Based on VRBPAC strain recommendations  
  — Trivalent vaccine H1, H3, one B  
• Annual immunization is required  
  — Vaccine effectiveness estimated at 50-70%  
• One licensed egg-based H5 pandemic vaccine  
  — 2 x 90µg dose  
• Is there room for improvement?  YES!
Pandemic Influenza Vaccine Implementation Goals

- Fortify existing influenza vaccine capabilities
- Support development of better influenza vaccines that afford greater surge manufacturing capacity
  - Cell-based Vaccines
  - Recombinant and Molecular Vaccines
  - Adjuvants for Dose- and Antigen-sparing
  - Universal Influenza Vaccines
- Establish pre-pandemic influenza vaccine stockpile
- Expand domestic manufacturing capacity
  - Retrofit existing facilities
  - Establish new facilities
National Pandemic Influenza Vaccine Development Strategy Is Multi-Step & Integrated Approach

“More and better vaccines sooner”
Progress so far
• Provide more robust, flexible, and scalable process for manufacturing influenza vaccines

• Awarded 6 contracts in 2005-06 for advanced development of US licensed cell-based seasonal & pandemic influenza vaccines ($1.2B) with commitment for domestic surge capacity of 150M doses within 6 mos. of pandemic onset

• Novartis, Baxter, sanofi pasteur, GSK, Solvay, MedImmune
  — Novartis vaccine was licensed for 18+ in November 2012
  — One completed pivotal Phase 3 clinical studies & expected to submit a BLA in 2013
  — One manufacturer in early stage development
  — Three programs are no longer active
Antigen Sparing Technology

• Adjuvants, immunostimulating molecules, provide dose-sparing effects, cross-strain protection (in animal models) and reactivity in serological assays, and enhanced immune responses to vaccines

• ASPR/BARDA awarded 3 contracts in 2007 ($133 M) for advanced development of US-licensed pandemic influenza vaccines with adjuvants
  – Novartis, GSK, Intercell (formerly IOMAI)
  – One manufacturer (GSK) has completed Phase 3 clinical studies & submitted a BLA in February 2012 with action on submission soon
  – One manufacturer has completed Phase 2 clinical studies
  – One contract is no longer active

< filled vaccine & adjuvant – Production skid >
Recombinant & Molecular Vaccine Technologies

• Recombinant & molecular technologies may provide vaccine sooner with less dependence on influenza virus strain properties

• BARDA awarded contracts in 2009 & 2011 for advanced development of US-licensed recombinant-based seasonal & pandemic influenza vaccines with commitment for domestic manufacturing surge capacity of 50 M doses in 6 months of pandemic onset & initial lot release in 12 weeks

• Protein Sciences, Novavax, & VaxInnate
  – One manufacturer (Protein Sciences) received their license approval in January 2013
  – Two manufacturers in Phase 2 clinical studies
US Influenza Vaccines
January 2013

• Licensed seasonal vaccines are egg based (6), cell-based (1) and recombinant (1)
  — Vaccine is split, subunit, purified recombinant protein or live attenuated
  — Virus replication is required for most vaccines (7)
• Vaccine is produced in a six month production window (January-June each year)
  — Based on VRBPAC strain recommendations
  — Trivalent or quadrivalent vaccine H1, H3, one B or two B
• Annual immunization is required
  — Vaccine effectiveness estimated at 50-70%
• One licensed egg-based H5 pandemic vaccine
  — 2 x 90µg dose
• Is there room for further improvement?  YES!
## Influenza Vaccine Landscape

