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Original Article

Universal influenza vaccines: a realistic option?

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ABSTRACT

The extensive antigenic drift displayed by seasonal influenza viruses and the risk of pandemics caused by newly emerging antigenically distinct influenza A viruses of novel subtypes has raised considerable interest in the development of so-called universal influenza vaccines. We review options for the development of universal flu vaccines and discuss progress that has been made recently. **R.D. de Vries, CMI 2016;22:S120**

Introduction

Influenza viruses are an important cause of acute respiratory tract infections and cause epidemics in the human population annually. In most cases infections are self-limiting and restricted to the upper respiratory tract. Certain patient groups, however, such as the elderly, are at risk of developing complications and severe disease. Seasonal vaccines are available to protect these high-risk groups. These vaccines are trivalent or quadrivalent and are designed to protect against circulating influenza A viruses of the H1N1 and H3N2 subtypes, and against one or both lineages of influenza B virus. However, continuous antigenic drift of seasonal influenza viruses complicates the production of effective vaccines.

Antigenic drift, caused by mutations in the membrane glycoproteins hemagglutinin (HA) and neuraminidase (NA), is driven by selective pressure mediated by antibodies, induced by previous infections. Especially HA, the receptor binding protein and main target for virus neutralizing antibodies, displays extensive antigenic drift. Amino acid substitutions at a limited number of residues around the receptor-binding site define the antigenic properties of the virus [1,2]. Thus, seasonal influenza vaccines are considered effective, provided that the HA of the strains used to prepare the vaccines antigenically matches the HA of the epidemic strains. To this end, the vaccine composition needs to be updated almost annually. When the vaccine strains do not match the circulating epidemic strains antigenically, vaccine effectiveness is considerably reduced, as was the case in the 2014–2015 influenza season [3–5].

Apart from the annual epidemics, occasional influenza pandemics occur when antigenically distinct influenza viruses, often of novel subtypes, are introduced into the human population. These pandemic viruses mainly originate from animal reservoirs. If these viruses are sufficiently transmissible from human to human, they have the potential to cause pandemic outbreaks of influenza because neutralizing antibodies against these novel viruses are virtually absent in the population at large. During the last decades, zoonotic transmission of highly pathogenic avian influenza viruses, in particular those of the H5N1 subtype, has been reported regularly. Interestingly, it has been demonstrated that only a few mutations in the HA molecule and polymerase proteins are sufficient for these viruses to become transmissible *via* the airborne route between ferrets [6–8], and some of these mutations have already been detected in naturally circulating H5N1 viruses [9]. Avian viruses of other subtypes have been demonstrated to be able to infect humans, including H5N6 [10], H6N1 [11], H7N3 [12], H7N7 [13], H7N9 [14], H9N2 [15] and H10N8 [16], sometimes with fatal outcome. Although these viruses are not transmitted between

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humans, or transmitted only inefficiently, a pandemic outbreak caused by any of these viruses is feared and has triggered the development of (pre-)pandemic vaccines.

Currently used inactivated seasonal influenza vaccines will afford little or no protection against novel pandemic influenza viruses, and therefore the availability of broadly protective or universal influenza vaccines is an unmet need. This was exemplified in 2009 in the face of the pandemic caused by swine-origin influenza virus of the H1N1 subtype. In some countries, tailor-made vaccines, in which the HA matched the pandemic strain antigenically, only became available after the peak of the pandemic [17,18]. This is of course an unwanted scenario, and availability of vaccines that afford protection not only against intrasubtypic variants of seasonal influenza viruses but also against other subtypes of influenza A virus is highly desirable. Several issues still need to be addressed for the development of universal influenza vaccines. For example, which arms of the immune systems need to be activated, and which viral proteins should be targeted? An overview of currently used approaches and vaccine targets is shown in Fig. 1. For a vaccine to be broadly protective, conserved proteins or regions thereof should be considered as vaccine antigens.

Broadly reactive antibodies

For the induction of cross-reactive antibodies that could contribute to protective immunity, matrix (M) protein 2 [19], nucleoprotein (NP), NA [20–22] and the stalk region of HA [23,24] have been identified as potential vaccine targets. The M2 protein is a minor antigen on virus particles, but is abundantly expressed on virus-infected cells. The protective effect of M2-specific antibodies has been demonstrated after hyperimmunization and passive administration [19] and was shown to be dependent on Fcγ receptors [25]. This indicates that antibody-dependent cellular cytotoxicity (ADCC) by NK cells or neutrophils, or antibody-dependent phagocytosis (ADPC) by macrophages plays a role [25,26].

