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Zika Virus: Molecular Biology and Inhibitor Discovery

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The focus of this talk is Zika virus which spread from mosquito bites, blood transfusion and sexual contacts. The virus survival and pathogenesis is governed from a range of viral and host proteins. Viral proteins include three structural and seven non-structural proteins. We are working on several aspects of ZIKV such as its dark proteome, structure-function-paradigm, disorder-function paradigm, folding-function relationships, and structure-based drug discovery, etc.

We have analysed the Intrinsically Disordered Proteins (IDPs)and Intrinsically Disordered Protein Regions (IDPRs) in ZIKV proteome revealing its highly dynamic and flexible nature. These IDPRs play central role in disease development and progression, and thus we are experimentally examining various disordered regions of Zika virus proteome such as N-terminal region of capsid protein, NS4A, etc. We have also investigated small molecule inhibitors against various proteins of ZIKV and found several compounds that can inhibit various targets in Zika virus proteins. We found that EGCG, a small organic green tea compound interacts with different ZIKV proteins. EGCG has been found to interact with key residues of a flexible linker present in between domain I and III of envelope protein. Further mechanistic insights into it revealed that EGCG blocks conformational changes required for membrane fusion process during viral particle release. Itstabilisesan intermediate form of envelope protein and blocks the fold-back event before domain III shape into a hairpin necessary for trimer formation. Another target of EGCG is the helicase activity of NS3 protein. In our studies, we have found that EGCG stabilizes the dynamic P-loop of ATPase site by interacting with key residues (THR 201, GLY 199, ARG 459, and ARG 462) around it. Through experiments and molecular dynamics simulations, we also investigated its capability to bind to RNA along with ATPase site.

Apart from these, we are also investigating the folding function relationship of Helicase, Envelope, Methyltransferase, NS1, NS2bB-NS3 Protease, etc.