Universal Influenza Vaccines and Their Role in Preparedness

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21 March 2018

Influenza Is a Constant, Ongoing Global Threat to Public Health

- Recent estimates indicate up to ~ 290,000- 650,000 deaths/year due to influenza-associated respiratory disease[1]

  - Important gaps in estimating true burden of influenza-like illness (ILI) in LMICs

- Emerging strains with pandemic potential are difficult to predict leaving global response mostly reactive

  - H5, H7, H9…

- Suboptimal seasonal vaccine effectiveness resulted in significant ILI activity in both hemispheres

  - U.S: Percentage of outpatient visits for ILI during 2017-2018 influenza season rivaled those seen during the 2009 H1N1 pandemic (7.7%)[2]

1) Lancet, 2017, Dec 14
2) MMWR, 2018; 67(6):169-179

National Institute of Allergy and Infectious Diseases

Overview

- Highlights of NIAID support of pandemic influenza preparedness

- Brief introduction to NIAID's newly released strategic plan to support the development of Universal Influenza Vaccine

  - Supporting the research agenda

National Institute of Allergy and Infectious Diseases

NIAID Centers of Excellence for Influenza Research and Surveillance (CEIRS)

St. Jude Children's Research Hospital
Memphis, TN

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Richard Webby

Co-PI
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Rochester, NY

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Adolfo Garcia-Sastre

Emory University
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PI
Walter Orenstein

Co-PI
Dick Compans

Johns Hopkins University
**Baltimore, MD**

PI
Richard Rothman

Co-PI
Andrew Pekosz

Updated 5/2014

- Established to support the research agenda of the HHS Pandemic Influenza Plan
    - 2009 H1N1 pandemic, CEIRS conducted early virus characterization studies and pre-clinical evaluation of vaccine material
    - During 2014, provided viral isolates in response to H5N8 outbreaks in birds in US and Europe
    - During 2015 H7N8 outbreak in U.S. poultry, provided >50 viral isolates
- 5 sites + 1 Core center, 62 sub-contracts

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# NIAID CEIRS
Surveillance Sites

Currently collaborates with 27 international and ~20 domestic surveillance sites
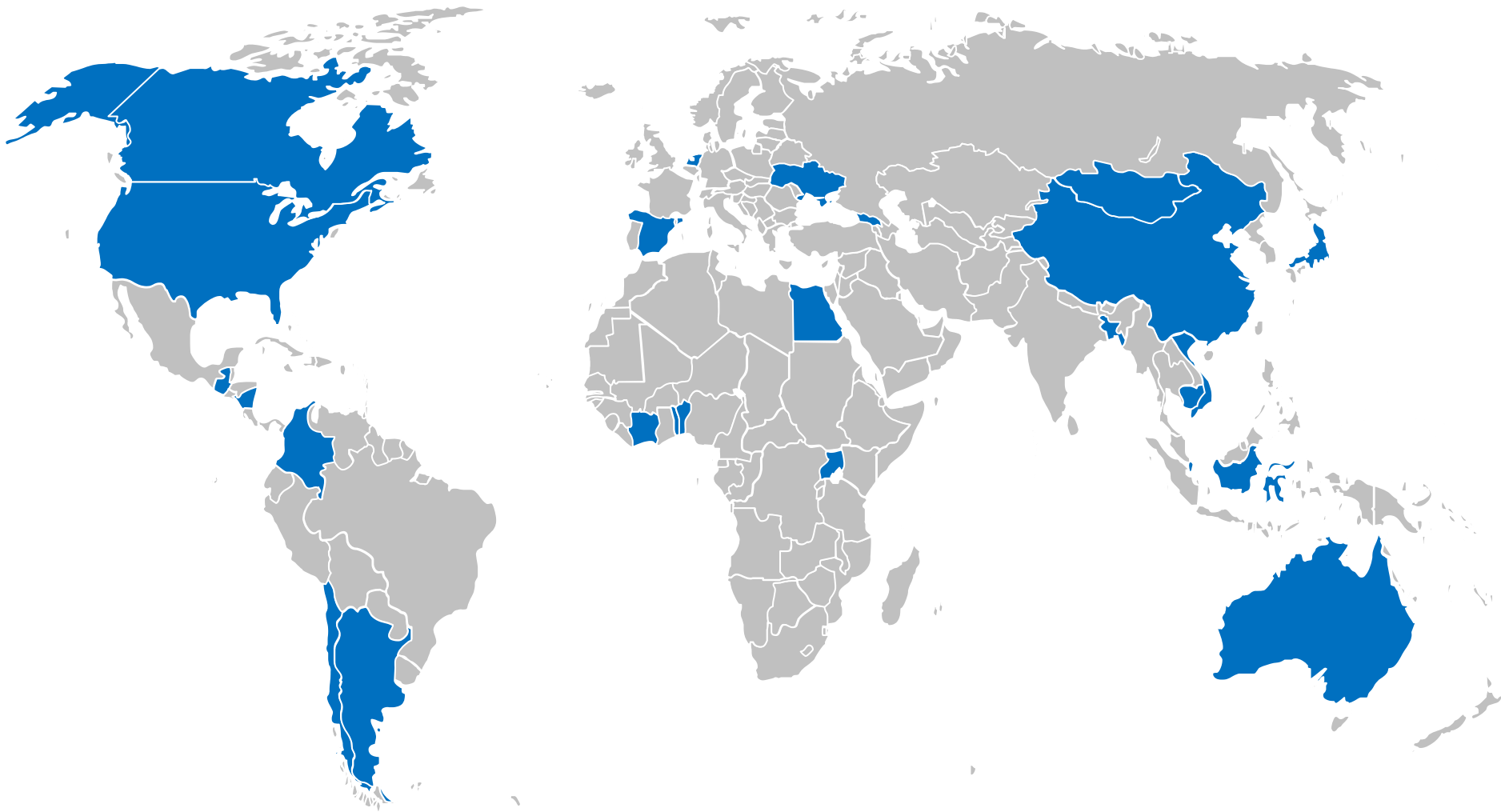
NIAID Support of H5 and H7 Pandemic Preparedness Clinical Trials

