Computational design of antiviral biologics targeting Zika virus envelope protein

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In the past two decades, the world has struggled with recurrent viral outbreaks, with viruses from diverse families demonstrating pandemic and epidemic potential. One of those viruses is the Zika virus. Despite disease cases having declined globally after 2017, Zika virus transmission persists at low levels in regions like the Americas and a total of 89 countries and territories have reported evidence of Zika virus infection. Despite active research, treatments for Zika virus infection are lacking, and vaccine development remains ongoing.

The field of protein design has arisen as a transformative discipline in molecular engineering, allowing precise tailoring of protein properties such as their stability and ability to bind to specific partners. Antiviral biologics, such as small proteins that can bind to and inhibit viral targets, appear as a promising therapeutic option. In the Zika virus, the envelope protein (E) has a pivotal role in viral entry, making it an ideal target for antivirals. The E protein comprises three structural ectodomains (DI, DII, DIII) and a transmembrane region. DIII is an immunoglobulin-like domain that contains receptor-binding sites. In this work we are developing tailor-made antiviral biologics that specifically target and bind to the E protein DIII, preventing viral entry into host cells. The methodology involves identifying epitope regions on the target surface regions, selecting binding motifs from a large “Atlas” containing a description of a large pool of protein binding motifs, and docking the binding motifs to the epitope. Binding affinity will be optimized using proteinMPNN, a deep learning-based protein sequence design method. Protein structure prediction tools, like AlphaFold2, will be used to filter the most promising designs. Additionally, molecular dynamics simulations will be employed for stability evaluation as an in silico control. Our collaborators will then experimentally evaluate the selected candidates for their binding affinity. This comprehensive approach seeks to redefine strategies in combating the Zika virus, holding the potential to enhance preparedness against emerging viral threats with pandemic potential.