Is It Possible to Develop a “Universal” Influenza Virus Vaccine?

Potential Target Antigens and Critical Aspects for a Universal Influenza Vaccine

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Influenza viruses cause seasonal epidemics as well as pandemics and are a significant concern for human health. Current influenza virus vaccines show efficacy when they are antigenically well matched to circulating strains. Seasonal influenza viruses undergo antigenic drift at a high rate and, therefore, current vaccines have to be reformulated and readministered on an annual basis. Mismatches between vaccine strains and circulating strains frequently occur, significantly decreasing vaccine efficacy. In addition, current seasonal influenza virus vaccines have limited efficacy against newly emerging pandemic viruses. A universal influenza virus vaccine that induces long-term protection against all influenza virus strains would abolish the need for annual readministration of seasonal influenza virus vaccines and would significantly enhance our pandemic preparedness. Here we discuss the characteristics of universal influenza virus vaccines, their potential target antigens, and critical aspects to consider on the path to successfully developing such vaccines.

GREAT DEBATES

What are the most interesting topics likely to come up over dinner or drinks with your colleagues? Or, more importantly, what are the topics that *don't* come up because they are a little too controversial? In ***Immune Memory and Vaccines: Great Debates***, Editors Rafi Ahmed and Shane Crotty have put together a collection of articles on such questions, written by thought leaders in these fields, with the freedom to talk about the issues as they see fit. This short, innovative format aims to bring a fresh perspective by encouraging authors to be opinionated, focus on what is most interesting and current, and avoid restating introductory material covered in many other reviews.

The Editors posed 13 interesting questions critical for our understanding of vaccines and immune memory to a broad group of experts in the field. In each case, several different perspectives are provided. Note that while each author knew that there were additional scientists addressing the same question, they did not know who these authors were, which ensured the independence of the opinions and perspectives expressed in each article. Our hope is that readers enjoy these articles and that they trigger many more conversations on these important topics.

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Influenza virus infections cause significant morbidity, mortality, and economic loss worldwide every year. It is estimated that seasonal influenza viruses cause 2–5 million severe cases and 250,000 to 500,000 deaths per year globally (WHO 2016). In the United States alone, seasonal influenza virus infections cause approximately 24,000 deaths (CDC 2010) and an economic loss of US\$87 billion per season (Molinari et al. 2007). In addition, influenza pandemics occur at irregular intervals and can claim millions of lives, as evidenced by the 1918 pandemic, which resulted in an estimated 50 million deaths worldwide (Palese 2004). Current influenza virus vaccines are efficacious but only if they are well matched to the circulating strains. The immunity induced by these vaccines is mainly focused on the immunodominant globular head domain of the major viral glycoprotein hemagglutinin (HA). This domain has a high plasticity and changes frequently, thereby escaping herd immunity (also called community protection, a type of indirect protection when a large proportion of a population has become immune to a pathogen) in a process called antigenic drift (Krammer and Palese 2015). Thus, influenza virus vaccines have to be reformulated and readministered on an annual basis. The annual vaccine strain selection is based on surveillance, but mismatches between vaccine strains and circulating strains occur frequently, leading to the loss of vaccine efficacy (de Jong et al. 2000; Tricco et al. 2013; Aquino et al. 2014; Flannery et al. 2015; Xie et al. 2015). Furthermore, seasonal influenza virus vaccines have low or no efficacy against novel pandemic viruses, and the generation and production of matched pandemic vaccines takes at

least 6 months (Krammer and Palese 2015). During this lengthy process, the population is at risk and pandemic vaccines, like the one in 2009, often come too late to the market to make an impact (www.virology.ws/2010/12/09/pandemic-influenza-vaccine-was-too-late-in-2009). Therefore, improved influenza virus vaccines that induce long-lasting and broad immunity against both seasonal and pandemic/zoonotic influenza viruses are urgently needed.

CONSERVED VIRAL TARGET ANTIGENS FOR VACCINE DEVELOPMENT

Whereas the globular head domain of the HA, the main target of currently licensed influenza virus vaccines, continuously changes, other parts of the virus are more conserved. These parts include the membrane-proximal stalk domain of the HA (Krammer and Palese 2013), several domains of the second surface glycoprotein neuraminidase (NA) (Wohlbold and Krammer 2014), the ectodomain of the ion channel M2 (M2e) (Schotsaert et al. 2009), as well as proteins that are located inside the virion, including the matrix protein (M1) and the nucleoprotein (NP) (Table 1) (Grant et al. 2014, 2016). Vaccines against all of these targets are currently under development and are reviewed in detail in Krammer and Palese (2015). The stalk domain of the HA, the NA, and M2e are accessible for antibodies on the surface of virions and of infected cells, and antibodies against these proteins can provide protection by directly inhibiting the virus and/or by eliminating infected cells via complement activation as well as via interactions between antibody Fc re-

