Is It Possible? A Different Approach to Creating a Universal Influenza Vaccine

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ABSTRACT The best way to combat influenza virus infection is to prevent it. However, the continual evolution of circulating influenza virus strains and the constant threat of newly emerging viruses forces the public health community to annually update seasonal influenza vaccines while stockpiling potential pandemic virus vaccines. Thus, there is an urgent need to develop a "universal" influenza vaccine that affords protection against all strains. In their recent article, L. M. Schwartzman et al. (mBio 6:e01044-15, 2015, doi:10.1128/mBio.01044-15) demonstrated that intranasal immunization of mice with a cocktail of viral-like particles (VLPs) expressing distinct influenza virus hemagglutinin (HA) proteins can broadly protect against infection not only with the same viral strains but also with unrelated strains. These findings suggest a promising strategy for developing a broadly protective "universal" influenza vaccine.

Outbreaks of influenza virus infections continue to cause considerable morbidity and mortality worldwide. Each year, influenza results in 3 to 5 million severe illnesses and 500,000 deaths (1), with higher estimates during a pandemic. Arguably, the best means to prevent influenza infection is through vaccination, and each year, approximately 40 to 50% of adults (18 to 64 years of age) in the United States are vaccinated against seasonal influenza viruses (2). Unfortunately, due to the evolution of the major outer viral surface protein hemagglutinin (HA) through antigenic drift, the annual vaccine components must be frequently updated in order to provide protection against emerging viral strains (3). Further, these vaccines are unlikely to protect against antigenically divergent strains, especially a new pandemic virus with a novel HA subtype (antigenic shift). To date, sixteen HA subtypes in various combinations with NA (H1N1, H3N2, etc.) have been found in nature, primarily in wild birds, the reservoirs for influenza viruses and ultimate source of pandemic viruses (4). Although humans are predominantly infected with H1 and H3 viruses, continual spillover of H5, H7, H9, and occasionally H10 and H6 strains highlights the ever-present risk of a new pandemic (5). Thus, there is a great deal of interest in developing a "universal" vaccine that can protect against all influenza A virus (IAV) strains.

The hunt for a universal influenza vaccine has been under way for decades (6–8). A number of strategies have been explored, including approaches to target individual viral proteins, such as the highly conserved viral matrix (M2) ectodomain and nucleoprotein (NP) (9), as well as neuraminidase (NA) (10) (Fig. 1). More recently, vaccines targeting the conserved HA stalk domain have shown promise. In contrast to canonical HA-neutralizing antibodies, which block the attachment of the HA receptor binding sites to the host receptor ligand, antibodies against the HA stalk prevent fusion of the viral and endosomal membranes during acidification of the endosome, inhibit viral egress by blocking access to the HA proteolytic cleavage site, and can limit viral spread through complement-dependent lysis and antibody-dependent cell-mediated cytotoxicity (11). In their recent article, "An Intranasal Virus-Like Particle Vaccine Broadly Protects Mice from Multiple Subtypes of Influenza A Virus" (12), Schwartzman et al. describe an interesting new approach to eliciting protection against multiple HA subtypes: vaccinating with a mixture of viral-like particles (VLPs) individually expressing a variety of different HA subtypes.

In their study, the authors intranasally immunized mice with a vaccine cocktail that included VLPs displaying one of four HA molecules: H1 from the 1918 pandemic virus and H3, H5, and H7 from weakly pathogenic avian influenza viruses. Immunization resulted in broad protection against challenge with the same viruses (homologous) as well as different IAV strains of the same subtype that were not antigenically matched to the vaccine HA (intrasubtypic heterologous). Protection against homologous and intrasubtypic challenges was also associated with significantly reduced lung viral titers. Why is protection against antigenically mismatched viruses of the same subtype important? These mismatches can cause the annual influenza vaccines to be less effective in protecting the population if the wrong antigen is incorporated—as we saw this past year with the H3N2 vaccine component (13). What happened? In brief, an H3N2 candidate vaccine virus (CVV) was chosen in February of that year based on the antigenic and genetic data available from World Health Organization National Influenza Centers (NICs) and collaborating centers around the world. Unfortunately, by summer it was evident that the H3N2 viruses had evolved (drifted) and that circulating viruses were antigenically and genetically less matched to the CVV, meaning that the H3 component of the vaccine would provide less protection against this apparently circulating drift strain. Having a vaccine that could broadly protect against these antigenically mismatched influenza viruses may alleviate problems encountered through antigenic drift.

