Dr. Emily Dykhuizen  
Purdue University, College of Pharmacy  
Associate Professor of Medicinal Chemistry and Molecular Pharmacology

Title: “Epigenetic drugs to reverse gene expression changes in cancer”

Abstract: In mammals, gene expression is highly regulated by hundreds of epigenetic regulators that dictate when, and how, genes are expressed. This allows for increased diversity of mammalian cell types and cellular responses. Because epigenetic regulators are so important for maintaining cellular identity, their mis-regulation can result in the initiation and progression of cancer. One set of epigenetic regulators that are commonly mis-regulated in cancers are called Polycomb proteins, which were originally identified and named in fruit flies for their role in body segmentation. Mammals have many more Polycomb proteins than fruit flies, many of them very similar with undefined functions. One Polycomb protein, CBX8, is specifically required for several cancers and has a domain called a chromodomain, which is an attractive target for inhibitors due to its essential role in binding to the genome. Due to the CBX8 chromodomain’s shallow, flexible binding pocket and high similarity to four other CBX proteins, no selective inhibitors have yet been developed. To make a selective CBX8 inhibitor, we optimized affinity selection assays of DNA-encoded libraries against a panel of highly homologous CBX chromodomains. Using quantitative metrics, we rapidly assessed the relative affinity and selectivity of chromodomain inhibitors for CBX8 in a single DNA sequencing run. We identified the first potent, selective, and cell-permeable inhibitor of the CBX8 chromodomain, and validated its ability to selectively prevent CBX8 binding to the genome. Further, we utilized the inhibitors to validate CBX8 as a target in leukemia with MLL-AF9 translocation, due to a specific interaction between AF9 and CBX8. Further, we find that the CBX8 chromodomain is required for MLL-AF9 mediated activation of HOX genes, adding new support for Polycomb proteins in modulating both activation and repression of gene targets.

Monday, October 28, 2019  
4:00 pm  
Chemistry Building, Room 1220