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Epitope-based approaches to a universal influenza vaccine

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ABSTRACT

The development of vaccines has been one of the most important contributions of immunology to public health to date. Although several infectious diseases have all but vanished thanks to effective vaccines, the most common infectious disease, influenza, still represents a major threat to public health. This is more concerning than ever before in light of potentially virulent avian pandemic strains which have emerged in the last decade and infected human hosts, causing high morbidity and mortality. Despite considerable efforts to improve production of influenza vaccines and vaccinate large portions of the population annually, the currently available influenza vaccines are strain-specific and not effective enough. Considering the vulnerability of infants and elderly to seasonal influenza-related complications and the ever present public health threat of a deadly influenza pandemic, there is urgent need for a new kind of influenza vaccine. Ideally, such a vaccine should provide enhanced long term, multi-strain protection without compromising safety and in this way, dramatically improve global protection against seasonal and pandemic influenza viruses. This review highlights one approach to developing a universal influenza vaccine, which is based on highly conserved viral sequences, 'epitopes', that specifically activate humoral and/or cellular immune responses. This approach to vaccinology was pioneered by Prof Arnon, who initiated development of an epitope-based universal vaccine called Multimeric-001 (M-001), which has already been validated in clinical trials to induce broad immunity against A and B-Type, seasonal and pandemic strains.

1. Influenza disease and today's influenza vaccines

Pathogens that exist as multiple strains present a challenge for vaccine design. Examples of such pathogens include *Mycobacterium tuberculosis*, HPV, *Streptococcus pneumoniae* that cause meningitis, and smallpox. To be effective, a vaccine must comprise virus antigens similar to those expressed by the pathogen strains infecting the population. Vaccines against diseases caused by polyvalent pathogens typically comprise several antigenically related strains belonging to the same bacterial species or viral family.

This approach is challenging in the case of influenza due to frequent and unpredictable mutations in two influenza envelope proteins, Hemagglutinin (HA) and Neuraminidase (NA), which result in a constantly changing assortment of numerous circulating viruses. 'These mutations occur mainly in influenza Type A strains, which represent around 80% of human influenza infections; influenza B strains are less susceptible to mutation. The mutations are introduced by viral RNA polymerases that lack a proof-reading function, so the errors frequently appear as nucleotide substitutions, some of which result in the amino acid changes that underlie most seasonal epidemics. Additionally, as the influenza viral genome is comprised of discrete units, a 'shift' can occur involving concomitant larger changes in multiple genes and this level of mutation is associated with emergence of new potentially pandemic strains [1–4].

Despite the complex mix of seasonal and potentially pandemic influenza strains circulating globally at any given time, the general approach to influenza vaccines has not changed for many decades and involves picking the strains considered most likely to be causing human disease. Most current flu vaccines are subunit vaccines, based on the surface of the virus. The virus is grown and inactivated, and ultimately, its surface proteins are used for immunization. The other common type of flu vaccine uses the live-attenuated virus to confer immunity an example is FluMist (MedImmune, USA). Typically, these influenza vaccines are nasal sprays or injections, and comprise the following A and B strains: one H3N2, one H1N1 and one or two influenza B virus strain. Strain selection for seasonal influenza vaccines is conducted annually by the World Health Organization (WHO) and is primarily based on surveillance of the strains circulating in the other hemisphere.

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These influenza vaccines rely predominantly on triggering humoral immune responses to the variable regions in the influenza envelope protein Hemagglutinin (HA) and consequently, are highly strain-specific. Therefore, current influenza vaccines afford incomplete protection as often there is low correlation between the vaccines' immunogenic substance and the influenza viruses actually circulating, a phenomenon termed 'mismatch'. Moreover, high risk populations such as the elderly typically respond poorly to these strain-specific influenza vaccines, resulting in limited immunity even to the strains contained within the vaccine. Indeed, vaccine efficacy is typically only 60% among the general population during seasons when most circulating flu viruses match those in the vaccine [5]. Further, among elderly persons and those persons with chronic medical conditions, the influenza vaccine has been shown to be between 30% and 70% effective in preventing hospitalization for pneumonia and influenza [6–8].

Pandemic vaccines differ from seasonal vaccines in several ways: first, the vaccines usually comprise an emerging influenza virus, not detected in previous seasons and not included in the seasonal vaccines. Pandemic influenza viruses are usually so different that they are not easily recognized by most human immune systems and quickly spread globally. Pandemic influenza vaccines contain only a single strain of the pandemic virus (for example, H1N1 virus) instead of the usual three (trivalent) or four (quadrivalent) virus types used in a seasonal vaccine mixture.