Two additional important findings resulted from these studies. The first is the surprising finding that the VLP cocktail also protected mice against viral strains not included in the vaccine (heterosubtypic challenge), the major goal of a universal vaccine. This would mean that we could immunize against IAV subtypes with

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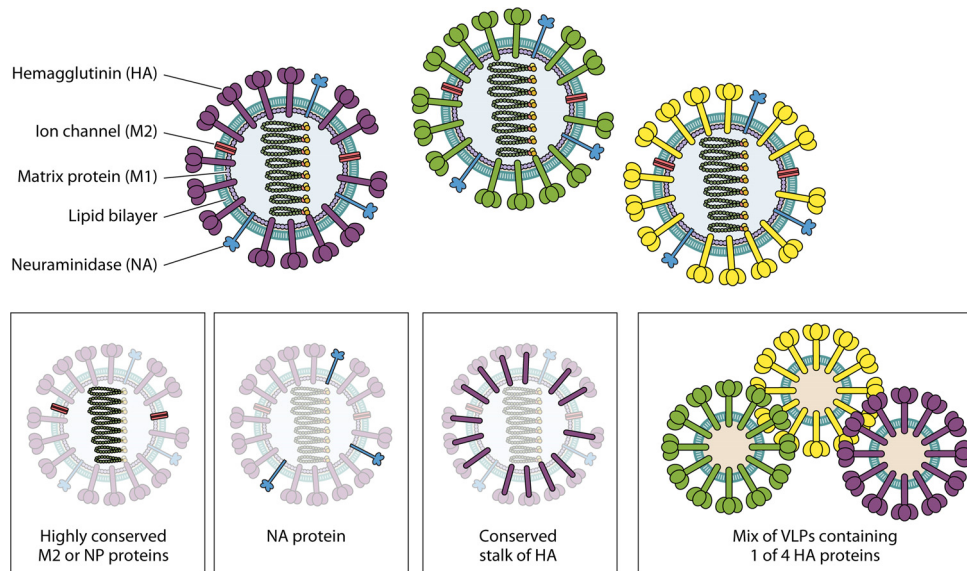
FIG 1 Influenza A virus schematic demonstrating the locations of proteins used in various universal vaccine strategy attempts (top). The different strategies (bottom) include targeting the highly conserved M2 and nucleoprotein (NP) proteins, neuraminidase (NA) glycoprotein, or the hemagglutinin (HA) stalk region and administering a mixture of virus-like particles (VLPs) expressing distinct HA subtypes.

pandemic potential, for example, emerging avian IAV H5 and H7 viruses. This would be invaluable for pandemic preparedness. Finally, this vaccine approach was shown to protect older animals against heterosubtypic challenge, suggesting that this strategy could be an interesting approach for our highest-risk populations.

This is an exciting study that furthers our quest for a universal influenza vaccine. Clinical studies demonstrated that influenza VLP vaccines are safe and effective in adults and can be made available for human use within 3 months of learning the circulating HA and NA sequences (14). Thus, this approach is not only possible but effective within an opportune time frame. Issues that still need to be addressed include determining the mechanism(s) of protection, as well as obtaining evidence of successful protection in other animal models, such as ferrets. Regardless, these studies demonstrate a novel approach to provide protection against diverse IAV subtypes. It is possible that using this strategy as a booster to the annual vaccine would be a quick and effective method to deal with emerging strains, whether they emerge through antigenic drift or shift. However, only time will tell if evolving virus sequences will continue to "outsmart" our best efforts to thwart infection.

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