

# Universal Influenza Vaccines Meeting Summary

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## Table of Contents

<b>Executive Summary</b> .....	<b>3</b>
<b>Key Challenges and Recommendations</b> .....	<b>4</b>
<b>Detailed Summary of Universal Influenza Vaccines Meeting</b> .....	<b>5</b>
<b>Session I: Scientific Questions</b> .....	<b>5</b>
<b>Session II: Early Development /Translation</b> .....	<b>8</b>
<b>Session III: Advanced Development /Commercialization</b> .....	<b>10</b>
<b>Session IV: Clinical Studies</b> .....	<b>12</b>
<b>Appendix 1: NIAID Extramural Accomplishments and Ongoing Activities</b> ...	<b>14</b>
<b>Appendix 2: Meeting Organization</b> .....	<b>16</b>
<b>Appendix 3: Participants List</b> .....	<b>17</b>

## **Executive Summary**

Influenza A virus (IAV) remains a deadly and costly pathogen throughout the world. Vaccination is the most cost-effective option for reducing influenza morbidity and mortality. Current vaccine strategies are based on inducing hemagglutination-inhibiting antibodies (Abs) as markers of virus neutralizing Abs. While existing vaccines are relatively effective for circulating viruses in non-elderly individuals, they become obsolete within a few years due to ongoing antigenic drift in the viral surface glycoproteins [(hemagglutinin (HA) and neuraminidase (NA)] or introduction of novel glycoproteins from animal reservoirs (antigenic shift, as occurred with the recent introduction of the swine origin influenza virus (SOIV). Highly conserved viral gene products (e.g., M2, NP) have been explored as drift/shift resistant vaccine targets, but such vaccines appear to be mostly suitable as adjuncts to current vaccines rather than as stand-alone products. Recent investigation of Abs recognizing the conserved stem portion of the HA support the principle that stem reactive-Abs (StRAbs) might provide the basis for a universal IAV vaccine that precludes the frequent reformulation of such vaccines. This opportunity to quantally advance vaccine efficacy provides the rationale for intensifying vaccine R&D. Advancing toward a universal vaccine necessitates examining current practices and assumptions, and developing new assays and methodologies.

This two-day meeting was co-sponsored by the U.S. Food and Drug Administration (FDA) and the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). It brought together internationally recognized experts in protective antibody responses to influenza with critical decision makers in industry and government to identify major challenges hindering universal influenza vaccine development, and to make recommendations for surmounting these challenges.

## **Key Challenges and Recommendations**

**Challenge:** There is need for better understanding of basic aspects of influenza HA antigenicity, immunogenicity, and function.

### **Recommendations:**

- Provide increased support for studies that expand knowledge and understanding of the biology of influenza HA. Examples include:
  - Basic B-cell biology related to vaccine response
  - How the immune response changes through the human lifespan from first exposure of children through senescence
  - Mechanisms of anti-viral activity of broadly cross-reactive Abs
  - Evolution of IAV in response to induction of effective cross-reactive Abs

**Challenge:** Current assays and experimental animal models for assessing vaccine potency are not suitable for next-generation vaccines that are based on induction of StRAbs and other alternative immune effectors. Reagents essential for developing next-generation influenza vaccines are difficult to obtain.

### **Recommendations:**

- Support clinical studies that establish the relationship between various parameters of the immune response to influenza and the outcome of influenza infection. These include retrospective studies that correlate serum Abs with clinical outcomes.
- Support development of animal models that better mimic the complexity of the immune response in humans who are exposed to multiple influenza infections and vaccinations.
- Expand distribution of reagents for the development of universal influenza vaccines through NIAID repositories. Examples of reagents may include well-characterized monoclonal StRAbs and other broadly neutralizing mAbs as well as a panel of antigenically disparate viruses to aid in developing common assays for measuring broadly neutralizing Ab responses.

**Challenge:** Industry is wary about embarking on large, costly clinical trials for novel products.

### **Recommendations:**

- Support multiple small-scale human trials for promising candidate vaccines.
- Establish public-private partnerships for large scale clinical trials of promising vaccines.

# Detailed Summary of Universal Influenza Vaccines Meeting

## Introduction and Background

This meeting was divided into four major topical sessions focusing on scientific questions, early development/translation, advanced development/commercialization, and clinical studies. Each session was guided by a discussion leader, and included presentations, discussion, and recommendations related to each topic area. Dr. Jonathan Yewdell, Chief, Cellular Biology Section, Laboratory of Viral Diseases, Division of Intramural Research (DIR), NIAID, NIH, served as overall meeting facilitator, and summarized key meeting recommendations upon its conclusion. Meeting organization details and a roster of participants are provided in attached Appendices.

