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Letter to the Editor

Dengue Virus Infection: Current Challenges and Future Perspectives

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Dengue infection is a zoonotic disease caused by Dengue virus, a single-strand RNA flavivirus. It is transmitted to humans through primarily Aedes aegypti (mosquito) bites. The disease prevalence is higher in tropical zones where there are high humidity and temperature as well as unplanned urbanization. According to the WHO, more than 100 tropical countries are afflicted by Dengue infection, leading to severe economic impact. Brazil is currently a major hotspot of Dengue infection. The number of infected people with dengue virus increased 240% in the first trimester of 2015 compared to the same period last year, surpassing the WHO estimative. In an attempt to stop the infection from spreading, the Brazilian Health Ministry has increased the budget to nearly $50 million to combat the vector. However, the bureaucracy of the Brazilian government has led to slow release of the allocated money to the affected cities and the results have been catastrophic. To make the situation worse, the slow diagnosis and the subsequent delay in starting the treatment has led to increased mortality rates. Currently, the only treatment available for Dengue infection is supportive, which is not very efficient against the most severe cases such as Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS).

Primary dengue virus infection induces a cross-reactive antibody response among all virus serotypes. However, the majority of those antibodies are non-neutralizing. The few/rare Neutralizing Antibodies (nAbs) are specific to the infection serotype. All those antibodies can be found in the serum for decades and their main targets are the viral outer core proteins such as prM, envelope and capsid [1]. A hypothesis to explain that low/ inexistent degree of virus neutralization for all serotypes is that the dengue virus could deliberately elicit a polyclonal antibody response in order to dilute the dengue-specific nAbs [2]. In fact, it has been demonstrated that cross-reactive anti-prM antibodies elicit Antibody-Dependent Enhancement of Infection (ADE) on Fc receptor-bearing cells instead of virus neutralization [3]. Moreover, there is a massive detection of dengue-specific plasmablasts (antibody-secreting cells) during the acute phase of infection, counting for almost 50% of all blood B cells [4,5].

Thus, considering the lack of available vaccine for dengue infection and the serious public health issue caused by that pathogen, pharmaceutical companies and research groups have worked together in the development of a protective tetravalent vaccine. The hope resides on few vaccine candidates currently settled for clinical trials. Those vaccine candidates were designed based on different strategies. Among them, there are 3 live attenuated (by Sanofi Pasteur, Takeda and NIH/ Butantan Institute), 1 inactivated (by GSK/Biomanguinhos/WRAIR); 1 subunit (by Merck/Hawaii Biotech) and 1 DNA vaccine (by the NMRC). The only vaccine that has reached the phase III in clinical trials so far is the Sanofi Pasteur candidate. This vaccine contains the Yellow Fever 17D virus as backbone, but with wild-type prM and envelope sequences replaced with ortholog sequences for all dengue serotypes [6]. During the phase III of clinical trials, it was administered in 2 children cohorts, eliciting levels of protection that ranged 35-78% and 42-78% among the different virus serotypes in Asia and Latin America respectively. The lowest level of protection was consistently obtained against the dengue serotype 2 in both cohorts [7,8]. Immunogenicity evaluations for that vaccine showed an induction of anti-viral response (type I IFN and ISGs) in vitro and elicitation of dengue serotype-specific T cells and broadly nAbs with low/absent ADE in vivo [6].

Recently, it was demonstrated that some dengue-specific plasmablasts secrete tetravalent nAbs after infection [9]. Despite the fact that B cell epitopes can be linear and short [10], dengue-specific nAbs seem to interact preferentially with conformational epitopes. In fact, some of those nAbs attach simultaneously to multiple regions of the dengue virion [11,12]. One of these conformational epitopes was recently identified as part of the viral Envelope Dimer (EDE) [9,13]. It would be extremely valuable to investigate whether any of the clinical trial vaccine candidates can induce tetravalent EDE-specific nAbs. Other issues to be further analysed regarding those EDE-specific nAbs are related to their differences in terms of sequence and function between the vaccine-derived

and infection-derived nAbs.

In addition to its role in preventing viral infections post-vaccination, antibodies could also be used therapeutically. It has been demonstrated that antigen-specific monoclonal antibodies (mAbs) can be rapidly produced after sorting single plasmablasts and cloning of their respective immunoglobulin genes [14]. Once the mAbs are characterized in terms of antigen binding, breadth, neutralization and ADE induction for all dengue serotypes, the best mAbs could be tested as AAV-based "vaccines" [15,16] or as "naked" proteins in therapeutic approaches [17-19]. Therefore, a detailed analysis of the antibody repertoire induced by these new vaccines candidates may significantly improve not only the vaccine development, but also the therapy against the dengue virus infection.

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