Considerations for the development of Zika virus vaccines


1. Introduction

The current Zika virus outbreak has galvanized the public health community, resulting in calls for rapid action from entities including the World Health Organization and the United States government. The response to Zika virus is perhaps the first of its kind, and it has been influenced by the lessons learned from the response to the 2014 Ebola virus outbreak in West Africa. However, Zika virus is not Ebola virus. Prior to 2016, there were only 133 publications on "Zika" in the PubMed database, and a large number of these publications were commentaries or reviews lacking primary research data. In contrast, work had been underway for decades on the development of an Ebola virus vaccine, laying the groundwork for an expedited response in 2014. The broader research community's extensive experience with dengue virus vaccine development and with the pros and cons of different vaccine platforms has led to speculation that a Zika virus vaccine can be accelerated, potentially with clinical trials initiating by the end of 2016 [1]. However, there are unique attributes of Zika virus, as well as many unanswered questions about the virus, that will need to be considered before a potential vaccine is administered to the public.

The close phylogenetic relationship between the flaviviruses has complicated diagnostic efforts for multiple members of this family, because antibody elicited by the viruses is cross-reactive [2]. Definitive diagnosis of Zika virus infection in individuals with previous flavivirus infection therefore requires detection of viral RNA by PCR, which is only achievable during approximately a two week window early in infection. Efforts are underway to develop serological assays to differentiate the flavivirus infections, particularly on "original antigenic sin" has not been assessed for Zika virus infection, Zika virus is transmitted by the same vectors that carry other flaviviruses. The possibility that pre-existing antibody specific for other flaviviruses, including dengue, yellow fever, and Usutu viruses. The possibility that pre-existing antibody specific for other flaviviruses might preclude the development of an optimal anti-Zika virus adaptive immune response is at this point theoretical, but it could have significant implications for vaccine development. Poorly immunogenic vaccine platforms like DNA or subunit based vaccines may therefore be suboptimal in an endemic population, even if they elicit robust immune responses in flavivirus-naïve populations. Studies dissecting the interplay between pre-existing immunity and the response to investigational vaccines would be of significance to investigators across the spectrum of basic and applied research.

2. Factors affecting vaccine development

2.1. Antigenic sin

The principle of "original antigenic sin" was first described in 1953 by Francis et al in the framework of influenza exposure [3]. The authors observed that successive exposure to closely related viral variants induced a preferential response to the initially encountered variant. Thus with each annual exposure to influenza virus, memory immune responses to conserved antigens are reactivated and dominate the immune response to the current viral agent. However, an immune response to these conserved antigens may not be the required, effective response. The immune response will be ineffective if neutralization of non-conserved antigen domains is required.

Dengue virus investigators are well acquainted with the principle of original antigenic sin [4,5]. As early as 1983, investigators observed that patients exposed to multiple dengue serotypes had higher neutralizing antibody responses to the initial infecting serotype than to the subsequent infecting serotypes [4]. While the relevance of original antigenic sin has not been assessed for Zika virus infection, Zika virus is transmitted by the same vectors that carry other flaviviruses, including dengue, yellow fever, and Usutu viruses. The possibility that pre-existing antibody specific for other flaviviruses might preclude the development of an optimal anti-Zika virus immune response is at this point theoretical, but it could have significant implications for vaccine development. Poorly immunogenic vaccine platforms like DNA or subunit based vaccines may therefore be suboptimal in an endemic population, even if they elicit robust immune responses in flavivirus-naïve populations. Studies dissecting the interplay between pre-existing immunity and the response to investigational vaccines would be of significance to investigators across the spectrum of basic and applied research.