Dr. Gary Nabel, Director, Vaccine Research Center (VRC), NIAID, NIH, welcomed meeting participants and thanked meeting organizers for assembling the leaders from academia, government, and industry needed for developing a universal vaccine. While universal vaccines for influenza have been discussed for a number of years, implementation of the concept is challenging. For example, to make progress it will be necessary to move beyond classical assays of vaccine efficacy. Furthermore, it may not be possible to immediately devise a vaccine that protects against all potential influenza A virus (IAV) strains. A reasonable goal is developing a vaccine that is effective for 5 to 10 years, avoiding the annual vaccine reformulation that is currently practiced. The goal of this meeting is to develop recommendations for advancing a universal influenza vaccine into clinical trials.

Dr. Anthony Fauci, Director, NIAID, NIH, noted that improved influenza vaccines are needed both to address annual seasonal illness caused by drifted viruses and for which there is partial immunity due to exposure to previous strains, and also for the rarer, but unpredictable, pandemic outbreaks due to shifted viruses for which much of the population is immunologically naïve. In the U.S., the annual burden of seasonal influenza can be as high as 49,000 deaths, more than 200,000 hospitalizations, resulting in \$27 billion in health costs alone. The annual global burden is estimated at 250,000 to 500,000 deaths. Pandemic influenza occurred in 1918, 1957, 1968 and 2009 and although the H5N1 virus has thus far not resulted in a large number of cases or deaths, there is the potential for this virus to cause significant pandemic illness in the future. The Federal government has a Pandemic Influenza Preparedness strategy that is being implemented, including international surveillance, domestic surveillance, vaccines, antivirals, communications, and state and local preparedness. NIH influenza research includes: basic research, clinical research, diagnostics, therapeutics, vaccines, and surveillance. Dr. Fauci concluded by emphasizing that a universal vaccine is essential given the unpredictability of seasonal influenza which makes it difficult to select an annual strain for reliable, efficient vaccine production; because of the ever-present danger of an emerging pandemic; and because of recent elevated concern regarding influenza virus as a bioweapon.

## Session I: Scientific Questions

In the currently used seasonal influenza vaccines, the globular head of the hemagglutinin molecule is immunodominant; thus, the Ab responses are directed to the HA domain with the greatest antigenic variability and least likely to induce Abs that cross-react with future drifted or shifted strains. Importantly, the anti-globular head Abs are detected by the hemagglutinin inhibition (HI) assay, which is the current gold standard for measuring vaccine immunogenicity. Structural, immunological, and sequencing studies show that the stalk/stem region of the hemagglutinin is much less variable. StRAbs are not detected by HI assay, and although the first StRAb was described in 1993, the potential importance of StRAbs was only recognized in the past few years.

Recent studies clearly demonstrate that many individuals have broadly neutralizing serum Abs, and that these Abs are reactive with the stalk. Surprisingly, a small subset of these antibodies also react

with the globular head. Broadly neutralizing StRAbs have been clearly demonstrated to greatly reduce viral titers when present prior to infection and also promote recovery and prevent death when given post-infection to even nearly moribund animals. With appropriate assays, broadly neutralizing Abs can be detected in humans who were naturally infected with 2009 H1N1 influenza or in individuals receiving seasonal or 2009 H1N1 influenza vaccines. Many of the broadly neutralizing mAbs isolated are limited to Group I IAVs, but some rare Abs also cross-react with Group II IAVs (the 16 different HA subtypes can be divided into two disparate groups). One human mAb has been identified which, surprisingly, cross reacts with both the IAV HA and the HA from influenza B virus, based on interaction with residues at the base of the stem. Several human mAbs have been shown to possess a loop that protrudes into the highly conserved sialic acid binding pocket of the HA. The extent to which these latter mAbs can be routinely elicited in humans is uncertain, but the isolation of such mAbs from peripheral blood plasmablasts demonstrates that the immune system is potentially capable of responding to sophisticated vaccine strategies designed to elicit broadly protective polyclonal antibodies (or cell mediated immunity [CMI]).

Although much of the work with StRAbs has been performed with mAbs, it has been clearly shown that StRAbs can be routinely elicited using various vaccine strategies in mice, ferrets and monkeys. Human monoclonal StRAbs largely consist of antibodies utilizing VH1-69 gene segment, and often exhibit only limited somatic diversification. VH1-69 genes are highly polymorphic in humans, and it remains to be determined how this polymorphism affects stem immunogenicity. The few Group I-II cross-reactive VH1-69 StRAbs identified to date exhibit extensive somatic mutations, raising the challenge to their induction by vaccines. VH1-69 Abs are important neutralizing Abs in other infections (e.g., HIV, hepatitis C) and, on the flip side, VH1-69 Abs may be overrepresented among auto-Abs. Structural studies demonstrate that extensively somatically mutated VH1-69 StRAbs have a more rigid loop structure on a key part of the molecule relative to germ line or less modified forms.

Basic advances in understanding protein structure and folding has led to the *de novo* design of a micro protein (50 residues) that binds to the H stem with high affinity and neutralizes IAV *in vitro*. This remarkable achievement paves the way towards novel passive immune strategies for preventing and treating IAV. More work is required to understand the precise mechanisms by which this protein and standard StRAbs mediate viral neutralization, particularly since there are significant strain-related differences in the triggering of conformation alterations in the stem region that lead to viral fusion with cell membranes to initiate infection.