<table>
<thead>
<tr>
<th>Pre Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approval</th>
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</thead>
<tbody>
<tr>
<td><strong>Egg-based inactivated</strong></td>
<td><strong>Egg inactivated</strong></td>
<td><strong>Vivalis</strong> H5N1 post DNA vac</td>
<td><strong>sanofi pasteur</strong> H5N1 Split w/ AF03</td>
<td><strong>CSL Biotherapies</strong> Split H5N1 AS03</td>
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<td><strong>GSK</strong> H5N1 WIV</td>
<td><strong>Corynebacterium</strong> H5N1, Thailand</td>
<td><strong>Novartis</strong> H5N1, WIV w/ Adjacent</td>
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<td><strong>Birmex</strong> H5N1</td>
<td><strong>Adimmune</strong> H5N1</td>
<td><strong>Vaxfectin</strong> H5N1</td>
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<td>&amp; Chinese Mfrs</td>
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<td><strong>Cell-culture inactivated</strong></td>
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<td><strong>LAIV</strong></td>
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<td><strong>Recombinant (VLPs)</strong></td>
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<td><strong>Universal</strong></td>
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<td><strong>Vectors/Adjuvant</strong></td>
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<td><strong>DNA</strong></td>
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**Updated:** 16JAN 2013
“Universal” influenza vaccines
Universal influenza vaccine

• Many definitions for a universal influenza vaccine
  — A single influenza vaccine that would provide “protection” against any given subtype of influenza A
  — Could be used for several influenza seasons before reformulation
    • Reduce annual “guesswork” for strain selection
    • Reduce production costs (thus vaccine costs/year round production)
    • Reduce vaccine “mismatches”
    • Reduce the potential for vaccine shortages
    • Increase the global supply of vaccine

• Could be stockpiled for epidemics/pandemics

• Surge capacity
  — Rapid scale-up, reduce production bottlenecks
Universal influenza vaccine

- Target conserved proteins or cross-reactive epitopes
  - Less sensitive to antigenic drift
- Identify less immunodominant, but more cross-reactive B and T cell epitopes on HA, NA and conserved proteins to “engineer” sequences that would direct the immune response to:
  - Induce humoral and/or cellular immunity
- Utilize recombinant technologies to optimize expression and delivery/uptake of the antigen
- Live virus vectors may offer advantage of inducing broader immunity
The Candidates
Is it possible to:
• Identify less dominant, yet more broadly reactive epitopes
• Engineer HA and/or NA genes to direct immune response
• Incorporate into vectored vaccine along with conserved Ags

Adapted from: Paul Lewis, MD
Oregon State Public Health
HA: surface, immunogenic
Highly variable. Drift. Shift.

NA: surface, immunogenic
Variable. Drift. Shift.

M2e: surface, immunogenic??
Fairly conserved. Ab-mediated.
Protective? Reduce severity.

NP (nucleoprotein): internal
Highly conserved.
Induces CMI. Reduce severity?

Matrix: internal
Highly conserved.
Induces CMI.

Adapted from: Paul Lewis, MD
Oregon State Public Health
HA Stalk or Fusion Peptide
Highly conserved.
Transiently accessible on infected cell surface.
Need to engineer a vaccine to target

Adapted from: Paul Lewis, MD
Oregon State Public Health
Universal influenza vaccine technology challenges

- “Universal” vaccines have “Universal” challenges
  - Often require alternate development/release assays
    - Most regulators are accustomed to SRID or SRH
  - Often induce an immune response to something other than the HA protein
    - Most regulators are accustomed to HAI antibodies for licensure
  - Are not always as “Universal” as they claim
    - A single amino acid change can render ineffective
    - Early candidates have not proven successful
  - May require large scale efficacy trials or other “creative” clinical development plans
    - Challenge studies
    - Measuring responses – antibody or T cell
Future?

• Licensed universal influenza vaccines
  — Made in recombinant, cell- and egg-based systems?
• Vaccine is produced year round
  — No annual strain change
  — Bivalent to quadrivalent?
• Annual/every ten year/ once in a lifetime immunization is required
  — Vaccine effectiveness estimated at >80%
• Pandemic may be covered by current universal or could be a separate vaccination
• Is this where we want to be in the future? YES!
Thank You for Your Attention

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