QCB
QUANTITATIVE AND CHEMICAL BIOLOGY
INDIANA UNIVERSITY

Christopher am Ende

Pfizer, Inc.

Host: Nikki Pohl

Design and Application of Clickable BACE and γ-Secretase Probes for Chemoproteomic Profiling and Mechanism of Action Studies

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a decline in cognitive function and is ultimately fatal. The accumulation of amyloid β (Aβ) plaques consisting primarily of Aβ42 have been implicated in the pathology of AD. The neurotoxic amyloid peptides are formed by sequential cleavage of the amyloid precursor protein (APP) by β-aspartyl secretase (BACE) and γ-secretase. Inhibition or modulation of both BACE and γ-secretase has emerged as promising approaches for treating AD. Initial BACE inhibitors in the clinic were plagued by ocular toxicity. Using quantitative chemoproteomics with a clickable photoaffinity probe, we reveal that inhibition of cathepsin D (CatD) is the principal off-target of BACE inhibitors and quantifying CatD target engagement in cells is predictive of ocular toxicity. Additionally, γ-secretase has also been beset by challenges with toxicity related to the inhibition of the Notch signaling pathway, which is critical for cell differentiation. γ-secretase modulators (GSMs) were developed to specifically reduce Aβ 40/42 production without affecting the processing of other substrates.

For further details, contact Mr. Steven Watkins at 5-9749

QCB
Seminar Series

Co-hosted by the Department of Chemistry and the Graduate Program in Biochemistry

FRIDAY

October 28

CHEMISTRY

C033

2:30 p.m.