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DESIGN OF A VACCINE AGAINST DENGUE AND ZIKA VIRUSES BASED ON A MIMOTOPE OF THE ENVELOPE DIMER EPITOPE

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Zika and dengue viruses are members of the *Flavivirus* genus that cause mild fever, rash and general body pain; but can cause severe reactions, as hemorrhages (dengue virus), congenital syndrome (Zika virus), or even death. Because of the structural similarity between these viruses, some antibodies generated after an infection can cross-react with different members of the flavivirus family. After a secondary infection, the cross-reactive antibodies can lead to more severe forms of the disease, through a mechanism named antibody-dependent enhancement of infection (ADE). Broadly neutralizing antibodies are antibodies that neutralize both, dengue and Zika viruses; and it has been demonstrated that they do not induce ADE. These antibodies are directed to a discontinuous quaternary epitope named the Envelope Dimer Epitope (EDE)[1], located in the envelope (E) protein. To obtain the EDE, it is necessary to express the complete E protein, which contains other epitopes that induce ADE. This study aims to generate a peptide that emulates the EDE epitope structure (mimotope) in order to be used as a dual vaccine against dengue and Zika viruses; without causing ADE.

Using the broadly neutralizing antibody EDE1 C8, that does not induce ADE at high titers [2,3], and a phage display library, we identified three peptides that are recognized by EDE1 C8, but share very low or no identity with the E protein sequence from dengue and Zika viruses. Thus, they are probably emulating the structure of the EDE epitope and are EDE mimotopes. The analysis by circular dichroism of the free peptides showed mainly a random coil folding, characterized by a lack of secondary structure. EDE1 C8 did not recognize these mimotopes attached chemically to a carrier protein, and free or phage-displayed peptides did not induce antibodies against native viruses when administered to mice. To improve the stability and folding of the peptides, we designed and produced adeno-associated virus-like particles (VLPs) that display the mimotopes on their surface. VLPs were obtained using the baculovirus-insect cell system, with similar size and structure to the native adeno-associated virus, as determined by cryo-electron microscopy. The modified VLPs were recognized by the EDE1 C8 antibody in a native Dot-Blot, but not under denaturing conditions, demonstrating that the three-dimensional structural conformation of the peptides displayed in the VLPs can mimetize the EDE epitope. The VLPs displaying mimotope 2, in combination with an adjuvant, elicited antibodies against Zika and dengue viruses when applied to mice.

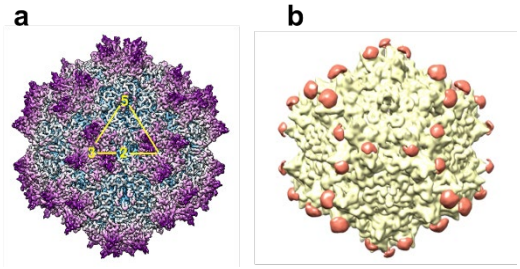

Figure 1- Cryo-EM map of VLPs displaying mimotope 2, colored by radius (a) or showing the site of insertion in red (b).

Here, we demonstrate that it is possible to emulate a very conserved epitope in dengue and Zika viruses, with non-related to protein E peptides. This information is valuable for the design of a safer dengue and Zika vaccine without ADE. More research is necessary and undergoing to study the neutralizing and ADE effect of the antibodies produced in response to the immunization with these VLPs-displayed mimotopes.

References

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