The Next Phase of Influenza Vaccine Development

Development of Universal Influenza Vaccines

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BARDA Industry Day
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Current Influenza Vaccines Have Limitations

- Moderately effective (overall 50%-70%)
  - Annual immunization
  - Dependent on vaccine match and virus
  - Lower effectiveness in high risk populations

<table>
<thead>
<tr>
<th>Season</th>
<th>Strain</th>
<th>Age Group</th>
<th>Vaccine Effectiveness (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 – 2012#</td>
<td>A(H3N2)</td>
<td>18 – 49</td>
<td>33% (-5 to 57)</td>
</tr>
<tr>
<td></td>
<td>A(H3N2)</td>
<td>50 – 64</td>
<td>39% (-13 to 67)</td>
</tr>
<tr>
<td>2012-2013*</td>
<td>A(H3N2)</td>
<td>≥65</td>
<td>9% (-84 to 55)</td>
</tr>
</tbody>
</table>

* Interim adjusted estimates Feb 22, 2013 CDC MMWR
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... And They Don’t Provide Immunity to Novel Viruses

1918: “Spanish Flu”
A(H1N1)
20-100 m deaths
~500,000 in US

1957: “Asian Flu”
A(H2N2)
1-4 m deaths
60-80,000 in US

1968: “Hong Kong Flu”
A(H3N2)
1-4 m deaths
~30,000 in US

2009 “H1N1 Pandemic”

Recent scares H5N1, 2012 H3N2v, 2013 H7N9, 2013 H10N8

We need better influenza vaccines!

We need universal influenza vaccines

Universal influenza vaccines elicit lasting, broad spectrum immunogenicity and efficacy in humans against the widest range of antigenically divergent influenza strains within and across subtypes.
2010 PCAST Report “Because a universal vaccine would completely change the outlook on protecting the population against influenza virus infections, the Federal Government should support and encourage efforts to design a universal vaccine through various mechanisms.”

2012 PHEMCE Implementation Plan programmatic priority “Develop a novel antigen or “universal” flu vaccine that will eliminate the need for annual modifications to the influenza vaccine or annual boosters”
New Technologies are Now Available for Influenza Vaccine Production

- **Cell-based Vaccines**
  - FLUCELVAX®
    - Licensed 11/20/12
  - Recombinant Vaccines
    - Flublok®
      - Licensed 01/16/13
- **Egg-based Vaccines**
  - H5N1 Vaccine
    - Licensed 04/17/07
- **Universal Vaccines**
  - Advanced Development Begins FY15
- **Antigen-Sparing Vaccine Technology**
  - Q-Pan H5N1 Licensed 11/20/2013

Viral Targets for Universal Vaccine Development

- **Non-structural proteins.** Conserved potential targets for T cell immunity

- **HA:** surface, highly variable immunodominant head, conserved stem

- **NA:** surface, variable, slower drift

- **M2:** surface, fairly conserved. Possible Ab-mediated protection

- **NP:** internal highly conserved. Induces CMI

- **M1:** internal highly conserved. Induces CMI

Adapted from: Paul Lewis, MD
Oregon State Public Health

Approach to Universal Vaccine Development

- This is a new vaccine – approach as if current influenza vaccines do not exist
  - 1/40 HAI titer (nice to have, but what else is needed?)
  - Think about other targets, other correlates, other types of immunity to improve effectiveness and duration of immunity
  - Multiple approaches will need to be investigated so a few can reach our target

<table>
<thead>
<tr>
<th>Candidates</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>BLA!</th>
</tr>
</thead>
</table>

http://www.niarchery.co.uk/history.php
http://heatherfuture.blogspot.com/
http://celindareyesblog.buzznet.com/user/journal/17433956/top-10-reasons-why-s/
### Universal Influenza Vaccine Landscape

#### Pre Clinical

**Protein Based**
- Chimeric HA Stalk Vaccine
- Computationally Optimized Broadly Reactive Antigen (COBRA)
- Self assembling nanoparticle
- M2e Conjugatable Adjuvant Lipid Vesicle
- Headless HA in VLP

