Epitope-guided flavivirus vaccine design for inducing neutralizing antibodies with minimal enhancement.

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Flavivirus infections, including dengue and Zika, pose a significant and growing threat to global public health, with their geographic distribution continuing to expand due to global warming and increased transportation. However, the widespread use of approved vaccines and the development of next-generation vaccines have been prevented from the risk of antibody-dependent enhancement (ADE), a phenomenon mediated by suboptimal or cross-reactive antibodies that facilitate viral entry via FcγRII (CD32) into host cells and exacerbate disease severity. ADE is primarily mediated by cross-reactive antibodies induced by different serotypes of dengue virus or antigenically related, yet distinct flaviviruses, increasing the complexity to elicit neutralizing antibodies without enhancement against different viruses. Thus, achieving an optimal balance between potent neutralization and low ADE activity remains a crucial challenge in flavivirus vaccine design. To address this issue, we recently identified human monoclonal antibodies that target novel epitope on the envelope (E) protein, demonstrating broad and potent neutralizing activity across multiple flaviviruses while exhibiting minimal ADE activity. Based on this breakthrough discovery, we aim to develop next-generation vaccine candidates against dengue, Zika, and other important flaviviruses by employing structure-guided computational design approaches. We will rationally engineer E proteins with enhanced antigenicity and immunogenicity. The research is composed of iterative design–test–refine cycles consisting of: (i) in silico antigen design, (ii) antigenicity evaluation based on biophysical stability, structural characterization, and binding affinity to target monoclonal antibodies, and (iii) immunogenicity assessment of candidate vaccines in relevant animal models. Selected antigens will be applied to recombinant protein-based vaccine formulations with appropriate adjuvants and/or mRNA vaccine platforms to maximize immune responses. A key milestone of this study is to demonstrate superior immunogenic profiles, including enhanced breadth and potency of neutralizing antibodies with reduced ADE activity, compared with wild-type E protein. Successful outcomes from this work will provide a strong preclinical proof of concept and inform the development of more effective flavivirus vaccines.