Table 1. Targets for universal influenza virus vaccines

Target	Direct inhibition of virus through antibodies	Clearance of infected cells through antibody-mediated cellular effector functions	Cytotoxic T-cell-mediated immunity	Stage of infection when immunity interferes with virus replication
HA stalk	+	+	?	Pre- and post-cell entry
NA	+	(+)?	?	Pre- and post-cell entry
M2e	-	+	?	Post-cell entry
Internal proteins	-	(+)?	+	Post-cell entry

HA, Hemagglutinin; NA, neuraminidase; M2e, ectodomain of the ion channel M2.

gions and Fc receptors on effector cells. The internal proteins of the virus can also be targeted by cytotoxic T cells resulting in the elimination of infected cells (Grant et al. 2016). Antibody-mediated effector functions may play a role as well but it is thus far unclear how—and to what degree—antibodies gain access to these internal proteins (Vandervlen et al. 2016). Importantly, antibody-based immune responses can prevent infection, while cellular immune responses, including antibody-dependent effector cells and cytotoxic T cells, act later when an infection is already established (Table 1). Therefore, antibody-based immunity, specifically if directed against the conserved regions of the HA and the NA, might block infection early by direct virus inhibition if antibody levels on the mucosal surfaces are high enough. As a second safety net, these antibodies can act through Fc-FcR effector functions leading to the elimination of infected cells. Antibodies against M2e (which do not inhibit the virus itself) and cytotoxic T-cell responses specific for conserved influenza virus epitopes might play an important role in protection from severe disease and death but cannot block infection early on. Therefore, vaccines based on antibody responses against conserved parts of the virus glycoproteins like the HA stalk and the NA might have advantages over M2e and NP/M1-based vaccines. Nevertheless, a vaccine that induces both humoral and cellular responses against conserved influenza virus antigens might be preferred.

WHAT ARE UNIVERSAL INFLUENZA VIRUS VACCINES AND WHY SHOULD THEY BE DEVELOPED?

Whereas there is a clear consensus that having a vaccine that protects against all seasonal and pandemic/zoonotic influenza viruses would be highly beneficial, the definition of the term “universal influenza virus vaccine” is still debated. A truly universal influenza virus vaccine should ideally induce lifelong protection against all drift and shift variants, including seasonal influenza A and B, pandemic, and zoonotic strains. Vaccines that induce protection against

a subset of influenza viruses (e.g., against all current seasonal strains and their drift variants or against all influenza A viruses) should be termed “broadly protective” but not “universal.”

Whereas broadly protective vaccines that are efficacious for multiple years would already be a favorable advance over current vaccines, a universal influenza virus vaccine would be a game-changing countermeasure against influenza virus infections. Ideally, this vaccine would be administered only a limited number of times (e.g., in a prime-boost regimen) like licensed vaccines against other pathogens (e.g., hepatitis A, measles, mumps, or rubella viruses). It is likely that such a vaccine would increase uptake and coverage because getting revaccinated every year is time-consuming and costly. Influenza virus vaccines in the United States typically sell for \$30–\$60 per dose depending on the formulation (www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list). During the 2015/16 influenza season, more than 146 million doses of influenza vaccines were distributed in the United States (www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm). Based on an average of \$45 per dose, this amounts to a total of \$6.6 billion. The current vaccine needs to be updated and readministered every year, resulting in annual costs of billions of dollars. Beginning at the age of 6 months, annual vaccination against influenza is recommended. Thus, if the current life expectancy in the United States is about 80 years (en.wikipedia.org/wiki/List_of_countries_by_life_expectancy), the cumulative costs of influenza virus vaccination per person per lifetime is greater than \$3500 (not including the cost of medical personnel needed to administer the vaccine). A universal influenza virus vaccine that is given 2–3 times in a lifetime, if sold at a reasonable price, would save significant amounts of money and lives as compared to the current standard of care.

It is likely that a universal influenza virus vaccine, which is given as a two- or three-dose regimen, would also be beneficial in low- and middle-income countries. Because current influenza virus vaccines have to be readministered on an annual basis, they cannot easily be incorporated into existing (childhood) vaccination

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programs. Annual revaccination is costly and, in many countries, the infrastructure for annual readministration of influenza virus vaccines is lacking. Finally, whereas seasonal vaccine formulations specific for the Northern and the Southern hemisphere exist, they are not available for tropical and subtropical regions where many of the low-resource countries are located. This makes the occurrence of a mismatch between vaccine strain and circulating strains even more likely. A universal influenza virus vaccine that is independent of a vaccine match and has to be given only as a two- or three-dose regimen would be less costly, could be easily administered as part of childhood vaccination programs, and would therefore be useful for low- and middle-income countries.