- **Mix and Match Studies +/- adjuvant**

  - Stockpiled vaccines: H5N1, H5N8, 2013 H7N9 and 2017 H7N9

  - Phase I/II studies: Dose ranging using monovalent split IIVs with and without adjuvant(AS03 and MF59)

- **Heterologous Prime/Boost Studies to broaden cross-clade response**

  - H5N1: A/Vietnam and A/Indonesia

  - H7: H7N7 and H7N9

  - LAIV prime followed by IIV boost

  - IIV prime followed by LAIV boost

- **System Biology and High Def Immunological Studies:**

  - "Omic" with comprehensive assessment of T, B and Innate Immune Responses

Influenza is Difficult to Predict and Remains a Moving Target for Pandemic Preparedness
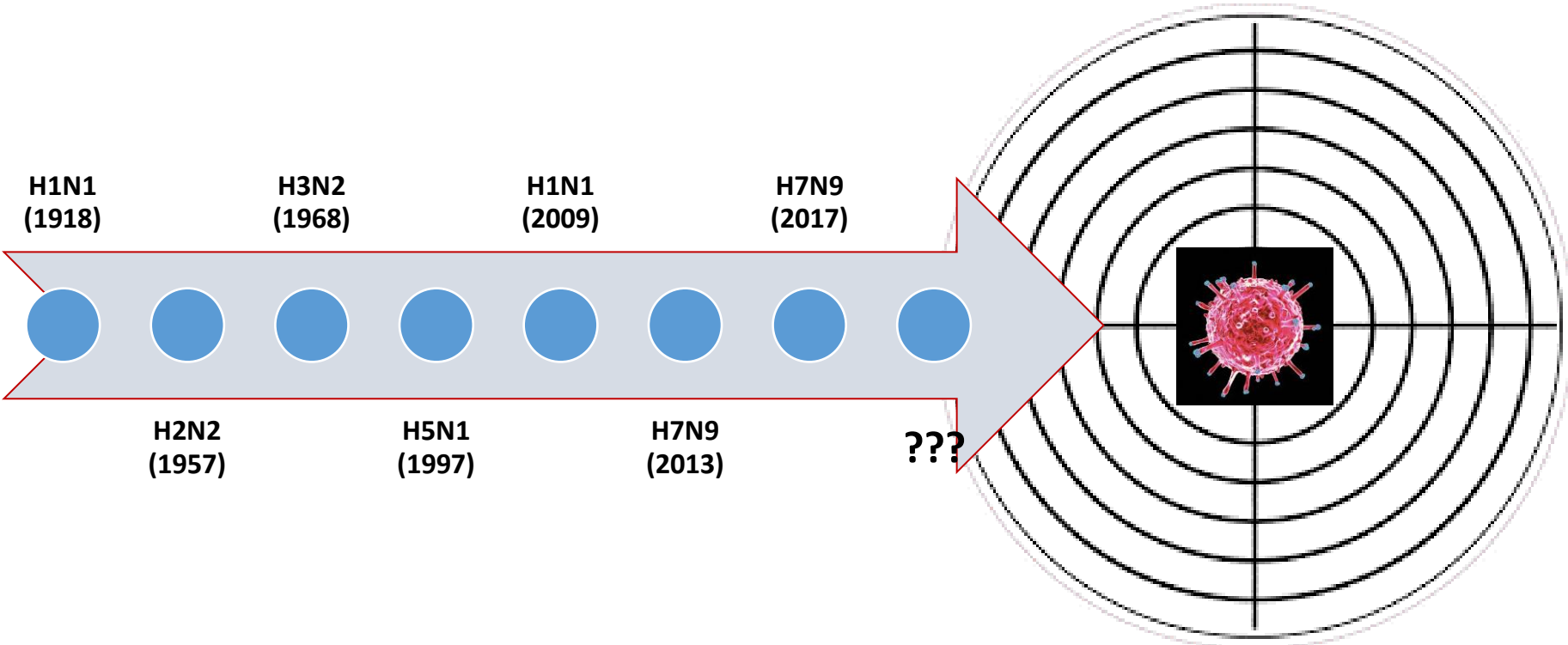
Need for a Universal Influenza Vaccine