Since a major goal of improving IAV vaccines is to prolong the period between immunizations, it is critical to understand the mechanisms that contribute to long-lived B cells that secrete high affinity neutralizing StRAbs. Ultimately the effectiveness of vaccination is determined by the mathematical product of the number of B cells multiplied by the amount of Ab synthesized by each B cell, multiplied by the affinity of the Abs, multiplied by the neutralization potency of the Abs. Pragmatically, deficiencies in one process can be counteracted by improvements in other processes. Studies in young adults immunized with trivalent inactivated influenza vaccine (TIV) as compared to tetanus vaccine revealed that the frequency of influenza virus-specific plasma cells in the bone marrow (BM) is relatively high and increases following vaccination. There was good correlation between the number of IAV-specific plasma cells in the BM and IAV-specific Ab levels in the serum, potentially making blood plasma cells a convenient proxy for vaccine efficacy. Although BM plasma cells increase immediately following influenza vaccination, they fall significantly over time, a process repeated by subsequent boosting. The antibodies produced by anti-influenza plasmablasts are highly diverse and extensively mutated. A comparison of *de novo* mutations as a measure of the ability to respond to new virus variants showed that there are few mutations in an aged population of persons when compared to younger populations. This is important, as it suggests that aging imposes an intrinsic limita-

tion in generating novel Ab specificities to keep pace with IAV drift, further increasing the importance of drift-resistant vaccination, with particular focus on boosting the immune response of memory StRAb specific-B cells. This is the key to the success of drift-resistant vaccines.

Although the meeting focused on HA, there are also opportunities for improving the breadth of vaccination by targeting the NA, which may also offer conserved vaccine targets for Abs. This may hold promise for designing future vaccines.

***Recommendations:***

Numerous scientific areas require more knowledge to develop drift resistant/universal influenza vaccines. Such knowledge is essential for developing and improving vaccines for other infectious agents, and will have far reaching impacts on therapeutic approaches for infectious and autoimmune diseases. Support of basic research in the areas listed below is recommended:

- B-cell biology related to vaccines, including:
  - Antigen trafficking to B cells, with particular emphasis on the effect of the physical form of antigen on its presentation to B cells (e.g., subunit vaccines vs. virions vs. infected cell-derived antigens).
  - Rules governing the generation of long-lived memory B cells and the long-lived plasma cells that reside in the bone marrow. An understanding of the factors that drive plasma cells to the bone marrow, and the niches in the marrow that provide survival signals.
  - Rules governing the immunodominance hierarchy of B-cell responses to the antigenic sites on the HA to enable antigenic site-specific vaccination against stem epitopes and other conserved targets on the HA (e.g., the receptor binding site).
  - Contribution of B-cell-T-cell collaboration to the above processes, with particular emphasis on the special properties of individual T-cell subsets, e.g., T follicular helper cells (Tfh), which impact B-cell outcomes (including affinity maturation).
- Mechanisms governing the influence of vaccine adjuvants on the above processes, with the recognition that advances in adjuvant science are critical to improving vaccines to influenza and other pathogens. We note that the enormous increase in basic knowledge regarding the innate immune system enables rational design and testing of novel adjuvants.
- Basic understanding of how aging compromises existing memory B-cell responses and impacts generation of memory B cells from naïve precursors with the goal of rationally designing vaccines that minimize the impact of aging. Given the remarkable success of modern medicine in lengthening life expectancy, it is imperative to understand how aging impacts the immune system.
- At the opposite end of the age spectrum, it is important to understand how first exposure of children to IAV infection or vaccine shapes the Ab response for the rest of their lives, with an eye towards shaping the initial response to generating life long protective Ab response to conserved elements on the HA.
- Mechanism of anti-viral activity of anti-HA Abs, including:
  - More sophisticated understanding of how standard anti-head Abs mediate neutralization.

- Detailed understanding of mechanism of neutralization mediated by StRAbs, including contribution of antibody dependent cellular cytotoxicity and the identity of the effector cells *in vivo*, as well as how they actually function to reduce pathogenicity.
  - Investigation of the various types of StAbs such as Abs that may bind stem but interfere with the action of StRAbs with high anti-viral potency.
  - Better understanding of how avidity and other thermodynamic factors influence anti-viral activity of Abs.
  - Effect of viral architecture on Ab activity, with particular emphasis on potential special features of filamentous viruses, believed to be typical of human IAV infections.
  - Further structural studies of interaction of HA with Abs, essential to realizing the aims stated above and also as a means of identifying other potential conserved Ab targets, and for constructing vaccine immunogens that elicit effective Ab responses.
- Understanding the mechanism of antigenic drift in IAV glycoproteins in humans and animal transmission models with particular emphasis on the ability of IAV to escape immunity to conserved HA epitopes.

