NIAID Universal Influenza Vaccine Portfolio

Teresa Hauguel, PhD
Program Officer, Respiratory Diseases Branch
Division of Microbiology & Infectious Diseases
NIAID, NIH, DHHS

February 7, 2018
Need for a Universal Influenza Vaccine

- Current seasonal influenza vaccines are not consistently effective
- Pandemics do occur and response after the fact is not effective
- “Chasing after” potential pandemic outbreaks (pre-pandemic viruses) is costly and ineffective
DMID Strategy For Advancing Universal Influenza Vaccines

DMID Strategic Plan

- Advance Pipeline Towards Clinical Evaluation
- Improve Vaccine Efficacy & Production
- Support Assay Development to Measure Efficacy & Safety
- Provide Reagents to Community for Development
- Outreach & Partnerships
DMID Universal Influenza Vaccine Research Portfolio

**Basic Research**
- Pre-existing immunity
- Innate immunity
- Humoral & cellular immunity
- Biomarkers
- Modeling

**Natural History Studies**
- Pre-existing immunity
- Serial exposure
- Humoral & cellular immunity

**Universal Vaccine Strategies**
- Whole HA
- HA Head
- HA Stem
- NA
- M2
- LAIV
- DNA
- Peptide
- Adjuvants

**Preclinical Services**
- Efficacy in animal models
- Safety & toxicology
- PDPs
- cGMP
- Assays
- Reagents

**Clinical Trials**
- Candidate universal vaccines
- Safety & immunogenicity
- Adjuvants
- Omics

*NIH National Institute of Allergy and Infectious Diseases*
DMID Immunology Research To Advance Universal Influenza Vaccines

Universal Vaccine Properties

- Robust humoral and cellular immune response
- Cross-strain protection
- Long-lasting protection

- Innate immunity
- B cell immunity
- T cell immunity
- Pre-existing immunity
- Impact of sex and age
- Biomarkers
- Modeling
- Systems biology

>50 active projects
DMID Universal Influenza Vaccine Research Portfolio

Basic Research
- Pre-existing immunity
- Innate immunity
- Humoral & cellular immunity
- Biomarkers
- Modeling

Natural History Studies
- Pre-existing immunity
- Serial exposure
- Humoral & cellular immunity

Universal Vaccine Strategies
- Whole HA
- HA Head
- HA Stem
- NA
- M2
- LAIV
- DNA
- Peptide
- Adjuvants

Preclinical Services
- Efficacy in animal models
- Safety & toxicology
- PDPs
- cGMP
- Assays
- Reagents

Clinical Trials
- Candidate universal vaccines
- Safety & immunogenicity
- Adjuvants
- Omics
Request for Information (RFI): Prospective Longitudinal Cohort Studies of Influenza Infection and Vaccine Effectiveness

Notice Number: NOT-AI-17-043

Key Dates
Release Date: September 21, 2017
Response Date: December 5, 2017

Related Announcements
None

Issued by
National Institute of Allergy and Infectious Diseases (NIAID)

Purpose
NIAID is seeking information related to prospective, longitudinal cohort studies on influenza infections. The primary goal of this request is to gather information about existing community-based, prospective, longitudinal cohort studies of influenza, or other acute respiratory infections that may allow assessment of influenza immunity from banked samples. Also of interest are longitudinal cohort studies examining the effectiveness of influenza vaccination.

NIAID seeks to understand the breadth of existing cohort studies including cohort characteristics (e.g., the size, participant population, ages, location, and period of time the cohort has been studied); the types of samples that have been collected; and the quantity of samples banked for future use. Of particular interest are cohorts (including international cohorts) that might be leveraged to examine gaps in understanding how immunity develops to influenza, especially in the context of vaccination vs natural infection. Information from this RFI will be used in developing a research agenda.
DMID Universal Influenza Vaccine Research Portfolio

Basic Research
- Pre-existing immunity
- Innate immunity
- Humoral & cellular immunity
- Biomarkers
- Modeling

Natural History Studies
- Pre-existing immunity
- Serial exposure
- Humoral & cellular immunity

Universal Vaccine Strategies
- Whole HA
- HA Head
- HA Stem
- NA
- M2
- LAIV
- DNA
- Peptide
- Adjuvants

Preclinical Services
- Efficacy in animal models
- Safety & toxicology
- PDPs
- cGMP
- Assays
- Reagents

Clinical Trials
- Candidate universal vaccines
- Safety & immunogenicity
- Adjuvants
- Omics
## DMID Universal Influenza Vaccine Strategies

