Universal Influenza Vaccine Development

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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

Photo Credit: NIAID
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
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

Influenza B

- Vic
- Yam

Current vaccines
Universal Influenza Vaccine Concepts

Influenza A

- H3N2
- Multi-seasonal
- Improved vaccines

Influenza B

- Vic
- Yam
- Pan-Group/ Multi-lineage

Pan-subtype
Universal Influenza Vaccine Approaches

• 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)
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
Antigenic Sites on Influenza HA

Hemagglutinin (HA) Glycoprotein

Head

Stem

Sequence Variability

0% ≤ 95%

Group 1

H13
H16
H9
H12
H17
H18

H1

H5

Group 2

H7

H3

H10

H4

H14
Specificity of Influenza NT Antibodies

Head-directed antibodies tend to dominate the response and those targeting RBD are generally potent, but strain-specific.

NT antibodies targeting stem can have broad NT activity, but have to avoid group-specific glycans and are less frequent and less potent than head-targeted NT antibodies.
# Influenza Vaccine Strategies

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<th>Strategy</th>
<th>Phase</th>
<th>Theoretical Mechanism</th>
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<tr>
<td>HA Rosettes, HA nanoparticles, VLP</td>
<td>I/II</td>
<td>Particle format for potency, multiple strains mixed or sequential delivery</td>
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<tr>
<td>M2 ectodomain</td>
<td>I/II</td>
<td>Broad cross-reactive Ab; ADCC (no NT)</td>
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<tr>
<td>HA head chimera (COBRA)</td>
<td>Pre-c clinical</td>
<td>Broad NAb (with HAI)</td>
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<tr>
<td><strong>HA stem or head-stem chimera</strong></td>
<td>Pre-c clinical</td>
<td>Broad NAb (no HAI) and ADCC</td>
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<td>Neuraminidase</td>
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<td>Additional antigen for NT breadth</td>
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<td>Live-attenuated and single-round whole virus</td>
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<td>mRNA, DNA, or vector subunit delivery</td>
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<td>Gene delivery for CTL in addition to Ab</td>
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<td>Peptides</td>
<td>Pre-c clinical</td>
<td>CTL response</td>
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VRC Universal Influenza Vaccine Designs

Design and structure of a headless HA stabilized-stem nanoparticle

Heterosubtypic protection by influenza HA SS-NP immunization

HA stem-directed NT antibodies

Hemagglutinin (HA)

Head

Stem

N38 Glycan (Group 2)

N21 Glycan (Group 1)

Footprint of F10, CR6261 (VH1-69)

Group 1

Footprint of 8020 (HV1-18), 8043 (VH1-3)

Group 2

Footprint of F16 (VH 3-30)

Group 1/2
Clinical Evaluation of Pandemic Strains

DNA Priming and Influenza Vaccine Immunogenicity: Two Phase 1 Open Label Randomised Clinical Trials
Ledgerwood JE, Graham BS, et al. the VRC 306 and 310 Study Teams.

Prime-boost interval matters: A randomized phase I study to identify the minimum interval to observe the H5 DNA influenza vaccine priming effect.
Ledgerwood JE, Graham BS, et al. and VRC 310 study team
JID 2013; 208:418-422.

DNA priming prior to H5N1 inactivated influenza vaccination expands the antibody epitope repertoire and increases affinity maturation in a boost-interval-dependent manner in adults.
Khurana S, et al. and VRC 310 study team
JID 2013; 208:413-17.
Applications of ΔSA HA Probes

HA-specific B cell selection

- Pre-vaccination
- Post-vaccination

mAb isolation

B cell phenotype

- Memory (IgD-, CD27+, IgG+)
- Naive (IgD+, IgG-, CD27-, IgM+)

B cell kinetics

- H5+H1+ B cells
- H5+ B cells

Germline identity (%)

- Pre-vacc
- 2 wks post-vacc
- 44 wks post-vacc

Wheatley, McDermott
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 increase trial size
  - Need to demonstrate durability will increase trial length
  - Outcome will depend on timing and emergence of 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
Conclusions

• Universal influenza vaccine goals are to increase durability and improve coverage against future and pandemic strains
• There are biologically plausible pathways to develop more universal influenza vaccines
• Major challenges include cost and complexity of advanced product development and demonstrating efficacy
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