## **Session II: Early Development /Translation**

As noted, anti-stem Abs are induced by both natural infection and vaccination. In animals, they can be elicited more efficiently by immunization with headless HA or HA chimeras, which consist of the globular domain of one HA subtype fused to the stem domain of another subtype. To study stalk-specific antibodies, chimeric hemagglutinin constructs have been developed that enable the measurement of antibodies that bind the hemagglutinin protein and neutralize virus but do not have hemagglutination inhibition activity. A number of chimeras have been successfully made representing various subgroups. The stem of such chimeric HAs is a more faithful mimic of the natural HA stem than the headless HA. Chimeric HAs have great value for eliciting and measuring cross-neutralizing Abs. The globular heads of such chimeras are derived from IAVs that have not been circulating in human populations in order to reduce the chance of pre-existing circulating antibodies and long lived memory B cells that may react with that part of the HA. IAVs expressing HA chimeras grow to high titers, and typically can simply be slotted into the standard egg-based production process used to manufacture seasonal vaccines. Other assays are available for measuring StRAbs in human sera. Their titers can be inferred by modified microneutralization assays using inter-clade avian IAV or in reporter gene based assays using pseudoviruses expressing avian HAs. StRAB responses in sera can be more directly measured by competition assays for binding to HA *vs.* defined StRAB Fab fragments. Such assays will greatly facilitate development of improved stem immunogens, including a promising platform based on self-assembling HA-ferritin nanoparticles (HA-nVLP).

Ultimately, improved IAV vaccines may incorporate multiple immunogens/strategies in a single vaccination. For example, vaccines could be designed to induce StRAbs as well as Abs to the M2 ecto-domain and/or NP, since the latter two targets are highly conserved and shown to diminish IAV morbidity and mortality in animal models. Like existing trivalent vaccines, future vaccines could contain multiple HA immunogens to cover Group I and II IAVs and influenza B virus. Moreover, novel vaccines could be used in combination with current vaccines, perhaps using multiple injection sites to avoid competition effects on immunogenicity. Animal studies and Phase I human studies will provide insights into the advantages and pitfalls of the various approaches. It is important to note that while useful, animals are imprecise measures of human immunity, and can differ in many fundamental



mechanisms and components, including the effects of adjuvants and the germ line Ab repertoire. Given the likely importance of VH1-69 Abs to the human anti-stem repertoire, it is important to use animals that contain a similar germ line gene family, and to test the suitability of humanized mice expressing VH1-69 Abs to model anti-stem Ab responses.

***Recommendations:***

- Perfect should not be the enemy of good. While it may be prove difficult to develop a truly universal IAV vaccine, developing novel vaccines that provide robust protection within one HA subtype, or even prove more-drift resistant than present vaccines, would represent a giant step forward that will potentially save millions of lives and hundreds of billions of dollars on a world-wide basis.
- Drift-resistant influenza vaccines will involve new targets and will require new assays to assess their effectiveness. Better neutralization assays will need to be developed that measure relevant immune responses corresponding to human protection from IAV while being sufficiently robust to enable standardization between laboratories and health authorities. Assays that measure reduction in virus replication kinetics (*e.g.*, plaque size reduction assay) may prove to be more indicative of clinical efficacy than standard all-or-none neutralization.
- A central strategy for characterizing broadly neutralizing Abs elicited by new vaccines will be binding competition with StRAbs of defined specificity. Making mAbs freely available to qualified scientists as resources for developing and characterizing novel vaccines is a key component of this strategy. For example, the BEI repository could provide mAbs from NIAID-supported investigators.
- Archived serum specimens from influenza vaccine studies/trials, particularly where clinical outcomes are known, represent a unique opportunity to correlate the magnitude of the StRAB response with protection from influenza infection or severe symptoms. It will be of particular interest to examine the ability of adjuvanted vs. non-adjuvanted formulations to elicit StRAbs. Data from such studies could provide support for StRAB-based vaccines and unique insights spurring novel vaccine designs.
- Emphasis needs to be placed on early proof-of-concept of new immunogens in humans. It should be recognized that animal models of vaccination can provide false negatives as well as false positives (*e.g.*, the absence of VH1-69 like genes in mice may greatly diminish the immunogenicity of the HA stem). Once it is deemed safe, vaccines should be tried at small scale in humans as quickly as possible to explore the greatest number of potential candidates. If proof-of-concept can be demonstrated in humans, further animal work can be performed for vaccine optimization.
- A central priority is designing and developing immunogens using structure-based design and knowledge of B-cell maturation pathways. This will require attention to novel immunogen delivery mechanisms, state-of-the-art antigen-presentation strategies and the use of adjuvants, all optimized in combination to elicit long-lived B cells secreting high avidity antigens to conserved epitopes. Gene-based vaccination approaches may produce more authentic antigenic structures and elicit responses to additional neutralizing epitopes including those on the HA stem.
- Animals used in vaccine studies are typically immunologically naïve while humans beyond infancy have had prior experience with influenza. Thus, the development of animal models that mimic immunological priming that occurs in humans will be important in moving forward with drift-resistant vaccine development. It is worth noting that such models are typical-

ly costly due to the need to house large numbers of animals for extensive periods and that sufficient resources are needed to support such studies.