### Preclinical Development

<table>
<thead>
<tr>
<th>HA nanoparticles + free HA &amp; NP</th>
<th>Antigenically advanced antigens (WISCONSIN)</th>
<th>M2e-HA stem (UCSF)</th>
<th>Chimeric HA (NIAID)</th>
<th>Germline-targeted HA stem (UCSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4xM2e HA LAIV (UCSF)</td>
<td>VLPs with HA stem, NP, TLR/CD40 (INDIANA UNIVERSITY)</td>
<td>Surface antigen/adjuvant vaccine engineering (SAAVE) (UNIVERSITY OF GEORGIA)</td>
<td>M2 Single Replication (M2SR) LAIV (Flugen)</td>
<td>Ad5 vectored centralized HA (UNIVERSITY OF NEBRASKA-LINCOLN)</td>
</tr>
<tr>
<td>DNA prime/subunit boost</td>
<td>M2e CpG gold nanoparticles (TEXAS TECH UNIVERSITY)</td>
<td>M2e-TLR5 fusion protein (GEORGIA STATE UNIVERSITY)</td>
<td>SAVE de-optimized LAIV (ODAGENIX)</td>
<td>Ad5 vectored Chimeric HA (UNIVERSITY OF LONDON)</td>
</tr>
<tr>
<td>Advax delta inulin adjuvant</td>
<td>Laser vaccine adjuvant (MASSACHUSETTS GENERAL HOSPITAL)</td>
<td>Nematode-secreted rASP-1 adjuvant (New York Blood Center)</td>
<td>Chimeric HA (NIAID)</td>
<td>Chimeric HA (NIAID)</td>
</tr>
</tbody>
</table>

### Phase I

| HA, NP, M1 peptides (M-001) | HA, NP, M1 peptides (M-001) |

### Phase II

| HA, NP, M1 peptides (M-001) | HA, NP, M1 peptides (M-001) |

### Text Only Version

- **Preclinical Development**
  - HA nanoparticles + free HA & NP
  - Antigenically advanced antigens (WISCONSIN)
  - M2e-HA stem (UCSF)
  - Chimeric HA (NIAID)
  - Germline-targeted HA stem (UCSF)
  - 4xM2e HA LAIV (UCSF)
  - VLPs with HA stem, NP, TLR/CD40 (INDIANA UNIVERSITY)
  - Surface antigen/adjuvant vaccine engineering (SAAVE) (UNIVERSITY OF GEORGIA)
  - M2 Single Replication (M2SR) LAIV (Flugen)
  - DNA prime/subunit boost
  - M2e CpG gold nanoparticles (TEXAS TECH UNIVERSITY)
  - M2e-TLR5 fusion protein (GEORGIA STATE UNIVERSITY)
  - SAVE de-optimized LAIV (ODAGENIX)
  - TLR5, TLR7/8 adjuvants
  - Nanoparticle adjuvant TNF, IL-12 (COLUMBIA UNIVERSITY)
  - Microneedle adjuvant GIFT4/IFN-lambda 2 (EMORY UNIVERSITY)
  - Advax delta inulin adjuvant
  - Laser vaccine adjuvant (MASSACHUSETTS GENERAL HOSPITAL)
  - Nematode-secreted rASP-1 adjuvant (New York Blood Center)

- **Phase I**
  - HA, NP, M1 peptides (M-001)

- **Phase II**
  - HA, NP, M1 peptides (M-001)
## Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>VaxArray® influenza potency assay</td>
<td>InDeVr, Inc.</td>
</tr>
<tr>
<td>Cypher One optical analysis of HA &amp; HI assays</td>
<td>InDeVr, Inc.</td>
</tr>
<tr>
<td>Improved ADCC assay</td>
<td>St. Jude Children’s Research Hospital</td>
</tr>
<tr>
<td>Binding of antibody to an array of expressed HAs</td>
<td>University of Rochester</td>
</tr>
<tr>
<td>Quantification of antigenic drift &amp; neutralizing antibody breadth</td>
<td>Mt. Sinai School of Medicine</td>
</tr>
</tbody>
</table>

## Reagents

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>General influenza reagents &amp; ferret immunological reagents</td>
<td>St. Jude Children’s Research Hospital</td>
</tr>
<tr>
<td>Reagents for analysis of stalk-specific immunity &amp; generation of stable chimeric HA expressing viruses</td>
<td>Mt. Sinai School of Medicine</td>
</tr>
<tr>
<td>Cell lines for highly efficient replication of vaccine viruses</td>
<td>University of Wisconsin</td>
</tr>
</tbody>
</table>
DMID Universal Influenza Vaccine Research Portfolio

