Opportunities and Challenges for a Broadly Protective Influenza Vaccine

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Mortality and Morbidity of 1918 Influenza

- 50-100 million deaths in 24 weeks
- High mortality in young adults: 8-10% of this segment of the population died within months.
- Post-infectious complications (Major Harvey Cushing, age 49, develops Guillain-Barre Syndrome, and never fully recovers).
Seasonal Influenza Vaccine Protection Against the 1918 Pandemic Virus

Protective immunity to lethal challenge of the 1918 pandemic influenza virus by vaccination

Cross-neutralization of 1918 and 2009 influenza viruses: role of glycans in viral evolution and vaccine design
Wei CJ, Boyington JC, Dai K, Houser KV, Pearce MB, Kong WP, Yang ZY, Tumpey TM, Nabel GJ
Limited and Variable Efficacy of Seasonal Influenza Vaccines

Strain-specific vaccines to 1918 influenza protect in animal models and against a related virus (2009 CA) in humans.

Seasonal influenza vaccines confer 40-60% efficacy, varies annually, and require yearly updates.
Broadly Neutralizing Antibodies for Prevention and/or Therapy

- Monoclonal abs have been identified that freeze HA and block influenza infection.

- There is considerable industry capability to manufacture bnAbs at large scale that could be used to prevent or treat influenza infection.

- Innovative approaches such as Ab gene delivery could allow more cost-effective and persistent protection.

- Can also be elicited by vaccination

Goals of a Universal Influenza Vaccine Program

- Definition of a universal influenza vaccine
- Clinical development pathway
- Regulatory strategy
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The Targets of Broadly Protective Influenza Vaccines

A vaccine with increased efficacy against current and future drifted and shifted influenza strains

Influenza A

Influenza B

Yamagata lineage-1970

Victoria lineage-1973
Where We Stand Today

Vaccine
- Strain-specific
- Subtype-specific
- Multi-subtype
- Pan-group/lineage
- Universal flu A
- “TRUE” Universal

Coverage
- Circulating Strains
- Multiple Strains within a Single HA Subtype
- Multiple HA Subtypes within Group 1
- Group 1,2 Influenza A and Influenza B Lineages
- Influenza A
- Influenza A and B
Range of Efficacy for Broadly Protective Influenza Vaccines

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![Vaccine Coverage Diagram]
Towards a Universal Influenza Vaccine

Development of a Pan-H1 Influenza Vaccine
Nicole Darricarrère, Svetlana Pougatcheva, Xiaochu Duan, Rebecca S. Rudicell, Te-Hui Chou, Joshua DiNapoli, Ted M. Ross, Tim Alefantis, Thorsten U. Vogel, Harry Kleanthous, Chih-Jen Wei, Gary J. Nabel

J. Virol. November 2018 Volume 92 Issue 22 e01349-18
doi:10.1128/JVI.01349-18

A protein nanoparticle cocktail approach induces broad immune responses against divergent H1N1 influenza viruses (Darricarrère et al.).

The search for broadly protective influenza vaccines remains a priority for public health. Such improved vaccines offer the potential to protect against diverse influenza strains, improving vaccine efficacy and reducing the likelihood of pandemic spread. Darricarrère et al. show that influenza hemagglutinins from divergent H1N1 strains presented on nanoparticles can be combined and used to elicit more effective anti-viral immune responses. This multivalent vaccine elicited antibodies that broadly neutralized diverse H1N1 viruses. The findings represent an advance in the effort to develop broadly protective or universal influenza vaccines by enhancing coverage against most H1N1 strains.
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Two Conserved Sites of Vulnerability
Induction of Broadly Neutralizing H1N1 Influenza Antibodies by Vaccination

C-J Wei, GJ Nabel et al.

- Vaccination with plasmid DNA encoding H1N1 influenza hemagglutinin (HA) and boosting with seasonal vaccine or replication-defective adenovirus 5 vector encoding HA stimulated the production of broadly neutralizing influenza antibodies.

- Antibodies were directed to the conserved stem region of HA and neutralized diverse H1N1 strains dating from 1934 to 2007.
Influenza Stabilized Stem Immunogen Elicits Broadly Neutralizing Protective Abs

Hemagglutinin-stem nanoparticles generate heterosubtypic influenza protection

Yassine, Jeffrey C Boyington, Patrick M McTamney, Chih-Jen Wei… Vaccine Research Center, NIAID NIH

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Pan-stem Broadly Neutralizing Abs against Influenza

Vaccine-Induced Antibodies that Neutralize Group 1 and Group 2 Influenza A Viruses

M. Gordon Joyce, Adam K. Wheatley, Paul V. Thomas, ..., Peter D. Kwong, John R. Mascola, Adrian B. McDermott

Cell 166, 609–623, July 28, 2016
July 28, 2016 Published by Elsevier Inc.

