UNIVERSITY OF RHODE ISLAND
Department of Chemistry
SEMINAR

Room 105 Beaupre
3:00 P.M., Monday, Oct. 28, 2019

Prof. Karen N. Allen

Boston University
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"Evolution of Protein Scaffolds for Phosphoryl and Phosphoglycosyl Group Transfer"

HOST

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Evolution of Protein Scaffolds for Phosphoryl and Phosphoglycosyl Group Transfer

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In order to identify and assess sequence markers that support structure and specificity, we have undertaken the study of enzyme superfamilies that enact phosphoryl transfer or phosphoglycosyltransfer through a covalent intermediate: the haloalkanoate dehalogenase superfamily (HADSF) and the phosphoglycosyl transferase superfamily (PGT). The HADSF occurs in all domains of life, has successfully evolved several forms of chemical transformation and has experienced expansion through substrate space. The expansion includes the invention and reinvention (pseudoconvergent evolution) of activities within branches of the family. β-phosphoglucomutase (βPGM), is used as a model to show how in the mutases of the family, interdomain conformational changes are coupled to ligand binding and govern the switch between mutase and phosphatase activity. Furthermore, we show that human phosphomannomutase can be "allosterically" regulated via dynamics and control of the catalytically competent conformation. Overall, our findings illustrate the concept that domain insertions act to increase the substrate range of the superfamily. In the phosphoglycosyl transferase superfamily (PGT) the family faces the challenge of utilizing one hydrophilic and one membrane-bound substrate. Our X-ray crystallographic study determined the first structure of a PGT superfamily member, *C. concisus* PglC, revealing a novel protein fold with an unusual re-entrant membrane helix which comprises part of the fold rather than adopting a membrane-spanning topology. Additionally, key structural motifs establish the co-facial positioning of the catalytic-dyad Asp/Glu and reveals how an alpha-helix associated beta-hairpin (AHABh) motif characteristic of this novel fold acts to activate the carboxylate nucleophile. The structure of PglC enforces placement of the active site at the membrane interface which is energetically favorable for use of a undecaprenyl phosphate substrate. Analysis of available monotopic membrane protein structures shows that the mode of membrane interaction of these enzymes in pathways can be used to promote substrate specificity and product composition.