MD627 893 Seminar in Medical Microbiology
Department of Microbiology, Faculty of Medicine, Khon Kaen University

Seminar title: Rational Design of a Conserved Epitope–Driven Strategy for Developing Safe and Broadly Protective Flavivirus Vaccines

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Date: 14th January 2026

Abstract

Flaviviruses, including dengue virus (DENV), Zika virus (ZIKV), Japanese encephalitis virus (JEV), and West Nile virus (WNV), remain significant global public health threats, yet the availability of effective and safe vaccines is limited. A major obstacle in flavivirus vaccine development is antibody-dependent enhancement (ADE), whereby sub-neutralizing or cross-reactive antibodies facilitate viral entry and exacerbate disease severity. Many existing vaccine strategies struggle to achieve strong neutralizing responses while avoiding ADE, underscoring the urgent need for next-generation vaccine designs that target conserved epitopes capable of inducing broad, protective immunity without enhancing infection (Pierson et al., 2020).

In the first study, Yen et al. (2023) identified a universally conserved neutralizing epitope within the bc loop (residues 73-79) of domain II of the flavivirus envelope (E) protein. Immunogens containing tandem repeats of this bc loop sequence (DV/ZV-NTE and JEV-NTE) elicited robust immune responses, significantly reducing viremia and improving survival in mouse models challenged with multiple flaviviruses. Notably, antibodies directed against the bc loop were intrinsically safe and did not induce ADE in either *in vitro* or *in vivo* assays, establishing this epitope as a rare example that combines high conservation, effective neutralization, and safety.

In a subsequent study, Lien et al. (2025), sought to enhance neutralizing potency which minimizing the risk of ADE. They developed a rationally engineered immunogen, muBCFL, which integrates the bc loop with a mutated fusion loop (FL), a region known for strong immunogenicity but commonly associated with ADE. By introducing four targeted mutations (T76A, W101A, G106Q, and L107D), the ADE-inducing properties of the fusion loop were effectively eliminated. Sera from muBCFL-immunized animals demonstrated markedly improved neutralizing activity against all four DENV serotypes, as well as ZIKV, and JEV, while maintaining an ADE profile indistinguishable from negative controls in both *in vitro* and *in vivo*.

Collectively, these studies represent a major advance in rational flavivirus vaccine development. The transition from identifying a intrinsically safe, conserved neutralizing epitope to engineering a hybrid immunogen with substantially enhanced breadth and potency provides a clear and innovative design framework. By overcoming the trade-off between neutralization and the risk of ADE, the muBCFL approach offers a robust and translatable strategy for the development of safe, broadly protective vaccines against multiple co-circulating flaviviruses.

Reference

Yen, LC., Chen, HW., Ho, CL. *et al.* Neutralizing antibodies targeting a novel epitope on envelope protein exhibited broad protection against flavivirus without risk of disease enhancement. *J Biomed Sci* 30, 41 (2023). https://doi.org/10.1186/s12929-023-00938-y

Lien SB, Yang QW, Huang HW, Chiu KC, Su SL, Liao CL, Yen LC. A novel immunogen comprising a bc loop and mutant fusion loop epitopes generates potent neutralization and protective abilities against flaviviruses without risk of disease enhancement. Vaccine. 2025 May 31;57:127219. doi: 10.1016/j.vaccine.2025.127219