- Investigators should be actively encouraged to use existing and expanded NIAID resources for early vaccine development translational stages, including animal models and vaccine testing services.

### **Session III: Advanced Development /Commercialization**

Industry has experience with candidate vaccines based on conserved components of influenza viruses, including M2- and NP-based vaccines. These vaccines appeared to be useful in modulating disease. However, the level of activity that would be necessary for clinical benefit from these vaccines is not known and trials to establish a clinical benefit would have been difficult as they would have had to objectively match or exceed benefits of existing vaccines. Given these uncertainties and the expense of clinical trials, these products were not pursued.

Industry is developing broadly reactive monoclonal StRAbs for use as a point-of-care diagnostic, as a prophylactic, and as a therapeutic. Most Abs effectively neutralize a single influenza group (Group 1 or Group 2 influenza A or influenza B), but one Ab binds both influenza A and B HAs. These Abs can also be used as an effective mixture. Although many of these Abs do not show activity in the classical virus neutralization assay, they are protective in animal challenge studies.

NIAID has numerous resources that could be used to assist development of drift-resistant influenza vaccines (see Appendix 1 for additional detail). There are more than 40 influenza vaccine research grants supported by NIAID's extramural Division of Microbiology and Infectious Diseases (DMID) under a variety of funding mechanisms, and NIAID's extramural Division of Allergy, Immunology and Transplantation supports an Adjuvant Development Program and several large programs focused on human immunology and vaccine responses. There are upcoming opportunities for multivalent vaccines including the Centers of Excellence for Translational Research, which are multidisciplinary translational research centers for highly innovative and synergistic approaches; and the FY 2014 Partnerships for Biodefense (R01) which are milestone-driven projects. NIAID also supports mouse and ferret models for H1N1, H3N2, and H5N1 subtypes. NIAID supports a number of preclinical development services including vaccine manufacturing services (e.g., feasibility, gap analysis, product development plan, process development, product release assay development, pilot and cGMP manufacture, and audits, regulatory activities and documentation) and vaccine testing services (assay development, non-clinical immunogenicity and efficacy studies, clinical and non-clinical sample testing, and safety and toxicity testing). NIAID also supports a number of relevant clinical services including the Vaccine and Treatment Evaluation Units (VTEUs), consisting of clinical centers across the U.S., and the Viral Respiratory Pathogens Research Unit, which has a translational research focus and investigator-initiated clinical trials.

For a new type of influenza vaccine to be introduced in the face of licensed vaccines that are widely used, they must demonstrate significant advantages. Extending the duration of immunity in the face of antigenic variation is clearly one potential advantage. Another is induction of immunity to zoonotic HA subtypes that could be introduced to the human population as a novel pandemic virus. Perhaps the most important is boosting existing StRAb responses in the elderly, many of whom respond poorly, if at all, to current seasonal vaccines. Influenza vaccines are marginally profitable by industry standards, a problem compounded by the need to discard existing supplies of vaccines due to ongoing drift. Drift-resistant vaccines would obviously decrease such wastage.

In the early stages of vaccine development, thought needs to be given to assays, preclinical models, and clinical studies that will be needed along the development and licensure pathway of products for target populations. Thinking about the package insert of the final product can help investigators to plan what will be needed. In designing assays, we need to consider the presence of Abs that are non-functional in the assay, but that interfere with it and lead to the inability to detect the functional Abs. There is a need to consider how neutralizing Abs elicited by a new vaccine candidate will be assessed in the context of the currently licensed vaccines. Other assays that would be used for testing clinical samples need to be standardized and validated. Lot release assays would need to be developed and validated. Other issues that need to be considered include use of adjuvant, route of administration and formulation. It is important to consider early on practical issues such as cold chain, need for multiple injections, and what properties of the vaccine would encourage its public health usage. In terms of licensure, a new vaccine would have to demonstrate non-inferiority to current products, not necessarily superiority. A demonstration of superiority is only needed if superiority is part of the manufacturer's label claim.

Published reports have demonstrated that cross-reactive antibodies induced during a primary infection can cause antibody-dependent enhancement of infection. Regarding the potential of enhanced disease resulting from use of new types of stem immunogens, it was noted that StRAbs are generated in many individuals following natural infection or vaccination; they have just not been detected by standard assays. However, some of these antibodies may have low affinity, resulting in enhanced pathology.

