Universal Influenza Vaccines

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Influenza

• Influenza virus first identified in the 1930s
• Segmented, negative-sense, single-stranded RNA
• 8 gene segments encoding 11 proteins
• Sialic acid receptor-dependent tropism
• Orthomyxoviridae family, 5 influenza virus genera
• Influenza A, B, and C species can infect humans
  – A - most common and usually most severe (18 HA; 9 NA)
  – B - can also cause epidemics, but tends to be milder
  – C - has never caused a large epidemic
Global Disease Burden

• 3-5 million cases of severe illness

• 250,000 to 500,000 deaths globally/year

• HIC - most influenza deaths occur in elderly
  – TIV has marginal efficacy in this population

• LMIC – higher overall severity of disease
  – Mortality greatest in children under 5 (28,000 to 111,500 deaths associated with ALRI)

Prevention and Treatment

• First influenza vaccine developed in 1945
• Seasonal Vaccines
  – Conventional TIV - 0-70% efficacy
  – LAIV - Tends to be more effective in children
    • Theoretical advantage over TIV because of delivery of more NA and M2 antigens, mucosal responses including IgA, and potential for induction of CD8 T cell responses
  – HA subunit – HA rosettes produced with baculovirus
• Pandemic Vaccines – small stockpiles of MIV
• Monoclonal antibodies in development
• Antivirals (NA inhibitors)
  – Short therapeutic window
  – Emerging drug resistance
**Unmet Public Health Needs**

- **Improved availability of seasonal vaccines**
  - 12% of the population receives 65% of vaccine doses

- **Development of a more universal influenza vaccine**
  - Improve magnitude or quality of response
  - Durability of protection extended beyond 1 year
  - Protect against future seasonal (drifted) and pandemic (shifted) strains
    - Protection within subtype
    - Protection within HA group
    - Protection against all known HAs
Target Populations

- Pregnant women
- Children aged 6 months to 5 years
- School age children
- Elderly (≥65 years of age)
- Individuals with chronic medical conditions
- Health-care workers

LMIC

HIC
Antigenic Sites on Influenza HA

Current influenza vaccines primarily elicit strain specific antibodies against the immunodominant and variable head region.

Target region for broadly neutralizing stem antibodies

H1N1 Sequence conservation

≤98%  100%
Genetic Divergence of Influenza HA

Time-resolved phylogenetic tree of influenza viruses

Influenza A
- H3N2
- H1N1

Influenza B
- Vic
- Yam

Bedford, T., et al., eLife 2014;3:e01914
Current Influenza Vaccines

Influenza A

H3N2

H1N1

Current vaccines

Influenza B

Vic

Yam

Universal Influenza Vaccine Concepts

- Influenza A
  - Multi-seasonal
  - Improved vaccines

- Influenza B
  - Pan-Group/Multi-lineage

- H3N2
- H1N1
- Vic
- Yam
- Pan-subtype
Commercial Influenza Vaccine
Research and Development (partial list)

**Quadrivalent Vaccine Manufacturers**
- MedImmune (FluMist)
- GlaxoSmithKline (GSK) (Fluarix) (also trivalent)
- Sanofi Pasteur (Fluzone) (also trivalent)
- Merck/CSL (Afluria) (also trivalent)
- ID Biomedical (FluLaval) (also trivalent)

**Trivalent and Cell-based Vaccine Manufacturers**
- Novartis (Flucelvax, Fluvirin, Agriflu)
- Protein Sciences Corp (Flublok)

**Vaccine Products in Various Research Stages**
- Alphavax
- Okairos
- GenVec
- Novavax
- Mymetics
- TechnoVax
- Mucosis
- Takeda
- AmVac
- Visterra
- Inovio Pharmaceuticals
- Emergent BioSolutions
- VaxInnate
- Liquidia Technologies
- Aphios
- Baxter
- NanoBio Corp. (Merck)
- Southern Research Institute
- Vaxin, Inc.
- Sarepta Therapeutics
- Abbott Laboratories
- Scripps Research Institute
- Johnson & Johnson/Janssen/ Crucell
Endpoints for Licensure

• An advantage for influenza vaccine development is ability to license based on achieving a threshold HAI response

• Otherwise a large field trial to prove efficacy is required. Complicated by need to include and control for available seasonal vaccines
Targeting Viral Surface Glycoproteins