- **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**
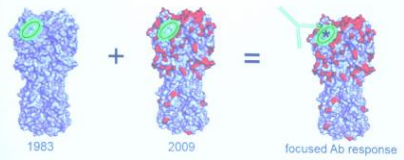
Slide Credit: Dr. Anthony Fauci, NIAID

Workshop Meeting Report

Immunity

Volume 47
Number 4
October 17, 2017

www.cell.com

The Pathway to a Universal Influenza Vaccine

Paules CI, Marston HD, Eisinger RW, Baltimore D, Fauci AS

October 2017

- Established definition for a **universal influenza vaccine to serve as a goal** for future research efforts

- Identified current **research tools** and discussed advantages/disadvantages

- **Coordination** of the influenza research field is critical for success

- Identified **key gaps in knowledge** to guide strategic planning

Slide Credit (*adapted from*): Dr. Anthony Fauci, NIAID

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Infectious Diseases

Definition of a Universal Influenza Vaccine

- **Protection: $\geq$75% against symptomatic influenza infection**

- **Breadth: Protection against group 1 and group 2 influenza A viruses**
  - **Influenza B a secondary target**

- **Durability: $\geq$1 year**

- **Population: Suitable for all age groups**

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NIAID Strategic Plan for a Universal Influenza Vaccine

Research Area 1: Improve Understanding of Transmission, Natural History, and Pathogenesis

Research Area 2: Precise Characterization of Influenza Immunity and Correlates of Protection

Research Area 3: Support Rational Design of Universal Influenza Vaccines

Develop/ improve animal models

Establish longitudinal cohorts

Increase capacity/capabilities for human challenge studies

Develop/apply systems biology approaches

DMID Extramural Universal Influenza Vaccine Research Portfolio

>160 Active Influenza Grants + 33 clinical trial studies

Basic Research	Natural History Studies	Universal Vaccine Strategies	Preclinical Services	Clinical Trials

