Elucidating the mechanism of dengue viral capsid assembly by molecular simulation (for NTU-Konstanz joint PhD program)

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This research project is offered by a joint PhD program of SBS/NTU and the Chemical Biology program of Konstanz University, Germany. The student will be supervised by the two PIs (listed above) from the two institutes and spend at least one year at Konstanz. Two return flight tickets will be provided for the whole candidature. This scholarship is only offered to local students or international students who pursued their undergraduate studies at NTU.

Dengue is the most prevalent mosquito-borne disease, caused by the dengue virus (DENV). The DENV RNA encodes some structured proteins (Capsid, pre-Membrane and Envelope) and Non-Structural proteins (NS1, NS2A/B, NS3, NS4A/B, NS5). Recent crystallography and Cryo-EM studies shed light on the envelope protein assembly and their mechanism of antibody-binding. Nevertheless, we have by far less understanding on the DENV capsid structure, as well as its assembly process. It is proposed in the literature that the DENV capsid structure is disordered rather than geometrical, and the interaction between C protein and cell lipids plays a critical role in the virus assembly. Moreover, a number of NS proteins are believed to participate in the virus particle replication-assembly process, which takes place in endoplasmic reticulum. In this PhD project, we propose to perform molecular simulations to investigate the complex molecular interactions among C proteins, NS proteins and cell lipids. The ultimate goal is to depict the roles of protein-protein interactions in virus capsid assembly and provide valuable information to experimental researchers who are searching potential drug targets on C proteins and NS proteins. Three sub-projects will be conducted for the span of four years of the PhD scholarship: a) Molecular simulations will be conducted to reveal interactions between NS proteins. In particular, we are interested in the NS3-NS5 interaction recently identified by groups at NTU and Duke-NUS. b) On the basis of recently experimental findings, we will investigate the molecular affinities between C proteins and cell lipids to understand the capsid assembly mechanism. c) Large scale simulations will be performed to construct structure models for the C protein assembly and its interplay with virus membrane.

The entire PhD project involves simulations at different length scales, from single protein to the whole capsid. Simulations for single- and two-protein systems will be performed in Lu's group, in line with the group's recent efforts on modeling protein-protein interaction. The large scale simulations on capsid structure (~120 C proteins) will be performed in Peter's group, taking advantage of the group's experience from modeling the capsid of cowpea chlorotic mottle virus. The group's experience with simulating intrisnsically disordered peptides and protein domains will be beneficial to this project as well.

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