Tata Institute of Fundamental Research
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Internal Webinar

Chemical peptide synthesis and protein engineering: A trilogy

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Malaria: The widespread resistance of Plasmodium falciparum, a deadly malaria parasite, against front line antimalarials warrants immediate alternatives for containing its outbreak. Employing unnatural D-peptide/protein-based inhibitors have huge potential as therapeutics due to their high protease resistance and low immunogenicity. We are utilizing a unique combination of chemical protein synthesis and 'Mirror-Image Phage Display', to find a suitable D-protein inhibitor for PfAMA1. In this talk, I will describe challenges associated with chemical protein synthesis[1,2] and folding of PfAMA1-Domain-1, and an approach to assist folding by cyclizing the large PfAMA1-D-1 polypeptide. I will also describe a strategy of hybridizing P. falciparum specific R1 and PfRON2 to generate a more potent parasite inhibitor. This hybrid peptide showed a spectacular 100 fold increase in growth inhibition of P. falciparum compared to its parent peptides.

COVID-19: The unprecedented health crisis caused by the ongoing COVID-19 pandemic demands immediate identification of potential diagnostics, therapeutics, and vaccine candidates. In this talk, I will brief our ongoing efforts to synthesize and screen a peptide library of multiple SARS-COV-2 proteins to identify immunogenic epitopes for efficient low-cost diagnosis and candidate vaccines.

Hydrogen production: There has been a huge interest in designing economically viable metal-free carbon-based catalysts for water splitting. I will describe a novel strategy of engineering protein on carbon nanotubes (CNTs) and bulk MoS_2 as effective catalysts for electrochemical hydrogen evolution reaction (HER).[3] The roles of protein denaturation, the effect of conductive residues, the nitrogen content of the proteins, the importance of the covalent connectivity of the protein with the CNTs, and a mechanistic insight of the observed phenomena will be discussed.

References:

1. Mannuthodikayil, J., Singh, S., Biswas, A., Kar, A., Tabassum, W., Vydyam, P., Bhattacharyya, M.K., and Mandal, K. (2019). Benzimidazolinone-Free Peptide o-Aminoanilides for Chemical Protein Synthesis. Org Lett 21, 9040.
2. Kar, A., Mannuthodikayil, J., Singh, S., Biswas, A., Dubey, P., Das, A., and Mandal, K. (2020). Efficient Chemical Protein Synthesis using Fmoc-Masked N-Terminal Cysteine in Peptide Thioester Segments. Angew Chem Int Ed 59, 14796.
3. Mannuthodikayil, J., Narayanaru, S., Thakur, P., Bawari, S., Narayanan, T.N., and Mandal, K. (2020). Protein Denaturation Induced Electrocatalytic Hydrogen Evolution. Carbon 165, 378.

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