<table>
<thead>
<tr>
<th></th>
<th>RSV F</th>
<th>Flu HA</th>
<th>HIV-1 Env</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine-induced NT Ab</td>
<td>Easy (structure-dependent)</td>
<td>Easy (strain-specific)</td>
<td>Very difficult (even autologous)</td>
</tr>
<tr>
<td>Genetic diversity</td>
<td>Low</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Glycosylation</td>
<td>Low</td>
<td>Moderate</td>
<td>Very High</td>
</tr>
<tr>
<td>Conformational evasion</td>
<td>High</td>
<td>Low</td>
<td>Very High</td>
</tr>
<tr>
<td>Immunodominance</td>
<td>Low</td>
<td>High</td>
<td>Very High</td>
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Universal Influenza Vaccine Options

- Improving current vaccines
  - DNA or LAIV prime
  - Novel adjuvant formulations (MF59 or AS03)
  - Improved formulations and delivery of HA antigens (e.g. mammalian cell production, nanoparticle or VLP delivery)

- Approaches to increase breadth
  - Consensus or chimeric HA head designs
  - Induction of broadly NT HA stem-specific antibodies
  - Multi-valent or multi-epitope designs
  - Use of NA or M2 antigens (ADCC)
  - Induction of CD8 T cell responses using peptides or gene-based approaches (e.g. RNA, DNA, live or replication-defective viral vectors)
# Influenza Vaccine Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Phase</th>
<th>Mechanism</th>
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</thead>
<tbody>
<tr>
<td>HA Rosettes, HA nanoparticles, VLP</td>
<td>I/II</td>
<td>Particle format for potency, multiple strains mixed or sequential delivery</td>
</tr>
<tr>
<td>M2 ectodomain</td>
<td>I/II</td>
<td>Broad cross-reactive Ab; ADCC (no NT)</td>
</tr>
<tr>
<td>HA head chimera (COBRA)</td>
<td>Pre-clinical</td>
<td>Broad NAb (with HAI)</td>
</tr>
<tr>
<td>HA stem or head-stem chimera</td>
<td>Pre-clinical</td>
<td>Broad NAb (no HAI) and ADCC</td>
</tr>
<tr>
<td>Neuraminidase</td>
<td>Pre-clinical</td>
<td>Additional antigen for NT breadth</td>
</tr>
<tr>
<td>Live-attenuated and single-round whole virus</td>
<td>Pre-clinical</td>
<td>Additional antigens, T cell responses, and mucosal immunity</td>
</tr>
<tr>
<td>RNA, DNA, or vector subunit delivery</td>
<td>Pre-clinical</td>
<td>Gene delivery for CTL and Ab</td>
</tr>
<tr>
<td>Peptides</td>
<td>Pre-clinical</td>
<td>CTL response</td>
</tr>
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Major hurdles for universal influenza vaccine development

• Commercialization unlikely if strategy does not use the HAI endpoint for licensure (Focus on HA head region may limit universality)

• Requirement for large field efficacy studies
  – May need to be done in children to diminish effects of pre-existing immunity
  – Comparison to licensed vaccines will be complicated
  – Will depend on timing and emergence of significantly drifted or shifted strains

• Many strategies are too complex for real-world deployment
  – More than one product used in multiple-administration combinations
  – Novel delivery platforms and formulations
  – Difficult to achieve low-cost, large-scale manufacturing
  – Still at the proof-of-concept stage
Novel Influenza HA Vaccine Designs

Design and structure of a headless HA stabilized-stem nanoparticle

Heterosubtypic protection by influenza HA SS-NP immunization

Potential Opportunities for Licensure

• For Improving Current Products
  – Evaluation of new adjuvant formulations and cell-grown products should proceed
  – Explore use of LAIV and gene-based priming in children

• For Universal Influenza Vaccines
  – No universal vaccine candidate sufficiently advanced to discuss licensure
  – Clinical field trial options
    • Studies in HIC or LMIC
    • More studies in young children
    • What would be needed to justify the comparison of 1 dose of experimental product to yearly dose of conventional vaccines
Potential Role for WHO

• Clarify HIC and LMIC goals for influenza vaccine
• Promote an incremental approach by defining Preferred Product Characteristics (PPC) especially for children in LMICs
• Define clinical trials options
• Guidance for using existing vaccines
  – Encourage use of more LAIV in children
  – Promote vaccination of pregnant women and children
  – Expand cell-based manufacturing capacity
  – Expand manufacturing capacity in LMIC
• Support surveillance and modeling efforts to identify and predict emerging strains more reliably
Discussion