Human Vaccines: Policy

A universal influenza vaccine
Where are we in the pursuit of this “Holy Grail”?
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Introduction. A number of pharmaceutical and biotechnology companies, hospitals and academic research institutions around the world are pursuing the development of a universal influenza vaccine. Due to the frequent mutations (antigenic drift and shift) of the influenza virus, current influenza vaccines, which are strain-specific, are not designed to offer protection against flu strains which are different from those contained in the particular vaccine itself. This necessitates annual reformulation of the vaccines, resulting in the public having to be immunized annually with the flu vaccine of that particular season. Clearly, a universal influenza vaccine, one that would be effective against all (or most) circulating influenza virus strains, would obviate the need for annual reformulation and repeated annual immunizations, and would significantly reduce the burden, both human and economic, of the disease. Global research and development efforts towards the development of such a universal flu vaccine have gained pace in recent years, and the prospect of such a vaccine reaching the market in the next few years is now increasingly becoming more tangible.

Various Approaches. Several companies and researchers are focused on the development of a universal vaccine, with a number of varying approaches being adopted. By necessity, the creation of a “universal” influenza vaccine dictates the use of conserved regions of the virus that are common to many strains. As such, some approaches are focused on the use of whole proteins, whereas other approaches employ the use of conserved immunogenic peptides (epitopes) within the viral proteins. In addition, the approaches also differ by way of the response elicited from the immune system – some approaches focus on stimulating antibody-mediated (humoral) immunity, while others focus on the stimulation of cell-mediated immunity, and some are designed to stimulate a combined humoral and cellular immune response.

A. Vaccines using whole virus / proteins. Gamma Vaccines is developing GammaFlu™, a whole inactivated virus (WIV) vaccine in which the virus is inactivated by use of gamma irradiation, a process which is designed to destroy the genetic material in the virus (preventing replication) while leaving all coating and internal proteins intact. This approach has been shown in pre-clinical studies to stimulate cytotoxic T-cell immunity that can protect against different influenza A virus strains.

B. Single epitope-based vaccines. Several companies are focused on the use of the M2e peptide – the ectodomain of influenza A virus M2 protein. This epitope is conserved in both human and avian influenza A viruses, being present in nearly all strains detected to date, including highly pathogenic viruses that infect primarily birds and swine, including the recent 2009 swine-origin H1N1 pandemic strain. It is composed of 24 amino acids and induces antibodies that can inhibit a broad spectrum of influenza A subtypes in-vitro and in-vivo.

Companies focused on the M2e epitope include Theracrine™ (in pre-clinical development with an as yet unnamed product focused on anti-M2e antibodies), Sanofi Pasteur (who are now in pre-clinical development of an M2e-based universal vaccine candidate formerly in Phase 1, the ACAM-FLU-A, which they acquired with the Acambis acquisition), and VaxInnate (who reported positive results from a Phase I trial with their M2e-flagellin combination product in 2008, showing that it was safe and induced a significant antibody response to the M2e).

It should be noted, however, that vaccines based solely on the M2e peptide cannot be considered to be truly “universal”, since the M2 channel activity in influenza B strains is mediated by a different protein, therefore rendering M2e-based vaccines ineffective against Type B influenza strains. Moreover, although the M2e epitope is relatively conserved across a broad spectrum of influenza Type A strains, 21 M2e variants have emerged in recent influenza A strains, with most of the mutations appearing in the middle part of M2e domain, raising questions on its ability to be a truly universal vaccine candidate.

C. Multi-epitope vaccines. In order to overcome some of the limitations of the M2e-based approaches, some companies have combined it with other conserved proteins. In addition to using the M2e epitope, Dynavax have added another highly conserved internal protein antigen, the Nucleoprotein (NP), which, together with their proprietary TLR9 agonist ISS (Immuno Stimulating Sequence), is designed to offer protection against divergent strains. In this combination, the NP provides cytotoxic T-cell immunity, while M2e stimulates the production of protective antibodies for protection against divergent strains. Dynavax have shown that this vaccine has the potential to boost the immune response and enable dose sparing, which could increase the quantity of standard flu vaccine available during a pandemic. Dynavax initiated a first Phase I trial in late June 2010 to assess the safety and immunity of this vaccine candidate, and has recently initiated a Phase Ib study to evaluate the safety of the combination of N8295, the novel component of Dynavax’s Universal Flu vaccine candidate, and Novartis’ investigational H5N1 avian influenza vaccine.

Inovio is in pre-clinical development with its VGX™-3400, a prophylactic DNA vaccine that combines the conserved regions of NA and M2e-NP together with variable influenza HA proteins from H1, H2, H3, and H5 (Avian) flu strains.

Juvaris’ universal flu vaccine is a rationally designed, synthetic tetrameric M2e-peptide antigen combined with the JYRS-100 adjuvant that has shown, in pre-clinical trials, to induce significant Th-1 biased antibody responses that have proven to be highly protective.

Other companies that are using combinations of multiple epitopes are SEEK (in Phase I trials with Flu-v, a vaccine that contains six highly conserved CTL epitopes) and Immune Targeting Systems (in Phase I trials with FP01, which is comprised of six long (35 a.a.) CD4+ and CD8+ conserved T-cell epitopes administered as synthetic fluoropeptides forming stable, immunogenic nanoparticles). However, both these approaches are uniquely focused
on the stimulation of cell-mediated immunity, which, being HLA-specific, may be limited as to the broadness of the sectors of the population that are covered by such vaccines.19 An additional drawback of stimulating only cellular immunity relates to the speed of induction of the cell-mediated immune response, which is slower than that induced by the humoral arm, and which may therefore not act quickly enough to prevent the infection.

One company that has adopted the multi-epitope approach, with a vaccine that is designed to stimulate both humoral and cell-mediated immunity, is BiondVax Pharmaceuticals.20 BiondVax’s Multimeric-001 vaccine candidate, currently in Phase II trials,21 is further advanced in terms of clinical development. This vaccine is based on 9 conserved epitopes from the HA, NP and M122 proteins that induce both humoral and cellular immunity against both Type A and Type B influenza strains.23 These epitopes are combined into a single recombinant protein expressed in E. Coli. This vaccine has been tested in two Phase I/II trials in younger (18-49 years old) and older (55-75 years old) adults. In both trials, the vaccine was found to be safe and to successfully induce both humoral and cellular immune responses.24

Conclusion. There is a clear and pressing need for the development of a universal vaccine against influenza, especially in view of the recent swine H1N1 pandemic. Several vaccine candidates based on varying approaches are currently being developed to achieve this goal. These include vaccines based on whole viral proteins, such as M2 and NP, that are comparatively conserved, and others that focus on conserved peptides (epitopes) from these proteins and others. The M2-based vaccines induce mainly humoral immunity, whereas those including NP and M1 induce cellular immunity as well. Although several such candidates are focused on the single M2e epitope, it seems that there is an advantage to including conserved regions from several viral proteins to enhance immunity to the wide divergence of influenza viruses and target the different HLAs. Research towards a universal vaccine is in different stages of pre-clinical and clinical trials, the most advanced of which is BiondVax Pharmaceuticals’ Multimeric-001 vaccine, currently in Phase II. No doubt, the coming years will bring with them further advancements in the quest for this “holy grail”.

References
20. www.dynavax.com