***Recommendations:***

- A committee should be formed to set new standards for *in vitro* methodology with appropriate virus panels to assess influenza vaccine efficacy and facilitate the development of new vaccines and comparisons between vaccines. Criteria should be established for reporting the degree of cross-protection induced by vaccines.
- The committee should coordinate efforts to develop the new assays, including assays for clinical use and lot-release.
- Academic and industry investigators should be made aware of NIAID resources that support development and evaluation of candidate vaccines. Efforts to establish public-private partnership for promising drift-resistant vaccines should be pursued.
- In terms of the public's understanding of universal vaccines, it would be important to distinguish universal *vaccines* from universal *vaccination*. It is also important to educate the public regarding the importance of new vaccines that represent significant improvements, while not yet achieving universal vaccine status.
- Although there are estimates of the burden of influenza disease, the total economic and social burden has never been rigorously examined and may still not be fully appreciated; efforts should be made to update assessment of the disease burden and to estimate the economic benefits of drift-resistant vaccination. Such studies are essential to quantitate the benefits of future vaccines relative to existing vaccines.
- There is insufficient understanding of the factors that determine severity of influenza disease, how much immunity is needed to prevent severe outcomes, and how the immune history of a person or population affects positive or negative outcomes. Studies in these areas should be encouraged.

- As work progresses toward universal vaccines, ongoing communication among the stakeholders (academia, government, and industry) would catalyze focusing efforts on fruitful areas and hasten the pathway forward. This meeting could serve as the template for future biennial meetings on the topic.

#### **Session IV: Clinical Studies**

Studies that are of value to inform the clinical development of vaccines include: (1) establishment of a correlate of protection, (2) field evaluation of natural disease and disease incidence; and (3) establishment of an experimental infection model.

The licensure pathway of the novel IAV vaccine must be tailored to the vaccine antigen under development. However, there are general considerations that will apply to all novel IAV vaccines. Pre-licensure vaccine clinical trials are typically done in three phases. Phase I studies are safety and immunogenicity studies performed in a small number of closely monitored subjects. Phase II studies are typically randomized and controlled and may enroll hundreds of subjects. These studies serve to further evaluate the safety and immunogenicity of the product and to determine the optimal vaccine dose, and dosing schedule. Phase III trials typically enroll thousands of individuals and provide the critical documentation of effectiveness and important additional safety data required for licensing. These studies are randomized and controlled and have a pre-defined clinical endpoint with a strong statistical plan. An influenza clinical endpoint efficacy study refers to a clinical trial in which influenza illness is assessed as the primary endpoint.

To support the effectiveness of a drift-resistant flu vaccine, clinical endpoint efficacy studies will likely be required. The design of Phase III clinical studies for a drift-resistant flu vaccine will depend on the indication that the applicant is seeking and the target population for the product. Placebo-controlled efficacy studies in the US may be challenging given that licensed influenza vaccines are available and universally recommended for all age groups. Additional aspects of clinical development may include a demonstration that the vaccine protects against flu illness over several seasons, as well as breadth and duration of protection, and the need for booster immunizations.

It is critical to prospectively define the case definition for influenza illness. Inclusion of culture confirmation, viral typing and antigenic characterization in the case definition increases the specificity. Immunogenicity evaluations in a substantial number of study participants are important elements of the study design. Characterization of the immune response elicited post-vaccination in the clinical endpoint efficacy study may allow for extrapolating the effectiveness to other populations if they have an immune response to vaccination comparable to that observed in the clinical endpoint efficacy study. Furthermore, immune response data collected in the course of a prospectively designed clinical endpoint efficacy study may lead to the establishment of an immune correlate of protection. Such a correlate could greatly facilitate future influenza vaccine development. However, the establishment of a correlate of protection is not a licensure requirement.

Other important aspects of clinical development of a drift-resistant influenza vaccine are the generation of clinical assays to detect vaccine-elicited immune responses, such as cross-protective antibodies or cell-mediated immunity. Also, assays to identify/characterize infections (immunologic, virologic, etc.) should be generated.

Controlled human infection models conducted during earlier clinical development may be of value to demonstrate “proof of concept” of the drift-resistant flu vaccine antigens. Such studies would poten-

tially provide information regarding: parameters of infection; vaccine protection against different strains; and the presence of cross-protective Abs.

***Recommendations:***

- Based on currently available knowledge, clinical studies moving toward translation of drift-resistant vaccines can be started in the near future so as to establish proof-of-concepts.
- Certified strains of influenza virus types should be made available to support controlled human infection models of novel IAV vaccines. This would greatly facilitate comparison between different vaccine formulations.
- Working groups of investigators could be established to focus on new assays and panels of viruses for use with clinical specimens including:
  - (1) Develop and optimize high-throughput assays for cross-neutralizing Abs.
  - (2) Develop assays to better discriminate between neutralizing and non-neutralizing responses.
  - (3) Establish a collection of monoclonal Abs as standards for comparative studies.
  - (4) Identification of potential correlates of protection and establishment of a panel of viruses to compare potential correlates of protection.
  - (5) Establish a panel of viruses to assess breadth and potency of immunological responses to candidate vaccines.
  - (6) Establish a panel of viruses for human challenge studies.
  - (7) Develop potency assays to show that a novel vaccine drug product is properly folded, stable, and presents relevant protective epitopes in an immunogenic form.
  - (8) Develop screening assays to classify and identify infections in vaccine study participants.
  - (9) Collect and analyze sera from representative groups of the general population to determine the background levels of StRAbs or Abs to other conserved neutralizing epitopes.
- Passive immunization study in humans using high potency StRAbs followed by experimental challenge would provide valuable proof-of-principle for StRAB-based vaccines. Although there are inherent limitations of such a study, it would, if successful, demonstrate biological effect and encourage the expenditure of the needed effort and cost to advance promising immunogens.

