HHS Public Access

Author manuscript

Expert Opin Drug Discov. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

Expert Opin Drug Discov. 2021 March ; 16(3): 213–216. doi:10.1080/17460441.2021.1828859.

ARE LONG-TERM INFLUENZA VACCINES POSSIBLE AND HOW DO WE DISCOVER THEM?

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1. Introduction

Influenza continues to pose a severe public health risk. In the United States, the annual economic burden of influenza is estimated to be USD 87.1 billion, USD 56 billion of which are used to treat the elderly. Both influenza A and B viruses can cause epidemics by rapidly accumulating mutations. Occasionally, influenza A can cause pandemics. The outbreak of another influenza pandemic continues to be “not a question of if, but when” [1,2]. Current seasonal influenza vaccines effectively protect individuals against well-matched strains, but mismatches frequently occur [2–6]. Based on the reports from the U.S. Influenza vaccine efficacy (VE) Network, the overall influenza vaccine effectiveness was below 40% in four seasons between 2009 to 2019. Also, the Centers for Disease Control and Prevention (CDC) reported that the average vaccine effectiveness (VE) was only about 40% over the past 14 years.

A long-term protective universal influenza vaccine will negate the need for vaccinations each season and serve as a countermeasure against the emergence of new pandemics by offering protection against all influenza viruses [5]. Because of the significant benefit and tremendous challenge of an affordable universal influenza vaccine, many countries, international research institutions, and drug companies have invested resources and funds to the research and development of such vaccines. The US government issued a Presidential Executive Order in September 2019 to modernize influenza vaccines in the United States [7]. The US National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes for Health (NIH) has made the development of a universal influenza vaccine a top priority and developed a step-based vaccine strategic plan to achieve the final vaccine universality [8]. Tremendous achievements have been made to understand the underlying mechanisms of influenza virus infection and identifying broadly neutralizing antibodies

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Declaration of Interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

(bnAbs), their epitopes, and their roles in broad immunity. Despite the confidence that a universal influenza vaccine is feasible, there is still a great deal to discover. Here we prioritize and highlight the following approaches that should be emphasized in the R&D of a universal influenza vaccine.

2. Approaches Toward Influenza Vaccine Universality

Is a universal influenza vaccine achievable? Recent research advancements provide insight into the answer. BnAbs have been identified as the immune correlates of broad cross-protection. A vast array of bnAbs and the conserved immunogenic structures (epitopes) that the bnAbs recognize have been identified from natural influenza virus infection and vaccination in humans, demonstrating that the human immune system can sense these shared structures to produce bnAbs [9–12]. These monoclonal or polyclonal antibodies conferred protection when given passively in both animal experiments and human clinical applications. A universal influenza vaccine can be realized if complementary conserved epitopes can be identified and orchestrated into an effective vaccine platform which triggers comprehensive bnAb responses conferring broad protection.

2.1. Structure-based Vaccine Design

The advantage of a structure-based vaccine construction strategy, as opposed to the specific strain-based approach of the seasonal influenza vaccine, is that it will exclusively trigger a broad range of cross-strain reactive immune responses. The success of this approach relies upon identifying bnAbs, characterizing the conserved epitopes that bnAbs recognize, investigating how these epitopes are exposed to the human immune system to trigger broadly reactive immunity, and then accurately designing novel immunogens which include multiple complementary conserved structures and mimic native-like immunogen-exposure during influenza virus infection. Many bnAb-recognized conserved epitopes have been identified from surface proteins. Instead, broadly reactive CD4 and cytotoxic CD8 T lymphocyte (CTL) epitopes have also been characterized from both internal and surface proteins. Matrix and nucleoprotein epitopes have been identified to stimulate CD8 T cells and CD4 T cells. In contrast, the epitopes in HA stimulate CD4 T cells and contribute to antibody production. These conserved structures and their combinations will meet the immunogen needs in different phases of the step-based universal influenza vaccine strategy.

