

## **Detection of active site conformation changes of gamma-secretase, a key enzyme associated with Alzheimer disease, with small molecules**

### **ABSTRACT**

Gamma-secretase is a membrane-bound aspartyl-protease that cleaves many membrane substrates including Amyloid Precursor Protein (APP), Notch, E-cadherin, Her4 and CD44. APP is a particularly notable substrate because of its association with Alzheimer disease. Together, gamma-secretase and beta-secretase cleave APP to produce amyloid beta peptides that aggregate in the brain as cytotoxic beta-amyloid plaques, which is one of the hallmarks of Alzheimer disease. Many small molecules are being developed to target gamma-secretase as a therapeutic strategy for Alzheimer disease. However, studying the effects of these molecules on the active site conformation of gamma-secretase is challenging due to the complexity of this enzyme. In our study, we have developed new biochemical techniques to probe the active site structure of gamma-secretase. We are able to show that different gamma-secretase inhibitors and modulators, when bind to gamma-secretase, affect the active site structure of gamma-secretase differently. More importantly, we discovered that these small molecules, which were developed to target gamma-secretase, also affect the active site structure of Signal Peptide Peptidase, a similar membrane-bound aspartyl-protease. This discovery has major implication on the development of gamma-secretase inhibitors as therapeutic drugs for Alzheimer disease due to potential off-target effects.

**Keyword:** Neurodegeneration; Alzheimer's disease; Therapeutic; Molecule; Gamma secretase