Basic Research
- Pre-existing immunity
- Innate immunity
- Humoral & cellular immunity
- Biomarkers
- Modeling

Natural History Studies
- Pre-existing immunity
- Serial exposure
- Humoral & cellular immunity

Universal Vaccine Strategies
- Whole HA
- HA Head
- HA Stem
- NA
- M2
- LAIV
- DNA
- Peptide
- Adjuvants

Preclinical Services
- Efficacy in animal models
- Safety & toxicology
- PDPs
- cGMP
- Assays
- Reagents

Clinical Trials
- Candidate universal vaccines
- Safety & immunogenicity
- Adjuvants
- Omics

NIH National Institute of Allergy and Infectious Diseases
DMID Vaccine Development Services

Supports vaccines, adjuvants, devices and challenge materials

**Vaccine Manufacturing**
- Feasibility, Gap Analysis, & Product Development Plan (PDP) Support
- Process Development
- Product Release Assay Development
- Potency Assays
- Pilot & cGMP Manufacturing
- Audits
- Regulatory Activities

**Vaccine Testing**
- Assay Development for Non-Clinical & Clinical Samples
- Non-Clinical & Clinical Sample Testing
- Non-Clinical Immunogenicity & Efficacy Studies (including non-GLP & GLP)
- Safety & Toxicity Testing

[Image of vaccine manufacturing setup]
[Image of laboratory setting]
DMID Universal Influenza Vaccine Research Portfolio

Basic Research
- Pre-existing immunity
- Innate immunity
- Humoral & cellular immunity
- Biomarkers
- Modeling

Natural History Studies
- Pre-existing immunity
- Serial exposure
- Humoral & cellular immunity

Universal Vaccine Strategies
- Whole HA
- HA Head
- HA Stem
- NA
- M2
- LAIV
- DNA
- Peptide
- Adjuvants

Preclinical Services
- Efficacy in animal models
- Safety & toxicology
- PDPs
- cGMP
- Assays
- Reagents

Clinical Trials
- Candidate universal vaccines
- Safety & immunogenicity
- Adjuvants
- Omics

NIH National Institute of Allergy and Infectious Diseases
DMID Vaccine and Treatment Evaluation Units (VTEUs)

- Rapid-response capabilities
- Testing novel vaccines
- Developing combination vaccines
- Testing novel delivery systems
DMID Supported Clinical Trials For Universal Influenza Vaccine Strategies

**MSSM/GSK/NIAID VRC Chimeric HA**
- DMID 17-0086, Phase I DNA prime (chimeric H8/1, N1 NA) & IIV boost (chimeric H5/1, N1 NA) in healthy adults
- Analysis of humoral NA and HA stalk-specific responses

**RedeeFlu (M2SR LAIV)**
- DMID 17-0112, Phase I H3N2 M2SR prime & IIV4 boost in pediatric subjects
- Analysis of humoral & CMI responses including NA immune responses & HA stalk-specific responses

**M-001 Peptide Vaccine**
- DMID 14-0112, Phase II M-001 prime & seasonal IIV3/IIV4 boost in healthy adults
- Analysis of CMI responses

**Imiquimod (Aldara) Topical Adjuvant**
- DMID 16-0050, Phase II: Imiquimod with H5N1 vaccine in healthy adults
- Analysis of humoral & CMI responses
NIAID Intramural Universal Influenza Vaccine Program
Viral Pathogenesis & Evolution Section (VPES) Influenza Program

- **Universal Influenza Vaccine Platform**
  - Cocktail of inactivated avian influenza viruses expressing at least 4 different HA subtypes
  - Currently in preclinical development
  - Demonstrated near 100% protection against influenza viral challenge regardless of subtype in animals
  - Phase I safety and immunogenicity studies to be conducted within one year

- **Human Volunteer Influenza Challenge Studies**
  - Key component of efforts to develop a universal influenza vaccine
  - Studies of viral pathogenesis and immune responses
  - Efficient model for early Phase II clinical evaluation of novel vaccines
NIAID Vaccine Research Center (VRC)
Influenza Vaccine Program
VRC Influenza Program

Research Approaches
- Reagent and assay development – probes, reporter viruses
- Application of single-cell sorting for repertoire analysis, antibody isolation, and phenotyping
- Structure-guided antigen design and nanoparticle display
- Clinical evaluation of novel products
- Animal model improvement