Furthermore, a protective effect of NP-specific antibodies has been demonstrated in mouse models [27,28], although the underlying mechanism remains unclear. The effect was dependent on Fc receptors and $CD8^+$ T cells. Therefore, it has been suggested that formation of NP immune complexes and opsonisation plays a role [27,28] although this could not be confirmed *in vitro* [29]. Additionally, antibodies to NA confer a certain degree of protection [30–32]. Because antibodies to NA have been shown to cross-react with different NAs of the same subtype, these antibodies may afford a degree of cross-protection in the absence of a matching HA (e.g. H1N1 vs. H5N1) [33].

The trimeric HA molecule consist of a relatively conserved stalk region and a variable head domain. The latter defines the antigenic properties of the molecule. Since the identification of virus-neutralizing antibodies directed to the stalk region of the HA molecule, the induction of these antibodies has attracted a lot of

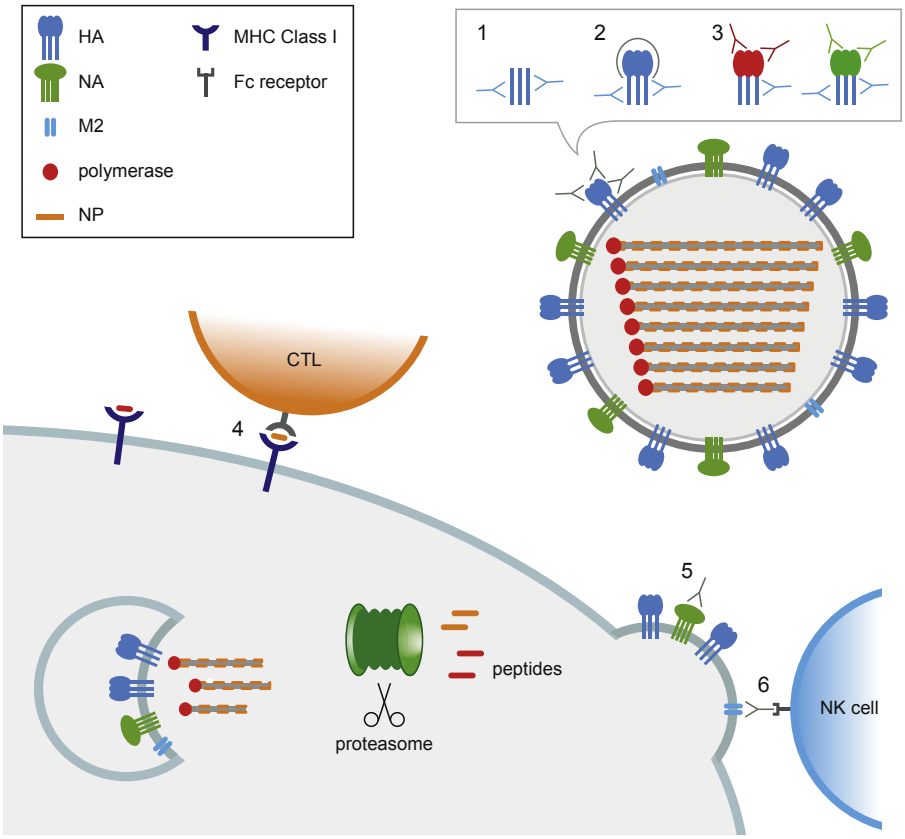

Fig. 1. Rational design approaches for novel universal influenza vaccines. Different approaches are currently used in design of novel universal influenza vaccines. Vaccines can be designed to induce HA stalk-specific antibody response (1, 2, 3), $CD8^+$ T cell responses (4) or nonneutralizing antibody responses (5, 6). In order to redirect antibody response towards conserved HA stalk domain, several modifications to HA have been made as vaccine approaches. These include headless HA molecules (1), 'shielded' head HA molecules, through introduction of glycosylation sites in head (2) and chimeric HA molecules (3). The latter could boost stalk antibody response through repeated vaccinations with molecules expressing similar stalk domains but different head domains. In order to induce virus-specific CTL response (4), conserved internal proteins like NP or polymerase complex can be used as antigens. Finally, it is known that vaccines inducing nonneutralizing antibodies (antibodies specific for M2, NA and HA stalk) can be important in protection from influenza, in particular antibodies that prevent virus egress from cells (5) or are capable of inducing ADCC/ADPC (6).