Another important advantage of a universal influenza virus vaccine is enhanced pandemic preparedness. Pandemics occur in irregular intervals when a novel influenza virus subtype is introduced into the human population, and they can cause millions of deaths. The most devastating example is the 1918/1919 pandemic that caused millions of deaths worldwide and sharply reduced life expectancy in the United States (Palese 2004). Because current seasonal influenza virus vaccines do not protect against emerging pandemics, new matched vaccines have to be produced. The process is lengthy, taking approximately 6 months, and leaves the population vulnerable during this time (Krammer and Palese 2015). Universal influenza virus vaccines that protect against any emerging pandemic virus would completely eliminate this threat. If the vaccine coverage is high enough, any emerging virus with pandemic potential would be stymied upon crossing the species barrier. If the vaccine coverage is lower, a universal influenza virus vaccine could be quickly employed (e.g., from stockpiles), shortening the response time from months to weeks.

Influenza A viruses have a vast animal reservoir that includes horses, pigs, chickens, turkeys, and many aquatic birds. This situation makes it unlikely that influenza A viruses—with its many subtypes—could be completely eradicated. However, it might be possible to eradicate currently circulating influenza A strains from the

human population if the vaccine coverage is high enough. Elimination of influenza A subtypes from the human population happened several times so far (H1N1 in 1957, H2N2 in 1968, and seasonal H1N1 in 2009) as a result of a pandemic influenza A virus that generated enough cross-protective herd immunity to eradicate the previously circulating virus; it seems therefore not impossible to achieve the same result with the right vaccination strategy (Palese and Wang 2011). In contrast to influenza A viruses, influenza B viruses do not have an extensive animal reservoir. Therefore, using the right vaccination strategy combined with high vaccine coverage, the influenza B virus could become the first respiratory virus to be eradicated.

CRITICAL ASPECTS FOR THE DEVELOPMENT OF A UNIVERSAL INFLUENZA VIRUS VACCINE

Independent of the vaccination strategy, several aspects are critical for the development of universal and broadly protective influenza virus vaccines (Fig. 1). These include immunological, virological, safety, logistical, regulatory, and economic considerations.

1. Duration of the immune response: Current inactivated influenza virus vaccines frequently induce short-lived immunity. In fact, vaccine effectiveness has been reported to wane quickly toward the end of the influenza season, specifically in the elderly (Castilla et al. 2013; Kissling et al. 2016). In contrast, immunity induced by natural infection with influenza viruses is usually long-lasting, and titers against a certain strain might persist throughout one's life (Yu et al. 2008). Ideally, universal influenza virus vaccines should induce lifelong immunity against conserved antigens but the duration of the immune response may strongly depend on the vaccine formulation. Obviously, a universal influenza virus vaccine that would need to be administered annually would be of limited use. Adjuvants have recently been used for inactivated influenza virus vaccines and have been shown

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Figure 1. Critical aspects for the development of a universal influenza virus vaccine. HA, hemagglutinin; NA, neuraminidase; M2e, ectodomain of the ion channel M2.

to significantly increase the duration of immune responses (Galli et al. 2009; Chen et al. 2016). In addition, prime-boost regimens involving live virus vaccines, RNA or DNA virus vectors, RNA vaccines, DNA vaccines, or virus-like particles (VLPs) could be used. Such vaccination regimens have been shown to induce broad and long-lasting immune responses against influenza virus antigens (Luke and Subbarao 2014).

2. **Viral escape from vaccine-induced immunity:** The second critical aspect is the potential of viruses to escape from broadly protective immune responses. For escape to occur, herd immunity/community protection against specific conserved antigens needs to reach a high enough level. It is unlikely that escape mutants emerge if only a small proportion of the global population is vaccinated. However, with increasing vaccination coverage, the chance that escape mutants arise increases. Importantly, the vaccine targets for universal influenza virus vaccines are conserved. In many cases, the conservation on the amino acid level is connected to a functional conservation. As an example, the stalk domain of the HA hosts a fusion machinery that undergoes extensive rearrangements during virus entry (Palese and Shaw 2007). Any mutation that nega-

tively impacts the function of this machinery will likely decrease virus fitness. This has already been shown for escape mutants generated with anti-stalk monoclonal antibodies. These mutant viruses lose pathogenicity in vivo as compared to their parental viruses (Henry Dunand et al. 2015, 2016; Chai et al. 2016). Of course, the possibility that escape mutants will arise can never be excluded and the likelihood of the emergence of escape variants depends on several factors, including the vaccine target and the mechanism of protection of the specific vaccine. It would therefore be a prudent strategy to include in a universal influenza virus vaccine more than one conserved target antigen (for example, the stalk of the HA and the conserved domains of the NA). This would significantly decrease the chance that escape from immunity to one of the targets would completely abolish the effectiveness of the vaccine.

