Influenza Vaccines with Broader Strain Protection

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Influenza Vaccine Challenges

- Antigenic changes (drift and shift) represent a major challenge for current licensed vaccines
  - Annual immunization is required
  - Vaccine effectiveness is moderate in adults and less so in the elderly

- Current production processes are predominantly egg-based
  - Growth properties of human isolates in eggs (H3 isolation, yield)
  - Pandemic surge demands

- Pandemic-like candidate vaccines (H5 and H7) are poorly immunogenic in humans
  - 2 x 90 µg dose for H5N1
  - Concerns about adjuvant safety and public perceptions

- Next generation influenza vaccines are needed
National Pandemic Influenza Vaccine Development Strategy: Multi-Step & Integrated Approach

Antigen-Sparing Vaccine Technology

Universal Vaccines

Recombinant-based Vaccines

FluBIOk licensed 01/16/13

Cell-based Vaccines

Flucelvax Licensed 11/20/12

Egg-based Vaccines

H5N1 Vaccine Licensed 04/17/07

# Influenza Vaccine Landscape

## Pre Clinical
- **Egg-based inactivated**
  - Sanofi Pasteur
  - CSL Biotherapies
  - GSK
- **Proprietary Adjuvant**
  - VACERA
  - GPO
- **Cell-culture inactivated**
  - GSK
  - EE66
  - MedImmune
- **LAIV**
  - GPO
  - Vivaldi Biosciences
  - BioPiem
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
  - salmonella, Oral
  - VaxGen
  - Gilead
- **Universal**
  - NYU / MSSM
  - Biond Vax
  - Dynavax
  - NIAID Nanoparticle

## Phase 1
- **Egg inactivated**
  - CSL Biotherapies
  - GSK
  - MedImmune
- **Cell-culture inactivated**
  - GSK
  - EE66; H5N1
  - MedImmune
  - BioPiem
  - AVI BioPharma
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
  - salmonella, Oral
  - VaxGen
  - Gilead
- **Universal**
  - NYU / MSSM
  - Biond Vax
  - Dynavax
  - NIAID Nanoparticle

## Phase 2
- **Egg inactivated**
  - CSL Biotherapies
  - GSK
  - MedImmune
- **Cell-culture inactivated**
  - GSK
  - EE66; H5N1
  - MedImmune
  - BioPiem
  - AVI BioPharma
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
  - salmonella, Oral
  - VaxGen
  - Gilead
- **Universal**
  - NYU / MSSM
  - Biond Vax
  - Dynavax
  - NIAID Nanoparticle

## Phase 3
- **Egg inactivated**
  - CSL Biotherapies
  - GSK
  - MedImmune
- **Cell-culture inactivated**
  - GSK
  - EE66; H5N1
  - MedImmune
  - BioPiem
  - AVI BioPharma
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
  - salmonella, Oral
  - VaxGen
  - Gilead
- **Universal**
  - NYU / MSSM
  - Biond Vax
  - Dynavax
  - NIAID Nanoparticle

## Market Approval
- **Egg inactivated**
  - CSL Biotherapies
  - GSK
  - MedImmune
- **Cell-culture inactivated**
  - GSK
  - EE66; H5N1
  - MedImmune
  - BioPiem
  - AVI BioPharma
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
  - salmonella, Oral
  - VaxGen
  - Gilead
- **Universal**
  - NYU / MSSM
  - Biond Vax
  - Dynavax
  - NIAID Nanoparticle

## Seasonal Vaccine
- **Egg inactivated**
  - CSL Biotherapies
  - GSK
  - MedImmune
- **Cell-culture inactivated**
  - GSK
  - EE66; H5N1
  - MedImmune
  - BioPiem
  - AVI BioPharma
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
  - salmonella, Oral
  - VaxGen
  - Gilead
- **Universal**
  - NYU / MSSM
  - Biond Vax
  - Dynavax
  - NIAID Nanoparticle

## Pandemic Vaccine
- **Egg inactivated**
  - CSL Biotherapies
  - GSK
  - MedImmune
- **Cell-culture inactivated**
  - GSK
  - EE66; H5N1
  - MedImmune
  - BioPiem
  - AVI BioPharma
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
  - salmonella, Oral
  - VaxGen
  - Gilead
- **Universal**
  - NYU / MSSM
  - Biond Vax
  - Dynavax
  - NIAID Nanoparticle

## US License
- **Egg inactivated**
  - CSL Biotherapies
  - GSK
  - MedImmune
- **Cell-culture inactivated**
  - GSK
  - EE66; H5N1
  - MedImmune
  - BioPiem
  - AVI BioPharma
- **Recombinant (VLPs)**
  - GPO
  - Maxygen
  - ASU
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- **Universal**
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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
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?

HA Stalk
Highly conserved
Transiently accessible on infected cell surface
Need to engineer a vaccine to target

Matrix: internal
Highly conserved.
Induces CMI.

Adapted from: Paul Lewis, MD
Oregon State Public Health
Universal Vaccine Strategies

- Identify broadly reactive targets (HA Stalk, M2e, NP, M)
- Combination vaccines
- Vector expression system

Vaccine Design

- Broaden immune recognition
- Th1 vs Th2 responses
- Humoral and Cell-mediated

Adjuvants

Route of Admin

- Intranasal stimulation of mucosal immunity
- Intradermal delivery to target dendritic cells

Source: NIAID http://tinyurl.com/69n9lap

Advanced Development of Universal Influenza Vaccine - Points to Consider

• Manufacturability and scalability

• Novel potency release assay
  – Most regulators are accustomed to SRID or SRH

• Clinical development
  – Non HI immune response
    • Current regulatory guidelines are based on HI
  – Potential safety concern/disease enhancement
  – Mono-specific immune response/drift potential
    • Will a single amino acid change render vaccine ineffective?
  – May require large scale efficacy trials over multiple seasons or other non-traditional clinical development plans
    • Challenge studies for cross protection
Universal Flu Vaccine Program
at BARDA

• Collaborating within HHS to develop projects

• Current activities
  – Developing a Request for Information and/or sponsoring international symposium on universal influenza vaccine
  – Planning for an Acquisition Plan to support advanced development of promising programs demonstrating improved cross-reactivity and/or duration of effectiveness.
  – Foster public-private partnerships
    • BARDA Industry Day!
• Novel influenza vaccine candidates that improve key vaccine attributes
  ― dose schedule
  ― time to onset of protection
  ― induction of improved immunogenicity
  ― broader cross-protection across influenza A virus subtypes,
  ― duration of protection

• Use of approved or novel adjuvants may be a component of the advanced development program.

• Technology readiness level 6
  ― Data demonstrating statistically relevant improvements in immunogenicity/efficacy as compared to existing vaccines.