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
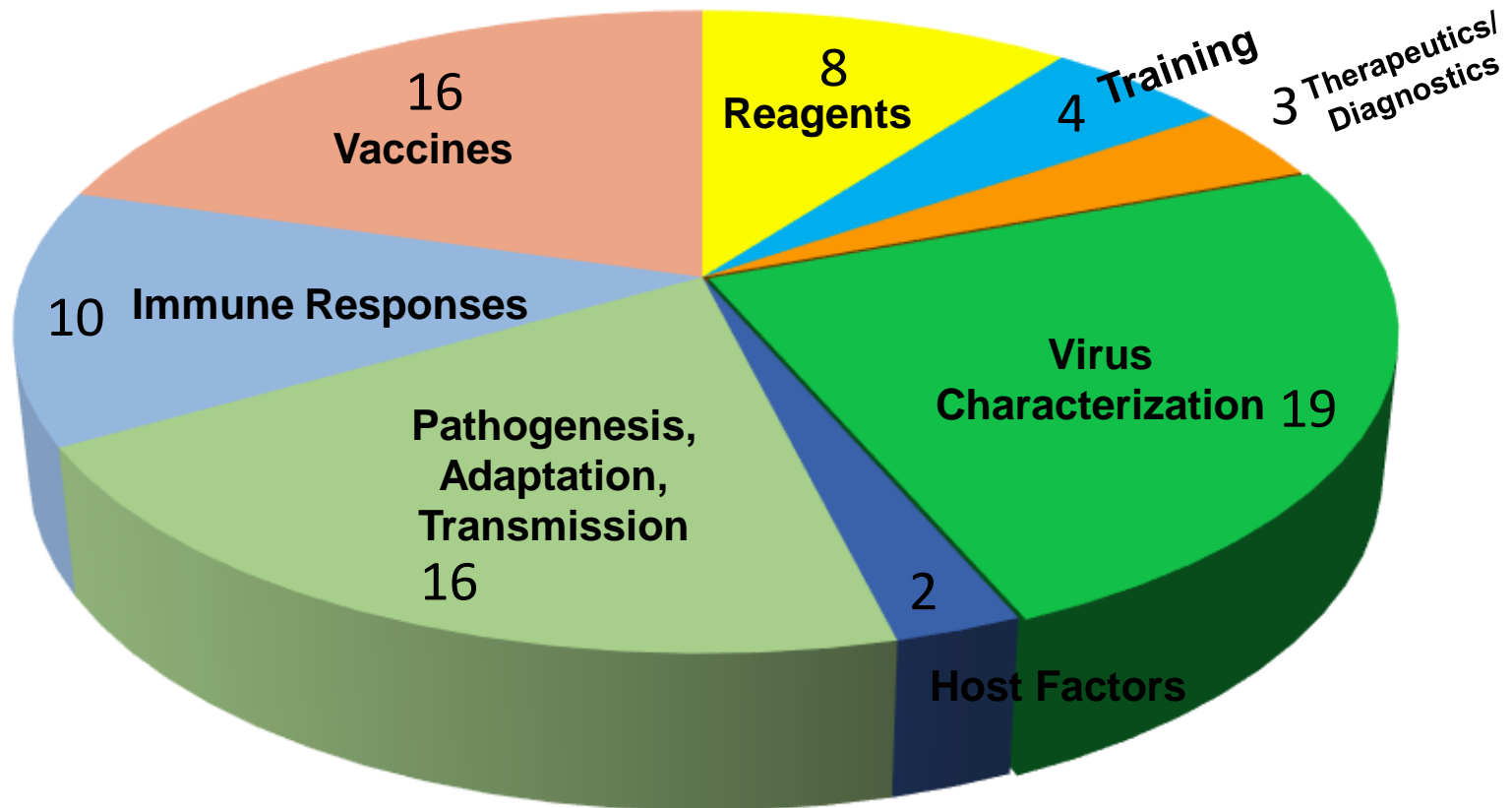- Safety & toxicology
- PDPs
- cGMP
- Assays
- Reagents

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

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CEIRS Network Basic Research