Highlights
- Isolation of group 1 and group 2 influenza A-neutralizing antibodies from H5N1 vaccinees
- Discovery of three classes of broadly neutralizing antibodies directed to the HA stem
- Detection of sequence signatures specific for broadly neutralizing antibodies
- Antibody quantification by NGS to guide the development of a universal vaccine

Accession Numbers
- SKBJ
- SKK
- SKD
- SKQ
- SKAN
- SKAQ
- KX086124-KX087227

Discovery and Quantification of Vaccine-Induced Group 1 & 2 Influenza A-Neutralizing Antibodies

Sources
- PDB: 5A9M, 5C3D
- Protein Data Bank
- 314 proteins from 63 influenza A vaccinees

Bioinformatics quantification of vaccine-induced antibodies

CellPress
## Range of Efficacy for Broadly Protective Influenza Vaccines

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**Universality**

- Influenza A
- Influenza B
Alternative Strategies to Develop Broadly Protective Influenza Vaccines

Strategy 1: Incremental Advance
Increased protection against future drifted influenza strains
  Vaccine protects against matched & mismatched strains

Strategy 2: Transformative Improvement
New technologies to prevent disease and replace the standard of care
  Engineering of broadly antigenic HA protein, assessments of added benefits of NA protein, HA2 (stem) and HA-Ferritin nanoparticles
Composition of Broadly Protective Influenza Vaccines

- HA = Hemagglutinin Design
- NA = Neuraminidase Design
- D = Dose
- Tr = Translational approach
- GMP = Clinical Materials (expression system)
- CMI = Cellular mediated immunity (CD4 T cells)
- Adj = Adjuvant
- CoP = correlate of protection
- F = Formulation

=> Efficacy, Breadth & Durability
The Enigma of Influenza Virus Vaccines

“An enigma for the field of influenza vaccinology is ….. that despite repeated exposures to influenza, most humans do not ultimately develop universal protection….. One potential explanation …..is that in natural infection, the virus does not readily expose to the host immune system those components of its structure that do not vary from strain to strain.”
Goals of a Universal Influenza Vaccine Program

- Definition of a universal influenza vaccine
- Clinical development pathway
- Regulatory strategy
Traditional Clinical Development Pathway

Phase I
- Safety
- Immunogenicity

Phase 2
- Expansion

Efficacy Studies
- Efficacy
- Immune correlates
- Disease prevention

Dose, interval
Adjuvants
Formulation, Cross-protective Abs

Licensure
Alternative Clinical Development Pathway

**Phase I**
- Safety
- Immunogenicity

**Clinical Investigation**
- Dose, interval
- Adjuvants
- Formulation, Cross-protective Abs

**Human Challenge Model**
- Target validation
- Comparative efficacy of bnAbs and vaccine candidates
- Establish benchmarks for therapeutic efficacy
- Rational and comparative analysis of candidates for efficacy trials
A By-pass Pathway to Accelerate Development of a Universal Flu Vaccine

Human clinical investigation to:
1. De-risk
2. Prioritize high quality candidates
3. Achieve ultimate goal
Goals of a Universal Influenza Vaccine Program

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Regulatory Concerns

Quality

• Consistent batch production as defined by the product specification
• Purity
• Potency

Safety

• Novel immunogens
• Novel delivery vehicles
• Adjuvants

Efficacy

• Non-inferior efficacy compared to Stand of Care (SOC)
• Superior protective immunity against drifted strains
• Extended immune durability in all populations

Approaching an Old Problem with a New Lens

- Consider criteria for licensure of a disease modifying vaccine
  
  Medically attended acute respiratory infection (MAARI) in RSV
  Predictive algorithms to identify potential mutations

- Adaptive clinical trial designs to identify optimal dose and adjuvants in humans (Phase 1 and 2)

- Develop new manufacturing platforms/capabilities beyond eggs that are more agile and less expensive

  Nanoparticle
  mRNA
  Designer adjuvants
A Novel Immunization Platform:
HA Ferritin Nanoparticles
Manufacturing Improvements: The Example of Continuous Biomanufacturing

The QL platform affords many advantages:

- **Universal** applicability
- **Simple** and **robust** process
- **Steady-state** production and quality

The ICB process seeks to take advantage of advances in **cell-line generation** and **continuous processing**.

ICB utilizes **QL** platform can achieve in **two 50L** reactors the same productivity as **four 2000L** reactors running the legacy process.
Continuous Biomanufacturing: A Potential Game-Changer for Vaccines

220 million doses produced in US, France, China and Mexico

Assuming:
1g/L/day
45 days
50% purification loss

50-liter bioreactor

1,125 grams, 100 million doses (10µg/dose)
Summary: This Problem Can Be Solved!

1. Structural biology, molecular virology and human immunology provide a strong base upon which to build an improved vaccine.

2. Humans produce antibodies that are broadly neutralizing, readily elicited, diverse, and not unusual. Sophisticated methodologies are available to characterize human T and B cell responses. The availability of human challenge models provide important validation for specific ab and vaccine candidates.

3. Knowledge of viral evolution and immune selection has advanced and has greater predictive power that informs vaccine design.

4. Manufacturing technology in biologics can accelerate production, safety, and reduce costs.
# Target Product Profile for Broadly Protective Influenza Vaccines

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<td>Mode of Action</td>
<td>Vaccine that induces neutralizing abs to influenza virus</td>
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<tr>
<td>Indication</td>
<td>Prevention of influenza virus infections</td>
</tr>
<tr>
<td>Target Population</td>
<td>Children/adolescents/adults</td>
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<tr>
<td>Dosage Administration</td>
<td>Single shot with potential 6-12 month boost</td>
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<tr>
<td>Efficacy Profile</td>
<td>Completely inhibits infection by &gt;X% of strains</td>
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<tr>
<td>Safety/Tolerability</td>
<td>Adverse event frequency less than 1 per million</td>
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Approach to Rapid Vaccine Development: Start with the End in Mind
Structures to Achieve the Goals

- Support of fundamental science to generate highly effective vaccines
- Mechanisms to promote early public-private collaboration
- Early stage manufacturing capacity
- Clinical trials networks with emphasis on phase 1 and human challenge
- Development of clinical immunology/biomarker capability and delineation of regulatory pathways