## Appendix 1

### NIAID Extramural Accomplishments and Ongoing Activities

In 2006, NIAID convened a 35-member Blue Ribbon Panel on Influenza Research to identify gaps and opportunities in order to accelerate influenza research, build on the current state of flu research, and capitalize on emerging technologies. In 2007, NIAID released the Report of the Blue Ribbon Panel on Influenza Research which outlined broad principles that would provide a framework to guide NIAID's influenza research activities. These research recommendations included support for vaccine, therapeutic, and assay development, and for development of animal models. Providing resources for the influenza community and supporting research on influenza at the animal-human interface, as well as in individuals and in human populations were also recommended.

(<http://www.niaid.nih.gov/topics/flu/documents/influenzablueribbonpanel2006.pdf>)

NIAID has been actively funding grants and contracts to support the goals of the Blue Ribbon Panel. Many of these goals dovetail with the recommendations of the working group on universal influenza.

Many NIAID opportunities and resources have been used in the development of drift-resistant influenza vaccines. There are more than 40 influenza vaccine research grants supported by NIAID's extramural Division of Microbiology and Infectious Diseases (DMID) under a variety of funding mechanisms, and NIAID's extramural Division of Allergy, Immunology and Transplantation supports an Adjuvant Development Program and several large programs focused on human immunology and vaccine responses. For example, NIAID supports:

- Basic research into the structural and genetic basis for broadly cross reactive antibodies.
- Research on novel vaccine technologies including developing and evaluating new vaccine formulations, adjuvants, immune response stimulators, protective T-cell and antibody epitopes, new routes of delivery, and common epitope ("universal") vaccines.
- Studies to develop broadly cross-reactive monoclonal antibodies as therapeutics for treating seasonal and pandemic influenza through basic research grants and contract mechanisms. These include grants to study the mechanism of action of Group 1 monoclonal antibodies as well as the use of animal models and preclinical development services to develop a candidate Group 1 therapeutic Mab. Additionally, NIAID awarded a contract to develop two human monoclonal antibodies targeting conserved regions of the influenza hemagglutinin (HA) protein.
- Projects to better understand and predict the mechanisms of antigenic drift, including examining how influenza viruses evolve to escape cross-reactive Abs, and developing methods to predict antigenic drift to improve vaccine strain selection.
- Reagents for qualified influenza researchers through the Biodefense and Emerging Infections Research Resource Repository Program (BEI; [www.beiresources.org](http://www.beiresources.org)). These include wild type and recombinant viruses, purified proteins and peptides, polyclonal & monoclonal antibodies and cell lines.
- Preclinical development services including vaccine manufacturing services (e.g., feasibility, gap analysis, product development plan, process development, product release assay development, pilot and cGMP manufacturing, audits, regulatory activities and documentation) and vaccine testing services (assay development, non-clinical immunogenicity and efficacy studies, clinical and non-clinical sample testing, and safety and toxicity testing). DMID has ongoing contracts to provide mouse and ferret models for H1N1, H3N2, & H5N1 subtypes (high and low pathogenic avian flu) to test vaccines and candidate therapeutics.

- A number of relevant clinical services including the Vaccine and Treatment Evaluation Units consisting of clinical centers across the United States; the Viral Respiratory Pathogens Research Unit, which has a translational research focus; and investigator-initiated clinical trials.

Additionally, there are several upcoming opportunities for further investigation of scientific questions through the Immune Mechanisms of Viral Control research initiative, the Cooperative Centers on Human Immunology Program, and the Immunity in the Elderly Program, as well as upcoming opportunities for developing and evaluating multivalent vaccines including through the Centers of Excellence for Translational Research, which are multidisciplinary translational research centers for highly innovative and synergistic approaches; and the FY 2014 Partnerships for Biodefense (R01) which are milestone-driven projects.