3. **Blocking influenza virus transmission:** Evidence from animal experiments suggests that current inactivated seasonal influenza virus vaccines show poor efficacy in blocking virus transmission (Lowen et al. 2009) and it is unclear how well these vaccines block transmission in humans. However, efficient protection of the population (in-

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cluding immunocompromised patients) from both seasonal and pandemic influenza depends on disruption of transmission chains. Inducing strong and long-lasting mucosal immunity should therefore be a critical attribute of a universal influenza virus vaccination strategy because both initial virus entry/infection as well as virus spread are features of the virus' replication in mucosal surfaces. Blocking transmission of virus would also help to prevent the emergence of viral escape mutants.

4. The effect of preexisting immunity on vaccine efficacy: Preexisting immunity might influence the efficacy of universal influenza virus vaccines. Several candidate vaccines under development rely on boosting preexisting memory responses. However, the magnitude and quality of preexisting immunity might be influenced by the age, exposure history, sex, and immune status of an individual (Klein et al. 2015; Nachbagauer et al. 2016). For example, children have lower levels of preexisting immunity than adults and might therefore require an additional priming dose. Specific vaccination regimens that are tailored to the preexisting immunity in different cohorts (e.g., children versus adults) may have to be developed to elicit the full potential of universal influenza virus vaccine candidates.
5. Vaccine safety: Virus infections and vaccines that induce strong immune responses may, in some cases, induce autoimmune diseases like Guillain–Barré syndrome and narcolepsy (Nguyen et al. 2016; Willison et al. 2016). In addition, cross-reactive antibodies as in the case of dengue virus infections can cause enhanced disease, and strong T-cell responses have been shown to contribute to immunopathology (Cedillo-Barrón et al. 2014; Duan and Thomas 2016). It is therefore imperative to test and monitor safety throughout preclinical and clinical development of universal and broadly protective influenza virus vaccines. Importantly, postmarketing surveillance will also be necessary to detect rare adverse events.
6. Challenge studies: To de-risk the development of universal influenza virus vaccine candidates early, these vaccines could be tested in human challenge studies (Memoli et al. 2016). This would allow a direct comparison with currently licensed influenza virus vaccines in challenge models with matched and mismatched seasonal influenza viruses. While not available at this time, human challenge studies with low pathogenic avian influenza viruses (e.g., H4, H6, H10, etc.) have been performed in the past (Beare and Webster 1991) and could also be employed to gauge protection against zoonotic (potential pandemic) viruses.
7. Regulatory strategy: An important consideration for both universal as well as broadly protective influenza virus vaccines will be the licensure strategy. To claim superiority over existing vaccines in terms of breadth will require multiyear efficacy studies that include years where the current seasonal vaccine is mismatched. A strategy could therefore be to first seek licensure as a “regular seasonal” influenza vaccine without superiority claims while testing efficacy over multiple years. In addition, it will be impossible to show efficacy in the field against pandemic influenza viruses until a new pandemic emerges. The establishment of correlates of protection (e.g., the anti-stalk antibody titer), during clinical development could facilitate the licensure process. An important remaining question is whether a vaccine that is inferior to a well-matched seasonal vaccine but superior in the case of antigenic drift or antigenic shift (when the seasonal vaccine is mismatched) is acceptable to regulators and the public.
8. Prohibitive development costs: The development of a broadly protective—and even more so—a universal influenza virus vaccine will require vast economic resources. Current influenza virus vaccines have to be readministered every year and produce a

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constant revenue stream for the vaccine industry. Therefore, the incentive to develop universal influenza virus vaccines might be limited. However, an efficacious universal influenza virus vaccine would be considered a disruptive technology and might completely change the influenza virus vaccine industry, giving a manufacturer an unrivaled position in the market. Because the development of a universal influenza virus vaccine is of broad interest, public–private partnerships might be an effective approach to overcoming the high initial development costs.

CONCLUSIONS

Several broadly protective and universal influenza virus vaccine approaches are currently in preclinical and clinical development (Berlanda Scorza et al. 2016). An efficacious universal influenza virus vaccine that induces long-lasting immune responses would abolish the need for annual revaccination and would significantly enhance our pandemic preparedness. It is very likely that such a vaccine would also increase vaccine uptake in the general population and in low- and middle-resource countries specifically. High global coverage with a universal influenza virus vaccine would significantly reduce the burden caused by influenza virus infections and could, if the herd immunity/community protection is strong enough, even eliminate influenza B and seasonal influenza A virus subtypes from the human population.

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