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Commentary

Pushing Forward With Zika Vaccines

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Approximately 70 years ago, new flavivirus was discovered in the Zika forest of Uganda (Dick et al., 1952). The eponymous virus is an arthropod-borne human pathogen that caused infrequent infections with relatively mild illness in Africa and received relatively little attention until recently. Over the last several years the virus has spread into Southeast Asia, across the Pacific and, in 2015, into Brazil causing larger and larger outbreaks. Most infected individuals (~80%) are asymptomatic, while those who develop clinical disease display short-lived symptoms including: rash, fever, arthralgia, and conjunctivitis (Barzon et al., 2016). Unfortunately, the recent outbreaks have corresponded with increased rates of severe fetal neurological defects, fetal malformations, and Guillain-Barre syndrome and subsequent studies have causally linked Zika virus to these serious clinical outcomes (Cao-Lormeau et al., 2016; Johansson et al., 2016). More recently, outbreaks have been reported in over 60 countries, with well over 1 million cases in, Brazil alone, leading the WHO to declare Zika a global public health emergency. Zika virus has been demonstrated to spread through sex and transfusion with blood produces, and to be transmitted from the mother to the fetus.

The development of a safe and effective vaccine against Zika virus is a public health priority, however several challenges stand in our way. First, relatively little is known about Zika virus biology or immunity. Fortunately, other flaviviruses such as yellow fever virus, dengue virus, and Japanese encephalitis virus have been well studied, and have existing vaccines with a wealth of immunogenicity and efficacy data which can serve as starting model systems as Zika-focused research efforts come online. Second, the need to protect women who are pregnant or are attempting to become pregnant introduces complications into formulating and testing new vaccines. Third, antibody dependent enhancement of disease (as seen with dengue virus) may occur with Zika, although data suggest that Zika virus exists as a single serotype (Dowd et al., 2016). Despite the challenges, it is imperative that we develop vaccines against Zika that can be effectively used in developing countries and that are safe for use in pregnant women.

Multiple vaccine candidates are currently in various stages of research and development (Tripp and Ross, 2016). Many of these are based on existing platforms known to be effective for other pathogens and include: inactivated viral particles, nucleic acid (DNA and RNA) vaccines, live vectored vaccines based (e.g., measles, vaccinia, and adenovirus), chimeric vaccines, and subunit vaccines based on individual Zika virus proteins. A recent study by Larocca et al. studied the effect of two Zika vaccines, a plasmid DNA vaccine expressing the prM and Env proteins and a purified, formalin-inactivated vaccine, in immunocompetent mice. A single dose of either vaccine elicited robust protective immunity in all mouse strains tested (Larocca et al., 2016). A follow-up study by Abbink et al., demonstrated robust immune responses and protective efficacy of the same two vaccines in rhesus macaques (Abbink et al., 2016). The same study went on to test a rhesus adenovirus serotype 52 vector-based vaccine which was also highly immunogenic and protective against live virus challenge. So far, two Zika vaccines are in phase I clinical trials (NCT02840487 and NCT02887482).

In this issue of EBioMedicine, Kim et al., report the on the early stage development of two Zika vaccines (Kim et al., 2016). The first vaccine is an adenovirus serotype 5-vectored vaccine expressing the Zika E protein (Ad5.ZIKV-Efl vaccine) derived from a Brazilian isolate (BeH815744). The second formulation is a subunit recombinant E protein vaccine delivered by carboxymethylcellulose microneedle array (MNA-ZIKV-rEfl). In both cases the Zika E protein was fused to the T4 fibrin foldon trimerization domain. The authors demonstrate that a prime-boost vaccination regimen of the Ad5.ZIKV-Efl vaccine elicits high titer neutralizing antibody in C57BL/6 mice. A major goal of any Zika vaccine is to prevent infection and/or neurologic impairment of the fetus, therefore the authors tested a passive protection suckling mouse model. In this model Ad5.ZIKV-Efl vaccinated females are mated with unvaccinated males and pups are challenged intraperitoneally with a heterologous Zika strain (DAKAR41542) at 7 days after birth. 100% of the pups from unvaccinated mothers develop disease with physical and neurological manifestations. Pups from mothers immunized with the Ad5.ZIKV-Efl vaccine displayed complete protection with 100% survival and no clinical evidence of disease. Furthermore,

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high titers of neutralizing Ab remained present in the pups 25 days after birth. In contrast, the subunit vaccine delivered by microneedle array (MNA-ZIKV-rEfl) was considerably less immunogenic. While it did elicit a humoral response in recipient mice, the response kinetics were delayed and the absolute magnitude of the response was considerably lower as neutralizing titers at 6 weeks post-priming were 10-fold less than those in the mice immunized with the Ad5.ZIKV-Efl vaccine. Pups born to MNA-ZIKV-rEfl immunized mothers were partially protected in that weight loss was significantly less than in the PBS-immunized controls, however 5/6 MNA-ZIKV-rEfl immunized mice still displayed signs of neurological disease, although the severity score was significantly lower. Furthermore, the survival rate for pups of MNA-ZIKV-rEfl vaccinated mothers was only 50% after viral challenge. Lastly, neutralizing Ab titers in the pups had decreased to baseline levels by day 25.

The data from this study make important contributions to our knowledge of immune responses to Zika virus and to the development of effective vaccines against Zika. The authors utilized purified E protein, which was characterized by low protein yields, indicating that prM protein may be required for optimal stability and that prM-E may be a more effective antigen. The effect of E protein trimerization was not specifically evaluated in this study and may serve as another useful technique to enhance protein production, stability, and immunogenicity. A large percentage of the human population possesses Ad5-specific antibodies, thereby limiting the usefulness of Ad5.ZIKV-Efl vaccine in humans. Nevertheless, the Ad5.ZIKV-Efl vaccine data are impressive and clearly demonstrate the robust immunogenicity of this platform, especially in light of the previously cited report (Larocca et al., 2016) using rhesus adenovirus vector for which this complication is minimized. The MNA-ZIKV-rEfl vaccine data is less impressive but potentially of greater value. The MNA-vaccine platform has multiple production advantages: reproducibility, low cost and ease of manufacturing, product stability, the potential to require lower doses of antigen, simplified and painless vaccination procedure, the possible elimination of the cold chain storage needs. The system is amenable to the introduction of adjuvants that can be lyophilized and encapsulated in the microneedle array (i.e., TLR ligands or cytokines). The goals of this study and the model system used to evaluate protection are important in light of the impact of Zika infection on the developing fetus. Future work evaluating these vaccines in additional animal models (e.g., A129, AG129, SJL mice) may provide important additional information regarding these two vaccine platforms.

A number of knowledge gaps concerning Zika virus still exist, posing questions that need to be answered in order to fully control this disease (Thomas et al., 2016). These gaps include: the How, Why, and When of Zika outbreaks, the risk factors for different clinical disease, the effects of co-infections with other arboviruses, details about transmission routes, the timing of risk during pregnancy, how age, immunocompetence, race, gender, and genetics effect disease susceptibility or clinical outcome, the development of safety and efficacy data in pregnant women, the degree of cross-reactivity of vaccine strains, the development of appropriate animal models accurately reflecting human disease, and the establishment of correlates of protection in humans to name a few. Fortunately, the global health community has come together to combat this global problem. The provision of adequate resources in terms of funding, infrastructure, manpower, and long-lived commitment to the goal on the part of government, private industry, academia and other organizations will be essential if we are to eventually control this disease.

Disclosure

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