To trigger strong bnAb and broadly reactive T cell responses, these conserved structures should be exposed to the human immune system in a pattern resembling natural viral infection. A deep understanding of the structures of influenza antigenic proteins including the hemagglutinin (HA) and neuraminidase (NA) is a means for structure-based novel immunogen designs. The designs of several HA stalk immunogens reflect these principles [13]. Despite recent advances, gaps are still existing in the understanding of antigen-immune system interactions in terms of the timing of antigen-exposure, routes, retention, and innate microenvironment. For example, the universal vaccines targeting the surface glycoproteins could provide protection to health adults. However, since the universal vaccines do not induce cytolytic CD8 T cell-mediated clinical protection against influenza related complications, other influenza vaccines that stimulate cytolytic T cell responses should be

used to clear influenza from the lungs after infection in combination with the universal vaccines for the high-risk populations, such as the aged.

2.2. Novel Non-Classical Vaccine Forms

Recent novel non-classical vaccine forms were found to emphasize important conserved epitopes to the immune system and generate more comprehensive immune responses. The human immune system senses the protein vaccines as extracellular pathogens and generates immune responses geared for terminating extracellular infection. However, influenza infection goes through both extracellular and intracellular stages.

New antigen forms that resemble the cellular stage of pathogens, when applied alone or in combination with the classic vaccine forms, can trigger the human immune system to generate a more comprehensive immunity conferring protection in both extracellular and cellular compartments in the body, although classical split vaccines induce T cell responses to internal T cell antigens over recombinant surface protein subunit vaccines. Both viral vector (replicating or non-replicating) and nucleic acid-based (DNA or mRNA) vaccines were found to be encouraging approaches. Particularly, mRNA can be stabilized by nucleoside modification and delivered via lipid-nanoparticles to resist degradation and avoid innate anti-RNA mechanisms in the body. Once inside a cell, the mRNA can produce antigens in large amounts for a long duration and stimulate robust B and T cell responses [14]. These new vaccine forms are promising approaches to be further studied as a standalone or synergistic part of a broadly cross-protective influenza vaccine.

2.3. Synergistic Combinations of Nano-vaccine Platforms, New Adjuvants, Drug Delivery and Controlled Release Advancements, and Alternative Vaccination Routes

To obtain suitable antigen exposure timing and retention and to program a comprehensive broadly protective immunity, researchers have employed the most recent advancements in several relevant fields of influenza vaccinology. In several important reports, nanoscale techniques were used to orchestrate immunogens and adjuvants into particles mimicking key viral attributes, such as particle size, immunogen orientation, and the controlled release of immunogens, to strongly stimulate the immune system.

Although natural influenza virus infection has been found to induce broadly protective immunity in some elite adults, a complete picture of all the immunological events is not yet clear. However, one known feature is that broad immunity can be induced when an individual is challenged by a strain that is phylogenetically distant from the individual’s historic immunity. A sequential heterologous prime-boost vaccination approach, designed to resemble the sequential infections by phylogenetically-distant viruses, has been investigated in both pre-clinical and clinical trials and shown promising results [15].

3. Conclusion

A universal influenza vaccine is possible. Many such conceptual vaccine candidates have been tested and shown to elicit encouraging broadly protective spectra in preclinical trials. To facilitate the realization of affordable universal influenza vaccines, clinical trials are necessary and should be carried out to test the safety, efficacy, and spectrum of protection.

The trials will be costly and require multiple sectors involving the efforts of different countries, pharmaceutical companies, and research institutions to invest resources in order to realize universal influenza vaccines.

As of July 2020, there are 17 clinical trial records in Clinicaltrials.gov under the topic of “universal influenza vaccine”. Of these clinical trials, 8 are in phase I, 6 in phase II, 2 in phase I/II, and 1 in phase III (Table 1). The majority of these trials have demonstrated the vaccine candidates safety in humans. Some trials have shown vaccine candidates with strong immunogenicity capable of inducing broadly reactive immune responses. However, more clinical trials are needed to identify more potent vaccine candidates and to further test their influenza preventive efficacy in their later clinical trial phases in different groups, including the aged and young children.

