NIAID Influenza Vaccine Development: Novel Strategies for Better Vaccines

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NIAID Research and Development

NIAID Countermeasure Research and Development

- Therapeutics
- Diagnostics
- Expansion of Research Capacity
- Clinical Research
- Genomics
- Basic Research
- Vaccines
Product Development Services & Research Tools and Technologies

http://www.niaid.nih.gov/labsandresources/resources/dmid/Pages/default.aspx

- Reagents
  - Biodefense and Emerging Infections Research Resources Repository (BEI)
  - Wild type and recombinant viruses, Purified proteins, Polyclonal & monoclonal antibodies, Cell lines

- Preclinical Development Services
  - Optimization, synthesis, formulation, medicinal chemistry, product development plans; cGMP manufacture

- Assays
  - In vitro antiviral screening of 2009 H1N1, Seasonal, & H5N1 (LPAI and HPAI) in MDCK cells

- Animal models
  - Animal models for H1N1, H3N2, & H5N1 subtypes testing of vaccines and candidate therapeutics.

NIAID Research: A Dual Mandate

Maintain and “grow” a robust basic and applied research portfolio in microbiology, infectious diseases, immunology and immune-mediated diseases

Respond rapidly to new and emerging disease threats

New/Improved Interventions
NIAID Dual Mandate
Strategy for Influenza

Seasonal
Influenza
Preparedness

Pandemic
Influenza
Preparedness

NIAID Responds to
Viral Respiratory Outbreaks

Advancing Influenza Vaccine Development

Seasonal Influenza
Pandemic Influenza
Seasonal Influenza
H5N1 Outbreak
Seasonal Influenza
SARS Outbreak
Seasonal Influenza
H1N1 Outbreak

1996
2002
2009
Current Goal: Building a Better Influenza Vaccine

- Improved production and surge capacity
- Vaccine platforms that allow for more efficient manufacturing and potentially better efficacy
- Dose optimization strategies
- A "universal" vaccine

NIAID Influenza Vaccine Activities

- Direct funding
  - 40+ grants within DMID
    - exploratory (R21s), R01s, SBIRs, U01s
    - contract supported activities
- Collaborations, availability of resources
- Seasonal and Pandemic influenza vaccine trials
Novel Approaches to Influenza-Vaccine Production

Current and New Approaches to Influenza-Vaccine Production

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Preclinical Development</th>
<th>Phase 1 and 2 Clinical Testing</th>
<th>Phase 3 Clinical Testing</th>
<th>Licensed or Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated vaccines</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Egg-based</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell-based</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>In Europe but not in the United States</td>
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<tr>
<td>With adjuvant</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>In Europe but not in the United States</td>
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<tr>
<td>Live attenuated vaccines</td>
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<td></td>
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<tr>
<td>Egg-based</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell-based</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Next generation</td>
<td></td>
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<tr>
<td>Recombinant proteins</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Viruslike particles</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Viral vectors</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>DNA-based vaccines</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Universal vaccines</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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</table>
Universal Influenza-Vaccine

- Universal influenza vaccine needs to
  
  1. elicit humoral and cellular responses like natural infection
  
  2. provide long-lasting and cross-strain protection

- Major “universal” or “common-epitope” targets are conserved epitopes from:
  
  - HA
  - NP
  - matrix 1 (M1)
  - matrix 2 (M2)

NIAID Support for Universal Influenza-Vaccines

- NIAID is supporting basic and preclinical research aimed towards generating a universal influenza vaccine.

- NIAID is promoting the advancement of universal flu vaccine products towards licensure and clinical trials.

- NIAID VRC has funded clinical trials of a universal influenza vaccine strategy and DMID can use VTEUs to support phase I/II trials for universal vaccine candidates
Major Universal Influenza-Vaccine Targets and Strategies

- HA2 epitope-VLP
- Chimeric/consensus HA DNA
- Headless HA-VLP
- Ablated HA immunodominant epitopes - VLP
- M2e-VLP
- NP T cell epitopes-nanoparticle
- M2e+HA2 fusion peptide recombinant protein
- M1+HA+NP peptide recombinant protein

Headless HA Universal Influenza-Vaccine Approach

- Antibodies to variable immunogenic globular head: Does not protect against challenge with different sub-types.
- Antibodies to conserved HA stalk domain: Protects against challenge with different sub-types.

Supported by RC1 AI086061-01 and U01 AI070469
**HA Stem Universal Strategy:**
**Induction of Broadly Neutralizing AB**

*CR6261*
Ekiert et al., Science 2009

*Group 1*
Sui et al., Nat Struct & Mol Bio 2009

*Both*
Adapted from Nabel and Fauci
Nature Medicine 2010

*CR8020*
Ekiert et al., Science 2011

*Group 2*

**Chimeric HA Universal Influenza-Vaccine Approach**

Refocusing the immune response by sequential immunization

Anti-stalk broadly neutralizing antibodies

Supported by UO1 AI070498, HHSN266200700010C, U19AI089987, U54 AI057158-04, and U19-AI057266 with American Recovery and
Reinvestment Act Supplement Funding Grants U19 AI057266-06S2,
HHSN266200700006C, and HHSN27220080003C
A Computationally Optimized Hemagglutinin Virus-Like Particle Vaccine Elicits Broadly Reactive Antibodies that Protect Nonhuman Primates from H5N1 Infection

Supported by U01AI077771

DNA-based Universal Influenza-Vaccines Approach

Supported by NIAID VRC
M2 Universal Influenza-Vaccine Approach

Matrix protein 2 → Broadly neutralizing antibodies

M2 VLP

Supported by AI0680003

Challenges in the Production of Universal Influenza-Vaccines

- No clear front-runners for universal influenza vaccine eliciting a broadly cross-reactive, durable response
  - Multiple targets, multiple technological platforms
  - Poor immunogenic response of universal targets

- Regulatory pathway to licensure is not clear
  - Unclear what strategy will be used to introduce a new vaccine into a market with very well tested, relatively efficacious vaccine

- Do not have certified assays to assess correlates of protection
# DMID Influenza Contacts

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
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<tbody>
<tr>
<td>Linda Lambert</td>
<td>Branch Chief</td>
</tr>
<tr>
<td>David Spiro</td>
<td>Section Chief</td>
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<td>Rachelle Salomon</td>
<td>Vaccine Research &amp; Development</td>
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<tr>
<td>Sonnie Kim</td>
<td>Clinical Trials</td>
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<td>Amy Krafft</td>
<td>Therapeutics &amp; Diagnostics</td>
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<tr>
<td>Teresa Bernaciak</td>
<td>Basic Biology</td>
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<tr>
<td>Diane Post</td>
<td>Centers Excellence for Influenza Research &amp; Surveillance (CEIRS)</td>
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<tr>
<td>Erik Stemmy</td>
<td>Health Specialist</td>
</tr>
<tr>
<td>Maria Giovanni</td>
<td>Sequencing &amp; Functional Genomics</td>
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