Vaccine Development Goals
- 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
VRC Influenza Vaccine Portfolio

Avoiding immunodominant strain-specific antibody responses allowing cross-reactive antibodies to emerge

Combined or serial heterologous antigen regimens to recruit and accumulate antibodies to diverse antigen sites and strains

Targeting conserved antigenic sites in stem to induce cross-reactive antibodies

Priming with DNA improves magnitude and avidity of vaccine-induced antibody
Primed in the 1980s influences antibody responses to the 2009 H1N1 virus

Pathway to a Universal Influenza Vaccine

June 28-29, 2017
5601 Fishers Lane Conference Center
Rockville, MD, USA

Slide Credit: Dr. Anthony Fauci, NIAID
Established definition for a universal influenza vaccine to serve as a goal for future research efforts

Identified key gaps in knowledge to guide strategic planning

Identified current research tools and discussed advantages/disadvantages

Coordination of the influenza research field is critical for success
Definition of a Universal Influenza Vaccine

- Protection: >75% against symptomatic influenza infection
- Breadth: Protection against group 1 and group 2 influenza A viruses
  - Influenza B a secondary target
- Durability: >1 year
- Population: Suitable for all age groups
Key Gaps & Priorities

- Improve understanding of transmission, natural history and pathogenesis of influenza infection
- Precise characterization of influenza immunity and correlates of immune protection
- Support rational design of universal influenza vaccines
- Develop research resources and cross-cutting tools to improve influenza vaccines
  - Develop/improve animal models
  - Establish longitudinal cohorts
  - Increase capacity and capability for conducting human challenge studies
  - Develop/apply systems biology approaches
DMID Universal Influenza Vaccine Research Portfolio

1. Basic Research
   - Pre-existing immunity
   - Innate immunity
   - Humoral & cellular immunity
   - Biomarkers
   - Modeling

2. Natural History Studies
   - Pre-existing immunity
   - Serial exposure
   - Humoral & cellular immunity

3. Universal Vaccine Strategies
   - Whole HA
   - HA Head
   - HA Stem
   - NA
   - M2
   - LAIV
   - DNA
   - Peptide
   - Adjuvants

4. Preclinical Services
   - Efficacy in animal models
   - Safety & toxicology
   - PDPs
   - cGMP
   - Assays
   - Reagents

5. Clinical Trials
   - Candidate
   - Universal vaccines
   - Safety & immunogenicity
   - Adjuvants
   - Omics
DMID Universal Influenza Vaccine Strategies

- **Preclinical Development**
  - HA nanoparticles + free HA & NP (with The University of Iowa logo)
  - Germline-targeted HA stem (with The Scripps Research Institute logo)
  - 4xM2e HA LAIV (with Georgia State University logo)
  - DNA prime / subunit boost (with Profectus Biosciences logo)
  - TLR5, TLR7/8 adjuvants (with Wake Forest University logo)
  - Advax delta inulin adjuvant (with Vaxine logo)
  - Antigenicall advanced antigens (with Erasmus MC, University of Cambridge, and University of Wisconsin-Madison logo)
  - VLPs with HA stem, NP, TLR/CD40 (with Indiana University logo)
  - M2e CpG gold nanoparticles (with Texas Tech University logo)
  - Ad5-vectored (with Etubics corporation logo)
  - Nanoparticle adjuvant TNF, IL-12 (with Columbia University logo)
  - M2e-HA stem (with Georgia State University logo)
  - Surface antigen/adjuvant vaccine engineering (SAAVE) (with University of Georgia logo)
  - M2e-TLR5 fusion protein (with Georgia State University logo)
  - Ad5-vectored centralized HA (with University of Nebraska-Lincoln logo)
  - Microneedle adjuvant GIFT4/IFN-lambda 2 (with Emory University logo)
- **Phase I**
  - Chimeric HA (with NIH National Institute of Allergy and Infectious Diseases, gsk, and Icahn School of Medicine at Mount Sinai logos)
  - M2 Single Replication (M2SR) LAIV (with FluGen logo)
  - SAVE de-optimized LAIV (with CodageniX logo)
- **Phase II**
  - HA, NP, M1 peptides (M-001) (with BiondVax Pharmaceuticals Ltd. logo)
VRC Influenza Vaccine Portfolio

Immunodominant strain-specific epitope

- HA REB
  - Heterologous Monomeric RBD
- Full-length HA
- HA head removal
  - Headless HA stem
- HA DNA Prime
  - Conventional vaccine