INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE
2A & 2B, Raja S.C. Mullick Road, Jadavpur, Kolkata-700032, India

Seminar Notice

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School Applied and Interdisciplinary Sciences

Title: From Designing Enzyme Mimetics to Probing Protein Citrullination

Speaker: Dr. Santanu Mondal
University of Massachusetts Medical School, Worceste, USA

Venue: C.V. Raman Hall

Time: 23rd December 2019, 3:30 PM

Abstract: In this seminar, I'll discuss my doctoral research on the biomimetic dehalogenation of thyroid hormones, their metabolites and halogenated nucleosides as well as my postdoctoral research on the development of small molecule inhibitors and chemical probes of protein arginine deiminases (PADs) that catalyze protein citrullination. Thyroid gland produces thyroxine (T4) as a prohormone and regioselective deiodination by a group of mammalian selenoenzymes, iodothyronine deiodinase type 1 (DIO1), type 2 (DIO2) and type 3 (DIO3) play important roles in the activation and inactivation of T4. I'll discuss the deiodination of thyroid hormones and various metabolites by naphthyl-based organo- sulphur and/or selenium compounds that functionally mimic DIO3. These nahthyl-based organochalcogen compounds were also used to dehalogenate the halogenated nucleosides that can be incorporated into DNA during DNA replication and cause potential DNA damages in the presence of UV irradiation. Citrullination is a post-translational modification of arginine, catalyzed by a group of hydrolases called protein arginine deiminases (PADs – PAD1, 2, 3 and 4). Despite various physiological roles, protein hypercitrullination is associated with various diseases including rheumatoid arthritis (RA), lupus, ulcerative colitis (UC), multiple sclerosis (MS) and certain cancers. These strong disease links have established PADs as potential therapeutic targets and numerous PAD inhibitors are known in the literature. To reduce the off-target toxicity, we developed an azobenzene-substituted PAD2 inhibitor that undergoes trans-cis photoisomerism and can be activated at the target cell/tissue with light. Notably, the cisisomer of this inhibitor is 10-fold more active than its trans-isomer. In addition, using a fluoroacetamidine warhead and iodo-substitutions in the molecular scaffold, we developed the first potent PAD1 inhibitor with 74-fold selectivity over other PADs. Structure-activity relationship studies indicate that the potency and isozyme-selectivity of this inhibitor is due to the formation of a halogen bond between the iodine atoms and PAD1 active site. Based on this molecular scaffold, we also developed a PAD1-selective activity-based probe with remarkable cellular efficacy and proteome selectivity. Although numerous proteins are known to be citrullinated at various positions, the effects of citrullination at each of these positions on the structure and activity of a given protein remain elusive. To aid this, we developed, for the first time, a photocaged-citrulline that can be incorporated into proteins using an engineered leucyl-tRNA synthetase (LeuRS)/tRNALeu pair and subsequently converted into citrulline using light. In addition to the aforementioned topics, I'll also briefly discuss my future plans for research and teaching.

References:

1. S. Mondal, K. Raja, U. Schweizer, G. Mugesh, Angew. Chem. Int. Ed. 2016, 55, 7606.
2. S. Mondal, D. Manna, G. Mugesh, Angew. Chem. Int. Ed. 2015, 54, 9298.
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4. S. Mondal, P. R. Thompson, Acc. Chem. Res. 2019, 52, 818.
5. S. Mondal, S. S. Parelkar, M. Nagar, P. R. Thompson, ACS Chem. Biol. 2018, 13, 1057.
6. S. Mondal, X. Gong, X. Zhang, A. J. Salinger, L. Zheng, S. Sen, E. Weerapana, X. Zhang, P. R. Thompson, Angew. Chem. Int. Ed. 2019, 58, 12476.

All are cordially invited to attend the seminar