4. Expert Opinion

A universal influenza vaccine would mark revolutionary progress over the current influenza strategy. It is a system’s engineering problem that must integrate the most recent progress in the three highly-relevant fields to influenza vaccinology for a solution: 1) Structure-based antigen designs and non-classical vaccine forms combined with new vaccination routes to emphasize conserved epitopes to the human immune system and mimic the interaction of influenza antigens with the human immune system to trigger broadly reactive immunity (such as bnAbs) in influenza infection; This will need further depth of understanding of influenza pathogenicity, the molecular structures of influenza virus, and the analysis of the human immune responses to influenza infection and vaccination. 2) New adjuvant systems to program an innate immune microenvironment for a comprehensive broadly protective influenza immunity in influenza vaccination. 3) Nano-technique-based vaccine platforms to synergize these antigens and adjuvants with the newest drug delivery, targeting, and controlled release technology.

Humanity has never been so close to the success of a universal influenza vaccine. With many conceptual universal influenza vaccine candidates demonstrating broad spectrum protection in laboratory animal models, several pioneers have moved into early phase clinical trials. It is expected that some candidates can be tested for the later phase of efficacy trials within 5 to 8 years and several commercial universal influenza vaccines are likely to be available within 10 years.

Acknowledgments

Funding

This work was supported by the US National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) under grants R01AI101047, R01AI116835, and R01AI143844. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

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Table 1.

Universal influenza vaccines in clinical trials

ClinicalTrials.gov Identifier (Status)	Study Title	Start-Completion Dates; Phase; Sponsor	Types of vaccines under investigation
NCT03275389 (Completed)	A Study to Evaluate the Reactogenicity, Safety, and Immunogenicity of GlaxoSmithKline (GSK) Biologicals' Investigational Supra-seasonal Universal Influenza Vaccine	September 8, 2017 – March 26, 2020; Phase 1; GlaxoSmithKline	Supra-seasonal Universal Influenza Vaccines (SUIVs) containing cHA
NCT03789539 (Active)	Reactogenicity, Safety, and I)mmunogenicity of a Universal Influenza Vaccine Uniflu	Not recruiting; Phase 1; VA Pharma Limited Liability Company	Non adjuvanted Uniflu (four copies of human M2e fused within the immunodominant loop of the HBc antigen)
NCT00921973 (Active)	Safety of VAX102 Vaccine Given With Seasonal Flu Vaccine in Healthy Adults	June 2009-September 2009; Phase 1 VaxInnate Corporation	Simultaneous administration of VAX102 (four copies of the ectodomain of influenza virus matrix protein 2, M2e, antigen fused to Salmonella typhimurium flagellin, a TLR5 ligand) plus TIV
NCT03300050 (Completed)	Safety and Immunogenicity of a Live-attenuated Universal Flu Vaccine Followed by an Inactivated Universal Flu Vaccine	October 10, 2017 – August 9, 2019; Phase 1; PATH	Chimeric H8/1N1 live-attenuated universal flu vaccine followed by a chimeric H5/1N1 or chimeric H8/1N1 inactivated universal flu vaccine; adjuvanted with AS03A or unadjuvanted
NCT00921947 (Completed)	Comparative Safety and Immunogenicity of 1.0 μg Intramuscular (i.m.) and 2.0 μg Subcutaneous (s.c.) Dosing With VAX102 (M2e-flagellin) Universal Influenza Vaccine in Healthy Adults	June 2009 – August 2009; Phase 1/Phase 2; VaxInnate Corporation	VAX102 (four copies of the ectodomain of influenza virus matrix protein 2, M2e, antigen fused to Salmonella typhimurium flagellin, a TLR5 ligand)
NCT03450915 (Active)	A Pivotal Trial to Assess the Safety and Clinical Efficacy of the M-001 as a Standalone Universal Flu Vaccine	August 1, 2008–December 2020 (estimated); Phase 3; BiondVax Pharmaceuticals Ltd.	M-001 (recombinant protein containing nine conserved epitopes of HA, NP and M1 from different strains of A and B subtypes) administered without adjuvant
NCT01265914 (Completed)	A Study to Evaluate the Safety, Tolerability and Immunogenicity of a Universal Influenza A Vaccine	August 2010 – August 2011; Phase 1; Immune Targeting Systems Ltd	A mixture of synthetic peptides, modified with a fluorocarbon vector administered without adjuvant
NCT00877448 (Completed)	A Double-Dose Safety Study of An Influenza Vaccine (Multimeric-001)	June 2009 – November 2009; Phase 1/Phase 2; BiondVax Pharmaceuticals ltd.	M-001 (recombinant protein containing nine conserved epitopes of HA, NP and M1 from different strains of A and B subtypes) administered with (Montanide ISA 51VG) or without adjuvant
NCT00921206 (Completed)	Study to Investigate the Immune Response to Two Doses of VAX102 Healthy Adults	June 2009 – December 2009; Phase 1; VaxInnate Corporation	VAX102 (four copies of the ectodomain of influenza virus matrix protein 2, M2e, antigen fused to Salmonella typhimurium flagellin, a TLR5 ligand)
NCT03816878 (Active)	Immunogenicity and Safety Study of Inactivated Subunit H5N1 Influenza Vaccine in Prior Recipients of Live Attenuated H2N2, H6N1, and H9N2 Influenza Vaccines and in H5N1 and Live Attenuated Vaccine Naïve Individuals	Not recruiting; National Institute of Allergy and Infectious Diseases (NIAID); Phase 1;	Inactivated subunit H5N1
NCT02293317 (Completed)	Phase II Study to Assess Safety & Immunogenicity of Multimeric-001 Influenza Vaccine, Followed by TIV (BVX006)	November 2014 – June 2015; Phase 2; BiondVax Pharmaceuticals Ltd.	Non-adjuvanted BVX006 (recombinant protein containing conserved linear epitopes from the HA, NP, and M1 proteins of influenza type A and type B strain) followed by a HA based seasonal trivalent influenza vaccine
NCT01419925 (Completed)	A Study to Assess the Safety and Immunogenicity of M-001 Influenza Vaccine as a Primer to TIV in Elderly Volunteers	August 2011 – January 2012; Phase 2; BiondVax Pharmaceuticals Ltd.	Aluminum phosphate adjuvanted and non-adjuvanted M-001 (recombinant protein containing conserved linear epitopes from the HA, NP, and M1 proteins of influenza type A and type B