## **Appendix 2**

### **Meeting Organization**

#### **Meeting Steering Committee**

The meeting was organized by a steering committee including representatives from NIAID and FDA:

**Dr. Hana Golding**, Chief, Laboratory of Retrovirus Research, Centers for Biologics Evaluation and Research, Food and Drug Administration

**Dr. Gary Nabel**, Director, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health

**Dr. Helen Quill**, Branch Chief, Basic Immunology Branch, Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health

**Dr. David Spiro**, Section Chief, Respiratory Diseases Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

**Abraham Mittelman, M.P.H., M.A.**, Associate Director for Management and Operations, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health

**Dr. Jonathan Yewdell**, Chief, Cellular Biology Section, Laboratory of Viral Diseases, Division of Intramural Research (DIR), National Institute of Allergy and Infectious Diseases, National Institutes of Health

### **Meeting Session Discussion Leaders**

#### **SESSION 1 - SCIENTIFIC QUESTIONS**

DISCUSSION LEADER: DR. RAFI AHMED

#### **SESSION 2 - EARLY DEVELOPMENT/TRANSLATION**

DISCUSSION LEADER: DR. PETER PALESE

#### **SESSION 3 - ADVANCED DEVELOPMENT/COMMERCIALIZATION**

DISCUSSION LEADER: DR. ROBIN ROBINSON

#### **SESSION 4 - CLINICAL STUDIES**

DISCUSSION LEADER: DR. JOHN TREANOR



## Appendix 3

# 2012 Universal Influenza Vaccines Meeting

June 19-20, 2012

Building 40, Conference Room 1201-1203

Bethesda, MD

## PARTICIPANTS LIST

Rafi Ahmed	Emory University
David Baker	University of Washington
Jack Bennink	National Institute of Allergy and Infectious Diseases
Rick Bright	Biomedical Advanced Research and Dev. Auth.
Robert Coffman	Dynavax
James Crowe	Vanderbilt University
Michel DeWilde	Sanofi
Ray Dolin	Harvard University
Armen Donabedian	Biomedical Advanced Research and Dev. Auth.
Philip Dormitzer	Norvartis
Jon Dushoff	McMaster University
Maryna Eichelberger	Food and Drug Administration
Suzanne Epstein	Food and Drug Administration
Anthony S. Fauci	National Institute of Allergy and Infectious Diseases
Bruce Gellin	Health and Human Services (HHS)
Ronald Germain	National Institute of Allergy and Infectious Diseases
Hana Golding	Food and Drug Administration
Jaap Goudsmit	Crucell
Adolfo Garcia-Sastre	Mount Sinai School of Medicine
Barney Graham	National Institute of Allergy and Infectious Diseases
Marion Gruber	Food and Drug Administration
Charles Hackett	National Institute of Allergy and Infectious Diseases
Stephen Harrison	Harvard University
Hillery Harvey	National Institute of Allergy and Infectious Diseases
Carole Heilman	National Institute of Allergy and Infectious Diseases
Carole Hudgings	National Institute of Allergy and Infectious Diseases
Wendy Keitel	Baylor College of Medicine
Surender Khurana	Food and Drug Administration
Harold Kleanthous	Sanofi
Linda Lambert	National Institute of Allergy and Infectious Diseases
Antonio Lanzavecchia	The Institute for Research in Biomedicine

## **PARTICIPANTS LIST (CONTINUED)**

Julie Ledgerwood	National Institute of Allergy and Infectious Diseases
Wayne Marasco	Harvard University
John Mascola	National Institute of Allergy and Infectious Diseases
Arnold Monto	University of Michigan
David Morens	National Institute of Allergy and Infectious Diseases
Gary J. Nabel	National Institute of Allergy and Infectious Diseases
Peter Palese	Mount Sinai School of Medicine
Stanley Plotkin	Sanofi Pasteur, Consultant
Graham Price	Food and Drug Administration
Helen Quill	National Institute of Allergy and Infectious Diseases
Rino Rappuoli	Novartis
Robin Robinson	Biomedical Advanced Research and Dev. Auth.
Dan Rotrosen	National Institute of Allergy and Infectious Diseases
Xavier Saelens	V.I.B. UGent
Rachelle Salomon	National Institute of Allergy and Infectious Diseases
Aaron Schmidt	Harvard University
John Schrader	The Biomedical Research Center
Richard Schwartz	National Institute of Allergy and Infectious Diseases
Alan Shaw	Vaxinnate
John Shiver	Merck
John Skehel	MRC, National Institute for Medical Research
David Spiro	National Institute of Allergy and Infectious Diseases
David Steinhauer	Emory University
James Stevens	Centers for Disease Control and Prevention
Klaus Stohr	Novartis
Kanta Subbarao	National Institute of Allergy and Infectious Diseases
Sriram Subramaniam	National Cancer Institute
Jeffrey Taubenberger	National Institute of Allergy and Infectious Diseases
John Treanor	University of Rochester Medical Center
Harold Varmus	National Cancer Institute
Wei Wang	Food and Drug Administration
Robert Webster	St. Jude Children's Research Hospital
C. J. Wei	National Institute of Allergy and Infectious Diseases
Jerry Weir	Food and Drug Administration
Carol Weiss	Food and Drug Administration
Ian Wilson	Scripps
Patrick Wilson	University of Chicago
Zhi-yong Yang	National Institute of Allergy and Infectious Diseases
Zhiping Ye	Food and Drug Administration
Jon Yewdell	National Institute of Allergy and Infectious Diseases