78 Basic Research Projects; 34 Universal Vaccine Related
(Base, Cross Collaborative & Pilot Projects)

http://www.niaidceirs.org/

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
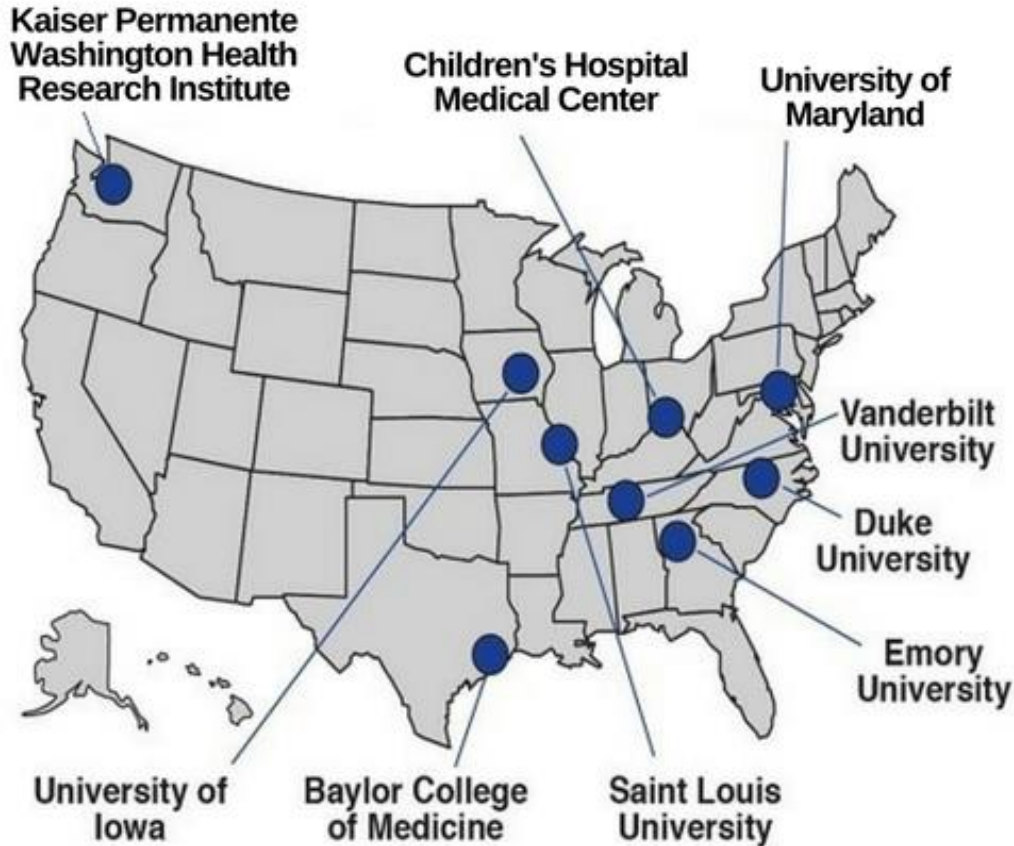- Audits
- Regulatory Activities

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

https://www.niaid.nih.gov/research/resources

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DMID Vaccine and Treatment Evaluation Units (VTEUs)

- Rapid-response capabilities
- Testing novel vaccines
- Developing combination vaccines
- Testing novel delivery systems

https://www.niaid.nih.gov/research/vaccine-treatment-evaluation-units

DMID Universal Influenza Vaccine Strategies

Preclinical Development			Phase I	Phase II
HA nanoparticles + free HA & NP THE UNIVERSITY OF IOWA	**Antigenically advanced antigens** Erasmus MC, WISCONSIN, UNIVERSITY OF CAMBRIDGE	**M2e-HA stem** Georgia State University	**Chimeric HA** NIH, gsk, Icahn School of Medicine at Mount Sinai	**HA, NP, M1 peptides (M-001)** BiondVax Pharmaceuticals Ltd.
Germline-targeted HA stem THE SCRIPPS RESEARCH INSTITUTE	**VLPs with HA stem, NP, TLR/CD40** IU INDIANA UNIVERSITY	**Surface antigen/adjuvant vaccine engineering (SAAVE)** UNIVERSITY OF GEORGIA	**M2 Single Replication (M2SR) LAIV** FluGen Focused on Influenza	**Imiquimod (Aldara) Topical Adjuvant** 3M
4xM2e HA LAIV Georgia State University	**M2e CpG gold nanoparticles** TEXAS TECH UNIVERSITY	**M2e-TLR5 fusion protein** Georgia State University	**SAVE de-optimized LAIV** CODAGENIX	
DNA prime/ subunit boost PROFECTUS BIOSCIENCES	**Ad5-vectored HA, NP, M** ETUBICS CORPORATION	**Ad5-vectored centralized HA** UNIVERSITY OF NEBRASKA–LINCOLN		
TLR5, TLR7/8 adjuvants WAKE FOREST UNIVERSITY	**Nanoparticle adjuvant TNF, IL-12** COLUMBIA UNIVERSITY	**Microneedle adjuvant GIFT4/IFN-lambda 2** EMORY UNIVERSITY		
Advax delta inulin adjuvant vaxine	**Laser vaccine adjuvant** MASSACHUSETTS GENERAL HOSPITAL	**Nematode-secreted rASP-1 adjuvant** New York Blood Center		

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Cohort Studies of Influenza Infection and Vaccine Effectiveness

Notice of Intent to Publish a Funding Opportunity Announcement to Investigate Impact of Initial Influenza Exposure on Immunity in Infants (U01 Clinical Trial Not Allowed)

Notice Number: NOT-AI-18-020

Purpose

The National Institute of Allergy and Infectious Diseases (NIAID) is issuing this Notice to promote a new initiative that will solicit applications to support research to determine how initial and repeated natural influenza infections and/or influenza vaccinations shape infant and childhood immunity to future influenza exposures, through support of prospective longitudinal human infant cohorts. The ultimate goal of this research effort is to provide key information to facilitate design of durable, broadly protective influenza vaccines.