ClinicalTrials.gov Identifier (Status)	Study Title	Start-Completion Dates; Phase; Sponsor	Types of vaccines under investigation
			strain) followed by a HA based seasonal trivalent influenza vaccine
NCT02691130; (Completed)	Assess the Safety and Immunogenicity of M-001 as A Standalone Influenza Vaccine and as A H5N1 Vaccine Primer in Adults	November 2015 – January 2017; Phase 2; BiondVax Pharmaceuticals ltd;	Non adjuvanted M-001 (recombinant protein containing conserved linear epitopes from the HA, NP, and M1 proteins of influenza type A and type B strain) followed by alum adjuvanted whole virion inactivated H5N1 vaccine
NCT01405885 (Completed)	A Study of DNA Vaccine With Electroporation for the Prevention of Disease Caused by H1 and H5 Influenza Virus	May 2011 – August 2013; Phase 1; Inovio Pharmaceuticals	DNA based vaccine that contained multiple combinations of H1 and H5 influenza hemagglutinin plasmids followed by in vivo electroporation
NCT03180801; (Completed)	Efficacy of FLU-v in an H1N1 Influenza Human Challenge Model	August 18, 2016 – May 25, 2017; Phase 2; PepTcell Limited	Montanide ISA-51 adjuvanted FLU-v (peptide vaccine derived from conserved regions of internal viral proteins) administration
NCT01146119 (Completed)	Further Investigation of an Intramuscular Influenza Vaccine (Multimeric-001)	July 2010 – June 2011; Phase 2; BiondVax Pharmaceuticals Ltd.	Adjuvanted M-001 (recombinant protein containing conserved linear epitopes from the HA, NP, and M1 proteins of influenza type A and type B strain) followed by commercial seasonal trivalent vaccine (season 2011)
NCT02962908 (Completed)	A Randomised, Double-blind, Placebo-controlled Phase IIb Trial to Test FLU-v Vaccine	August 2016 – July 18, 2017; Phase 2; PepTcell Limited	Montanide ISA-51 adjuvanted and non-adjuvanted FLU-v (peptide vaccine derived from conserved regions of internal viral proteins) administration