2.2. Antibody dependent enhancement

Dengue virus vaccine development has been an active area of research for years, but the virus has proven to be a complex candidate for vaccine development. There are four serotypes of dengue virus, and primary infection with one serotype can actually enhance the pathogenicity of secondary infection with a different serotype [6]. Therefore a vaccine designed against serotype 2 could
potentially enhance the symptoms associated with a subsequent infection with serotype 4. One proposed mechanism behind this phenomenon is antibody dependent enhancement (ADE) of infection. ADE is the phenomenon whereby antigen-specific antibodies bind the virus and target the immune complex to Fc-receptor expressing cells, which are highly permissive to dengue virus infection, resulting in higher titers of virus [7]. Consequently, the antibody is actually enhancing the infectivity of dengue virus. To circumvent this complication, millions of dollars and countless man hours have gone into developing optimized antigen and vaccines to elicit protection against all four serotypes. Multiple vaccines are currently in clinical trials, and investigators are exploring the relevance of preexisting immunity on vaccine mediated protection. The role for ADE in enhancing infection of other flaviviruses has been minimally explored, but is considered a relevant risk, as discussed in this review article [reviewed in [8]].

Just as Zika virus is not Ebola virus, with a plethora of vaccine options advanced in the pipeline, neither is it dengue virus. Zika virus, as far as we know, does not have multiple serotypes like dengue virus. However, Zika virus is closely related to other flaviviruses, and cross-reactive antibody has the potential to exacerbate secondary flavivirus infections through ADE. A recent publication has demonstrated that human dengue virus antibodies enhance in vitro infection with Zika virus, suggesting that ADE is not merely a theoretical concern [9]. Vaccine development for Zika virus should therefore include evaluation of whether antibody targeting Zika virus can induce ADE of subsequent flavivirus infection. In parallel, a better understanding of whether pre-existing antibody, which cross-reacts with Zika virus, enhances disease severity will be of great value.

2.3. On the bright side...

When dealing with a pathogen about which so little is known, it is critical to consider the worst case scenarios and evaluate safety and efficacy in the most thorough manner possible. However, cross-reactive antibody may be beneficial rather than detrimental. In a study of yellow fever disease severity, the presence of pre-existing dengue virus specific-antibody appears to reduce the severity of yellow fever pathogenesis, suggesting a partially protective effect of the cross-reactive immune responses [10]. In another study, individuals previously vaccinated with Japanese encephalitis virus or yellow fever virus vaccines appeared to experience a boost in titers against these viruses upon natural infection with West Nile virus (WNV), though the previous vaccinations had no protective effect on the WNV infected individuals [11]. Such studies encourage optimism that multiple flavivirus exposures may have a neutral or beneficial effect rather than a detrimental one.

3. Summary

The development of a vaccine for Zika virus is unequivocally an important goal. The associations between fetal abnormalities and Guillain-Barre Syndrome (GBS) with Zika virus infection appear conclusive, and a vaccine will be preferable to a therapeutic if the virus is persisting in immune privileged sites. However, expediency will have to be balanced with rigorous evaluation, which takes time. Zika virus has surprised us already with its ability to be transmitted sexually and its association with microcephaly [12,13]. Additionally, the link between GBS and Zika virus must be considered during vaccine development and perhaps suggests that development of a live-attenuated vaccine is unadvisable until the cause of GBS is defined. Consideration of additional complications, in the form of ADE or other manifestations not covered here, will be imperative for effective vaccine development.

In this discussion, we have highlighted two of the possible complications associated with the development of a safe and effective vaccine: one, the immunogenicity of a potential vaccine may be adequate in a flavivirus-naive population but inadequate in an endemic population; two, vaccination with a Zika virus-targeting vaccine may have a negative impact on subsequent dengue or other flavivirus infections (or vice versa) due to ADE. Retrospective and prospective clinical studies will undoubtedly investigate the relationship between Zika virus pathogenesis and pre-existing flavivirus exposure, potentially explored concurrent with vaccine development efforts. This coordinated effort, conducted in the appropriate populations with the appropriate controls, will be the most efficient route to truly accelerating the development of a safe and effective Zika virus vaccine.

4. Disclaimers

Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

Conflict of interest

The authors report no conflict of interest.

References