BIOCHEMISTRY SEMINAR

Understanding ABC Transporters for Better Therapeutics

Ruchika Bajaj

Associate Specialist, University of California San Francisco

Abstract: Membrane proteins constitute 30% of the genome in organisms and are involved in numerous physiological processes. ABC transporters is a class of membrane proteins which are ubiquitously present in all organisms, bind and hydrolyze ATP to power the solute transport and are associated with several human diseases like multidrug resistance in cancer, macular degeneration, cystic fibrosis, retinitis pigmentosa etc. ABC transporters consist of two transmembrane domains (TMDs), which form the permeation pathway and nucleotide binding domains (NBDs) to bind and hydrolyze ATP and follow alternating access mechanism. Bacterial ABC transporters like binding-protein-independent mutant of maltose transporter, MalG511 from *E.coli* and FtsEX-PcsB from *S. pneumoniae* have been characterized biochemically and biophysically to study mechanism and future higher resolution studies. Structure-function relationships were studied in mammalian ABC transporters, bovine MRP4 and human P-glycoprotein. High resolution cryoEM structures of bovine MRP4 in three different states (apo state, nucleotide bound state and substrate bound state) are determined which revealed the architecture, asymmetry of NBDs, interpreted functional effects of genetic variants, located substrate binding site, deciphered associated conformational changes in catalytic cycle of bovineMRP4. Structure based drug designing and targeting MRP4 in context of cancer and cardiac diseases will be helpful to the field of medicine. Oral excipients were screened against P-gp using calceinAM fluorescence assay and digoxin flux assay were found to be inert for their effect on P-glycoprotein. beta-Cyclodextrin and light green SF yellowish were found to be inhibitory at high macromolecular range in digoxin flux assay. This information will be helpful in preparing novel generic formulations. Additionally, the meta-analysis study provides an overview of the revolutionizing field of structural biology of ABC transporters.

Monday, November 11th, 2024 | 3:30 pm | BRWN 4102

PURDUE UNIVERSITY

James Tarpo Jr. and Margaret Tarpo Department of Chemistry