Today, the industry can produce ~500M doses of seasonal vaccine per year [9] or divide this production capacity between seasonal and pandemic formulations. In recent years, great efforts and resources have been devoted to shortening the influenza vaccine production cycle, reducing it from around 8 to 4 months. The influenza vaccine cycle includes production, testing for safety and immunogenicity, approval by regulatory bodies, distribution, and administration. Until 2013, all commercially available influenza vaccines were made from viruses cultivated in chicken eggs, which were then collected, purified, and formulated before being tested for safety and efficacy, and once approved, distributed to care providers. In 2013, Flublok (Protein Sciences Corp, US) was approved for use; this is a trivalent vaccine produced in an egg-free system using insect cells containing recombinant DNA that encodes viral hemagglutinins (antigens). To date, the Improvements in the influenza vaccine cycle include: 1) Modifying production such that the live viruses are propagated in cell culture instead of in eggs: [10]; 2) Modifying production such that recombinant HA proteins are produced in cell culture; 3) Addition of extra virus subtypes into the vaccine, as exemplified by the quadrivalent seasonal vaccines; and 4) addition of adjuvants, which can somewhat broaden the cross reactivity of the vaccine to non-constituent flu strains. Adjuvant is added to the vaccine to increase the body's immune response to the vaccine and often allows using smaller amounts of the immunogen. Many commercial adjuvants are based on aluminum salt that is added to the active component. Although alum is able to induce a good antibody (Th2) response, it has little capacity to stimulate cellular (Th1) immune responses that are so important for protection against many pathogens. In addition, the use of alum raises safety concerns as it has the potential to cause severe local and systemic side-effects including sterile abscesses, eosinophilia and myofascitis [11]. Indeed, seasonal influenza vaccines used in the United States do not contain adjuvants to avoid yearly exposure to the adjuvants. During the recent 2009 swine flu pandemic, the widespread administration of H1N1 vaccine that contains AS03 adjuvant was associated with rare cases of narcolepsy, a chronic neurological disorder caused by the brain's inability to regulate sleep–wake cycles. The Centers for Disease Control (CDC) is currently sponsoring an international study on the associations between adjuvanted monovalent 2009 H1N1 influenza vaccines and narcolepsy; the study is expected to be completed in 2014.

Notably, the most challenging feature of today's influenza vaccines, namely strain-specificity, is hardly addressed by such improvements in the influenza vaccine cycle. The cumbersome and sometimes inaccurate annual (or pandemic) strain prediction/selection procedure is still inclined towards inadequate and inflexible supply and, most worryingly, prolonged exposure of the public to the circulating virulent virus in the event of pandemic [12].

The limitations inherent in today's set-up became acutely apparent during the recent 2009 A/H1N1 swine flu pandemic that spread globally in a few weeks. The inability of manufacturers to produce enough of the relevant vaccine in time resulted in a low impact of vaccination on the spread of the pandemic despite best efforts to produce as much as fast as possible [13,14]. Further, as the pandemic progressed, it became evident that an oversupply of vaccines would occur [15]. Fortunately, this swine flu pandemic was low in severity, but the next one may not be mild and so there is an urgent need to develop a new generation of broad specificity influenza vaccines that will prevent seasonal and pandemic influenza disease.

2. The clinical and economic impact of influenza

The clinical impact of seasonal influenza infections is typically considered to be marginal. Primarily at-risk populations are in danger, namely the elderly, very young toddlers and people with chronic illnesses and health authorities generally recommend that these discrete population groups get vaccinated. However, health authorities have been changing their approach in recent years in view of the emerging pandemic strains, which appear either highly pathogenic (avian strains) or highly infective (swine strain), and have the potential to cause morbidity and mortality in healthy segments of the population not previously considered susceptible to influenza infection. Health authorities have recognized that population-wide annual vaccination against seasonal influenza not only ensures sustainability of vaccine manufacturers, which is essential if they are to provide vaccines during a pandemic, but expands immunity against influenza that could lower the burden of pandemic disease. In the USA, for example, the recommendations of the Advisory Committee on Immunization Practices (ACIP) for 2013–14 are routine annual influenza vaccination of all persons aged 6 months and older [16]. Nevertheless, based on the influenza vaccine industry infrastructure available today, it is estimated that a deadly pandemic flu virus still has potential to cause 175–350 million deaths worldwide [17].

The economic impact of seasonal influenza was estimated in 2007 as $10.4B in direct medical costs, with a total economic burden to society of $87.1B [18]. An estimate for the potential societal economic burden of a deadly influenza pandemic ranges to a remarkable 8% of GDP [19]. This alarming statistic combined with the obligation to better protect their population against pandemic influenza has prompted governments worldwide to promote development of next generation influenza vaccines.

3. The unique benefits of a universal influenza vaccine

A truly universal flu vaccine would immunize against all strains, regardless of antigenic drift or shift, and thereby prevent disease caused by both seasonal and pandemic viruses. This would mean an immunized population was no longer vulnerable to emergence of new influenza strains, a goal of governments and health authorities worldwide. An additional benefit of such a vaccine is that it could be produced and administered year-round and stockpiled,