Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Internal Webinar

Development of targeted covalent inhibitors of the bacterial c-di-GMP synthase, WspR

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The predominant bacteria in the natural environment form community biofilms. Biofilm formation benefits bacteria by providing resistance to detrimental substances (such as antibiotics, disinfectants, and host immunological stimuli) and facilitating the coordination of their gene expression via quorum sensing (QS). Cyclic diguanylate monophosphate (c-di-GMP) is a universal secondary messenger that primarily controls biofilm production. The intracellular concentration of c-di-GMP is tightly regulated by opposing enzymatic activities of its synthase (diguanylate cyclases or DGCs) and hydrolases (phosphodiesterases or PDEs). We focus on a protein named WspR, a hybrid response regulator-diguanylate cyclase that plays a central role in this process. Our study focuses on developing novel strategies to disrupt biofilm formation by targeting WspR. These compounds were identified as potent covalent inhibitors, specifically targeting the conserved allosteric inhibitory I-site. These compounds effectively reduced biofilm formation and intracellular c-di-GMP levels in *Pseudomonas aeruginosa*, a model organism for studying biofilm formation. Our results open broad avenues for developing new therapeutic strategies to cure biofilm-related diseases. In addition, I will talk for a few minutes about my side projects, focusing on *N*-terminal site-selective protein modification, followed by a research proposal on the spatial organization of protein-lipid clusters using nMS.

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11:00 Hrs