



INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Programme of Study : **Ph.D.**

Thesis Title:
Design, Synthesis, and Evaluation of Peptide Conjugates for Alzheimer's Amyloid Disruption

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Thesis Submitted to the Department/ Center : **Department of Chemistry**

Date of completion of Thesis Viva-Voce Exam : **02.03.2020**

Key words for description of Thesis Work : Amyloid, Alzheimer's Disease, Artificial α -Secretases, Targeted protein degradation

SHORT ABSTRACT

The cleavage of the backbone of a peptide or protein-related disease may treat the disease to heal. We noted that supramolecular interactions govern all of the protein aggregation. Therefore we hypothesized that a novel way of intervention may be outlined by combining the supramolecular interactions and chemical reactions. So, we engineered a small peptide to cleave the disease-prone Amyloid- β ($A\beta$) selectively and its toxic oligomers at the enzymatic cleavage sites, especially that of α -secretases (and hence we termed them artificial α -secretases, $A\alpha$ Ss), to facilitate excretion in a non-catalytic manner. With prolonged treatment in physiological conditions, $A\alpha$ Ss also cleaves $A\beta$ at the cleavage sites of other metabolic enzymes, finally dissolving the stone-stable toxic amyloid fibrils and making it non-toxic. While proteolytic enzymes present in the body cannot degrade amyloid plaques, our added molecules chemically destroy amyloid aggregates and facilitate excretion. This work is the first report on a pre-programmed metabolism of aggregated $A\beta$ by an externally added agent. Next, we wanted to achieve another type of functional mimic of $A\beta$ -degrading proteases, keeping their catalytic activity intact by peptide-based molecule design. For that, we mimicked the active site of chymotrypsin by Gly integrated new main chain framework, unlike the DHS catalytic triad that exists in different folding scaffolds and attached that with the $A\beta$ recognizing peptide sequences, and collectively called as the Miniature Artificial Proteases (mAPs). mAPs were designed in such a way that its active site has a pocket where Asp, His, and Ser are linked via intramolecular hydrogen bonding so that Ser participates the hydrolysis of a peptide bond adjacent to it through the co-operative mechanism. A relatively lower dose of mAP3 was found to inhibit significantly and also disrupt the preformed amyloid aggregation of $A\beta_{1-40}$ in vitro and may reduce the side effects. Hence our innovative paradigm based on mAPs offers a new platform for direct, rapid, and targeted protein degradation. We also designed a new catalytic triad based on the active site of some of the native peptidases. The rest of the design moto was similar to the objectives mentioned above. Some transition-metal ions, mainly Cu^{2+} , Zn^{2+} , and Fe^{3+} , can bind to $A\beta$ and influence the aggregation process. Such metal-bound $A\beta$ complexes cause oxidative stress and directly involve in the physiological toxicity to the adjacent neurons. In our next goal, we designed taurine containing peptide conjugate that acts as a metal ion chelator for the inhibition of aggregation.