

**TITLE:** Chemical biology tools for probing and perturbing carbohydrate processing enzymes in mammalian systems.

**ABSTRACT:** Mammals use several monosaccharides as building blocks to assemble glycans that are, in turn, attached to all other classes of biomolecules. In recent years these glycoconjugates have gained increasing attention as their diverse roles in cellular and organismal homeostasis continue to be uncovered. In the Laboratory of Chemical Biology we have focused on the design and use of chemical biology tools to probe and perturb glycans and carbohydrate processing enzymes in cells and in vivo. In this presentation I will discuss our studies on the enzymes that regulate levels of the intracellular O-GlcNAc modification of proteins, the creation and characterization of potent inhibitors of these enzymes, and how these have led to industrial efforts that have successfully advanced such compounds into human clinical trials. I will also describe our research toward the synthesis and optimization of live cell fluorescence quenched substrates that can be used to quantify the activities of disease-associated glycosidases in live mammalian cells. The uses and benefits of these discovery-focused chemical probes will be presented. Examples will include studies on examining the roles of O-GlcNAc in nutrient sensing as well as developing high-throughput array-based and genome wide screening methods to identify modulators of carbohydrate processing enzymes implicated in various diseases ranging from cancer to neurodegenerative diseases including Alzheimer's and Parkinson's.