TIFR Centre for Interdisciplinary Sciences
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Internal Seminar

Structural investigations of selected microbial penicillin G acylases and a protozoal N-myristoyltransferase

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Penicillin acylases (penicillin amidohydrolase; EC 3.5.1.11), members of the N-terminal nucleophilic (Ntn) hydrolase superfamily, are a group of enzymes responsible for the major commercial production of 6-APA, an intermediate used in the preparation of semisynthetic antibiotics. Large-scale production of semisynthetic penicillins and cephalosporins focuses on the condensation of the appropriate D-amino acid derivative with 6-APA, is also catalyzed by penicillin acylases. In addition, penicillin acylases can also be employed in other useful biotransformation, such as peptide synthesis, removal of protecting groups and the resolution of racemic mixtures of chiral compounds.

Almost 85% of 6-APA production is by using penicillin G acylase (PGA), the enzyme that hydrolyses penicillin G (benzyl penicillin), with the major share of the enzyme comes from E. coli. However, for pharmacological applications when factors such as tolerance for environmental parameters such as temperature, pH and nature of solvent, along with ease of immobilization are important, attention has turned to PGA enzymes from other sources such as K. citrophila (KcPGA). Another PGA produced by *Alcaligenes faecalis* (AfPGA) has clear industrial advantage over other well-characterized penicillin acylases in β-lactam conversion because of its higher thermostability and synthetic efficiency in enantioselective synthesis.

Another enzyme, N-myristoyltransferase (NMT; EC 2.3.1.97) presented in the talk is relevant for therapeutics. Past studies have identified Myristoyl-CoA–protein NMT as a suitable candidate for drug development against protozoan parasitic infections, including those caused by *Leishmania major*, the causative agent of cutaneous leishmaniasis, as well as *Plasmodium falciparum* and *Trypanosoma brucei*, causative agents of human malaria and African sleeping sickness, respectively. NMT is ubiquitous in eukaryotic cells in which it catalyses the co-translational addition of the C14:0 fatty acid, myristate, via an amide-bond, to the N-terminal glycine residue of a subset of proteins. N-Myristoylation plays a role in targeting proteins to membrane locations, mediating protein–protein interactions and stabilizing protein structures.

This talk describes the structure, stability, activity and structure-function relation of three enzymes: PGAs from *Kluyvera citrophila* (KcPGA) and from *Alcaligenes faecalis* (AfPGA) and myristoyl-CoA–protein N-myristoyltransferase from *Leishmania donovani* (LdNMT) using various biochemical and biophysical techniques that has provided information for further protein engineering to improve their application potential or for designing better inhibitors for therapeutic purpose.

Talk also briefly describes the experience obtained during the construction and commissioning of a Macromolecular crystallography beamlines (XRD2) at Elettra Sincrotrone, Trieste, Italy.

Friday, Feb 17th 2017

11:30 AM (Tea/Coffee at 11:15 AM)

Seminar Hall, TCIS