Key Dates

Release Date: February 15, 2018
Estimated Publication Date of Funding Opportunity Announcement: 04/02/2018
First Estimated Application Due Date:07/02/2018
Earliest Estimated Award Date: 03/01/2019
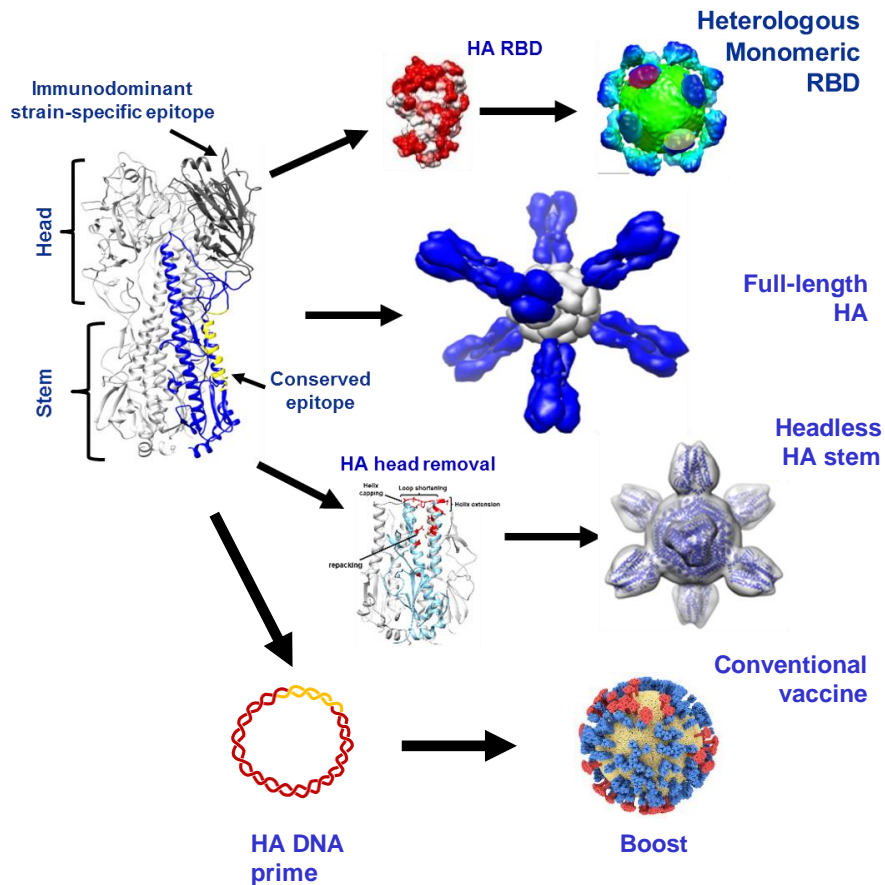**Earliest Estimated Start Date:** 03/01/2019

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NIAID Intramural Universal Influenza Vaccine Program

- **Vaccine Portfolio**

- **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
  - Human challenge models

https://www.niaid.nih.gov/research/vaccine-research-center-labs

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DMID Strategy For Advancing Universal Influenza Vaccines
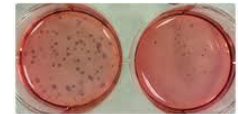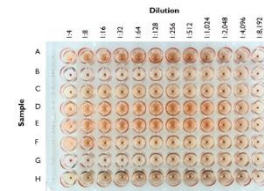
DMID Strategic Plan

- Advance Pipeline Towards Clinical Evaluation
- Improve Vaccine Efficacy & Production
- Support Assay Development to Measure Efficacy & Safety
- Provide Reagents to Community for Development
- Outreach & Partnerships
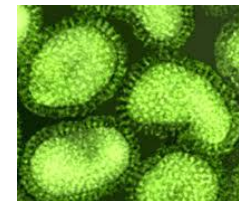
National Institute of Allergy and Infectious Diseases

Thank you

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Steps Toward a Universal Influenza Vaccine

Vaccine	Coverage
Strain-specific	Current circulating strains
Subtype-specific	All strains within a single HA subtype (e.g., H1)
Multi-subtype	Multiple HA subtypes within single group (e.g., H1/H5/H9)
Pan-group	Covering all group 1 or 2
Universal influenza vaccine	All influenza A (+/- *influenza B*)

Universality

Courtesy Gary Nabel

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