

JOSEPH F. FOSTER MEMORIAL CHEMICAL BIOLOGY AND BIOCHEMISTRY SEMINAR

**Monday, January 29, 2024
3:30 PM, BRWN 4102**



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At AbbVie

Abstract:

The ubiquitin proteasome system plays a pivotal role in the degradation of cellular proteins; proteins are post-translationally tagged with a small protein, ubiquitin, often serving as a degradation signal, through the interplay of 3 enzymes. The final enzymes acting in this cascade are E3 ubiquitin ligases, a diverse family of approximately 600 ligases that catalyze the transfer of ubiquitin onto a lysine residue of a substrate protein by formation of an isopeptide bond. Recently, targeted protein degradation (TPD) has emerged as a novel therapeutic modality, offering an alternate approach to traditional occupancy-based inhibitors. Rather than inhibiting a protein of interest (POI) with small molecules, TPD harnesses heterobifunctional molecules designed to bring the POI into proximity with E3 ubiquitin ligases, allowing the cell's intrinsic degradation machinery to naturally destroy the protein. In addition to relying upon the enzymatic activity of ligase proteins, these molecules are believed to behave catalytically, in principle leading to a reduction in dosage and off-target effects. Moreover, TPD imparts added selectivity for POIs and broadens the scope of potential targets by accessing the undruggable proteome. My seminar will delve into the mechanisms of targeted protein degradation, exploring the catalytic role of E3 ubiquitin ligases and diverse mechanisms of ubiquitination. Furthermore, we will shed light on another therapeutic application of proximity-inducing molecules that instead stabilizes proteins that are aberrantly turned over in disease by recruiting deubiquitinating enzymes to POIs. This seminar aims to provide insights into the expanding landscape of induced-proximity technologies and its implication in drug discovery and development.

“Proteins on the chopping block: targeted protein degradation as a next generation therapeutic.”



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