Ackert Hall, Room 120
Wednesday, April 16, 2025
4:00 P.M.

Coffee and Cookies
Chalmers Hall, Room 168
3:45 P.M.

Biochemistry & Molecular Biophysics Seminar

Cracking the AlkB Homologues' Code: How an α-ketoglutarate conformational equilibrium controls iron accessibility, activation and substrate selection

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We use solution NMR, molecular dynamics (MD) simulations, and enzymatic assays to investigate regulation of human FTO and Alkbh5, two AlkB homologue enzymes whose overexpression results in metabolic diseases. We show that modulation of protein conformational dynamics is essential to orchestrate the sequential binding of primary and secondary substrate to these enzymes, while a conformational transition in the secondary substrate is responsible for activation of the catalytic reaction. Finally, we obtain a conformational ensemble for FTO based on NMR and MD data. The ensemble highlights the presence of cryptic pockets on the enzyme surface. An in-silico screening effort targeted to the FTO cryptic pockets resulted in the discovery of C6, an allosteric and non-competitive inhibitor of FTO with subfamily selectivity.