

MS091.P01

*Gamma secretase activating protein as profound target for Alzheimer's disease*

Deekshi Angira<sup>1</sup>, Vijay Thiruvengadam<sup>1</sup>

<sup>1</sup>Discipline Of Chemistry, Indian Institute Of Technology Gandhinagar, Gandhinagar, India

E-mail: deekshi.angira@iitgn.ac.in

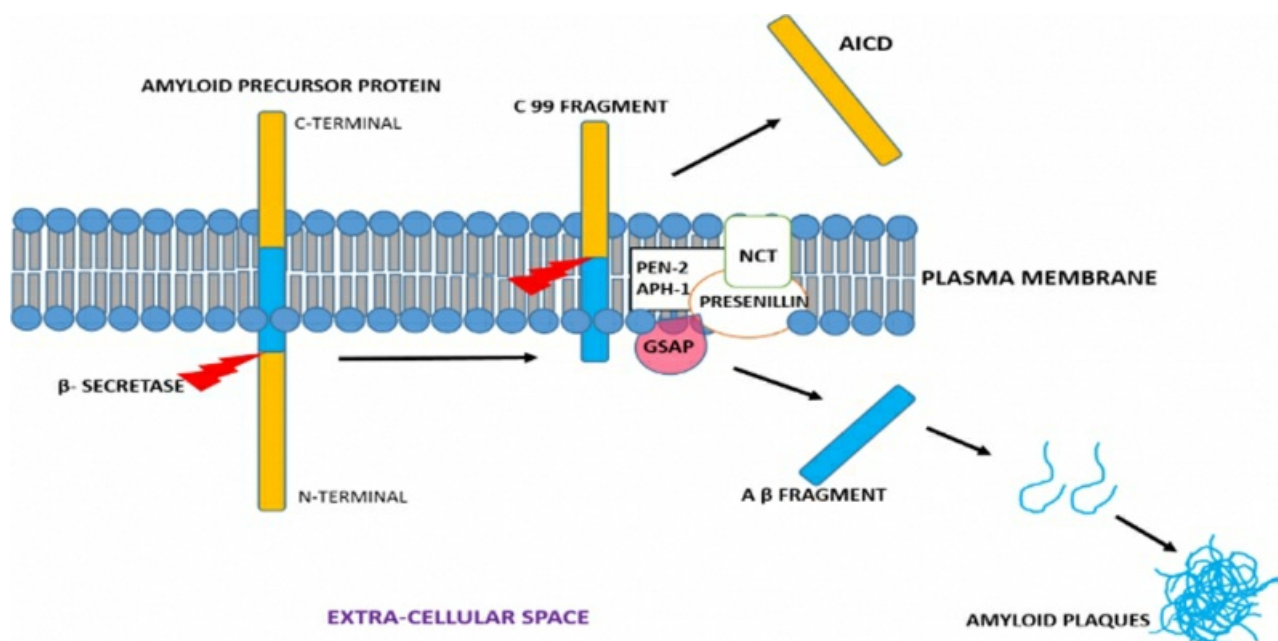
Alzheimer's disease is a form of progressive dementia followed by decline in cognitive abilities, neurological reflexes and learning ability characterized by the presence of amyloid beta plaques and neurofibrillary tangles, their progression being complemented by several cross talks between interconnected cell signaling pathways predominant in brain cells.

Gamma Secretase Activating Protein (GSAP) involved in beta amyloid pathway is a 854 amino acid long protein (around 98 kD) which is post translationally modified into an active 16kD protein with the help of regulators like Caspase 3 and 5 Lipoxygenase at Caspase 3 processing domain present towards the C terminal at 737'DLD'739 position. In a sequential proteolytic cleavage of APP and C-99 fragment by BACE-1 and  $\gamma$ -Secretase respectively, active GSAP is assumed to bring C-99 fragment and  $\gamma$ -secretase in close proximity by forming a ternary complex which leads to the production and deposition of A $\beta$ 40 and A $\beta$ 42 amyloid plaques. Through our work we target towards filling the voids that have been left unattended in the field of GSAP, like its macromolecular structure determination through X-Ray crystallography or NMR, studying and exploring the other isoforms of GSAP to find out their structure and activity and to discern the role and action mechanism of GSAP within the cell. Hence, we aim to clone and express GSAP in prokaryotic as well as in eukaryotic cells, in highly efficient ex-expression vectors (such as pET19b, pET 32a, pMalc5X His, pcDNA 4) having different tags, and further to study the binding efficiency of GSAP with potent inhibitors using X-ray crystallography. Along with GSAP isoform I, we also focus on GSAP isoform IV exploiting the fact that it has maximum similarity to canonical 16 kD GSAP isoform I. GSAP's role as an activator of  $\beta$ -amyloid production makes it a promising and ingenious therapeutic target for treatment of Alzheimer's disease thus making it a prospective candidate to be probed for Alzheimer's cure and prevention.

[1] He, G. et al. (2010) Nature 467, 95-98.

[2] Deatherage, C. et al. (2012) Biochemistry 51, 5153-5159.

[3] Hussain, I. et al. (2011) Alzheimer's & Dementia 7, S387.



**Keywords:** [Gamma Secretase Activating Protein](#), [Beta amyloid pathway](#), [Alzheimer's disease](#)