Tata Institute of Fundamental Research
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Internal Webinar

Investigation of important loop movements in protein therapeutic targets of Plasmodium falciparum using atomistic molecular dynamics simulations

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Malaria remains a major challenge to global healthcare and is one of the leading causes of morbidity and mortality. Of the six plasmodium species which are pathogenic to humans, Plasmodium falciparum is the most common. The invasion of malarial merozoites into erythrocytes is a complex process, which is achieved through formation of a moving junction (MJ) between the invading apicomplexan parasite and the host cell. The MJ contains two key parasite components: the surface protein Apical Membrane Antigen 1 (AMA1) and its receptor, the Rhoptry Neck Protein (RON) complex, which is targeted to the host cell membrane during invasion. In particular, RON2, a transmembrane component of the RON complex, interacts directly with AMA1. Understanding the AMA1-RON2 complex from a structural perspective is crucial due to its immense therapeutic potential. One of the important components of AMA1-RON2 recognition is the role played by domain II (DII) loop of AMA1. The role of DII loop of AMA1 has so far remained elusive. Only one crystal structure solved so far could locate the electron density of the DII loop due to its highly flexible nature, that too without the presence of native RON2 helix. We have conducted micro second level molecular simulations to understand the dynamics of DII loop. To this end, in this talk I will present important results obtained from these efforts. A similar problem, encompassing another important therapeutic target system is basigin-RH5-CyRPA which is not much explored so far. Here, using homology modelling techniques we have constructed a crucial loop from RH5 which is absent in the crystal structure and investigate its dynamics pertaining to its interaction with CyRPA.

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