

***UNIVERSITY OF RHODE ISLAND***  
***Department of Chemistry***  
***SEMINAR***

***3:00 P.M., Monday, April 1, 2024***  
***Room 105 – Beaupre Center***

***Dr. Christopher am Ende***

***Pfizer, Groton, CT***

***Discovery of a  $\gamma$ -Secretase Modulator  
for the Treatment of Alzheimer's  
Disease: Interplay of Medicinal  
Chemistry and Chemical Biology***

***HOST***

***Brad Lipka***

***Department of Chemistry***

# **Discovery of a $\gamma$ -Secretase Modulator for the Treatment of Alzheimer's Disease: Interplay of Medicinal Chemistry and Chemical Biology**

***Dr. Christopher am Ende***

*Pfizer, Groton, CT*

This presentation will highlight the design of a potent gamma secretase modulator (GSM) clinical candidate for the treatment of Alzheimer's disease (AD) and the interplay of chemical biology in the drug discovery process. Key components of the GSM design relied on a pharmacophore model to identify a 2,5-cis-tetrahydrofuran (THF) linker to impart conformational rigidity, locking the putative bioactive structure and affording a balance in potency and physiochemical properties. Additionally, through the development of gamma secretase photoaffinity probes, we show differentiation between different series of gamma secretase inhibitors and modulators. Further emphasis on the value of chemical biology in drug discovery for off-target ID and imaging will also be showcased in several vignettes.