

Seminar Abstract: Carol Beth Post, “Allosteric regulation of receptor interactions of Syk tyrosine kinase” Nov 1, 2016, University of Illinois, Chicago

Protein interactions of protein tyrosine kinases are fundamental to their function in signaling. My research group has focused on understanding the tight relationship between function and protein-protein interactions, including the regulation of Syk association with membrane immune receptors and the recognition of substrate by Src family kinases. These two kinases are often observed to work together in various signaling pathways. This seminar will focus on our efforts to define an unusual allosteric mechanism of regulating Syk binding to immune receptors. The phosphorylation of a linker region between two tandem SH2 domains of Syk tyrosine kinase regulates the binding affinity for Syk association with ITAM regions of membrane receptors; affinity for receptor mediated by the Syk SH2 domains decreases more than 100-fold upon phosphorylation of the remote tyrosine site on linker A. The mechanism of this allosteric regulation has been suggested to be a switch from a high-affinity bifunctional binding, mediated through both SH2 domains binding two phosphotyrosine residues, to a substantially lower-affinity binding of only one SH2 domain. Nonetheless, this postulated switch to a single-SH2-domain binding mode was recently refuted by NMR experiments. Instead, we find the allosteric mechanism for inhibiting binding by tyrosine phosphorylation is fully driven by entropy, with essentially no enthalpic compensation. The structural basis for this unusual regulatory mechanism was explored by molecular dynamics computer simulations and these results will also be described.