**Vectors/Adjuvant**
- MVA Vector with M2e
- PanAd3 Vector with M1 and NP
- Listeria Vector with NP
- ΔM2 LAIV
- MVA Vector with HA and NP

**DNA**
- Cationic lipid-DNA complex

#### Phase 1

**Protein Based**
- M2e + NP + Immunostimulatoty Sequence (ISS)
- NPA + NPB + M1 + M2 polypeptides T-cell vaccine
- M2e-VLPs
- Li-Key H5 Hybrid T-cell vaccine

**Vectors/Adjuvant**
- Ad4 Vector with H5 HA
- Nanoemulsion T-cell vaccine
- ΔNS LAIV
- MVA Vector with NP and M1

**DNA**
- DNA Vaccine instruct with HA, NA, M2e-NP

#### Phase 2

**Protein Based**
- Conserved epitopes from HA + NP + M1 proteins
- Fluorocarbon-linked conserved influenza peptide set T-cell vaccine

**Vectors/Adjuvant**
- MVA Vector with HA + NP + M1 proteins

**DNA**
- DNA prime + TIV boost

*No Phase 3 or Market Approved universal influenza vaccines*

**ASPR:** Resilient People. Healthy Communities. A Nation Prepared.
# Universal Influenza Vaccine
## Target Product Profile – 5 Key Features

<table>
<thead>
<tr>
<th>Property/Vaccine</th>
<th>Acceptable Primary Characteristics</th>
<th>Desired Primary Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breadth of Protection</strong></td>
<td>Protection against most influenza A strains of the same subtype</td>
<td>Protection against multiple influenza A subtypes and most influenza B strains</td>
</tr>
<tr>
<td><strong>Efficacy</strong>**</td>
<td>70% or greater in healthy adult, young and elderly</td>
<td>80% or greater in healthy and special populations</td>
</tr>
<tr>
<td><strong>Duration of Immunity</strong></td>
<td>One full year</td>
<td>Five years or more</td>
</tr>
<tr>
<td><strong>Age Indication</strong></td>
<td>6 months and above</td>
<td>2 months and above</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Reactogenicity similar to licensed influenza vaccines</td>
<td>Reduced reactogenicity compared to licensed influenza vaccines</td>
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Universal Influenza Vaccine Challenges

• Most improved or universal influenza vaccine candidates rely on a single technology or immunological target
  — Many will be unable to meet TPP for universal vaccines by themselves

• Many projects are in early/pre-clinical development

• Large scale multi-year efficacy trials may be required
  — Young, healthy adult, elderly populations

• Funding is limited
  — Each promising candidate could cost over $100 M USD for development
Technology Combinations?

Universal Influenza Vaccine – Needs for Success

• New partnership and a different way of thinking
  — Programs not projects
    • Combinations of technologies that will result in the development of vaccines that stimulate broadened, long lasting antibody, cellular and/or mucosal responses to influenza viruses that meet the universal TPP
  — New ways to design, evaluate and regulate these vaccines
    • New vaccine approaches and targets
    • Human challenge
    • New surrogates of immunity need to be identified
      — Validated assays will need to be developed
    • Alternate potency/release assays will be needed
  — Financial commitment
    • High development costs
BARDA Universal Vaccine Forecast
Parting Thoughts

• Don’t let currently licensed vaccines constrain your thinking!
• Technical advances over the last decade have created the opportunity to develop universal influenza vaccines
  — Expression systems, vectors, adjuvants, etc.
• Advances in our understanding of influenza have identified a number of vaccine candidates that could contribute to the development of a universal influenza vaccine
• Universal influenza vaccine licensure will require a well-planned and executed program that addresses the technical, clinical and regulatory challenges of universal influenza vaccine advanced development
• A combination strategy will likely have the best chances of achieving the HHS goals for universal influenza vaccines
Are You (and Your Team) Ready and Interested?

• Contact information
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  Email: robert.huebner@hhs.gov

• www.medicalcountermeasure.gov
  — Information on the open influenza funding opportunities
  — Information on setting up a TechWatch meeting with BARDA to discuss your technology