# Abstract

## Title: Investigations on the Structural and Kinetic Features of Amyloid Aggregation

Index No.: **75/19/Life Sc./26**


Amyloid aggregation is associated with a number of severe diseases, including Alzheimer's disease (AD), Parkinson's disease, and type 2 diabetes. Comprehensive understanding of the assembly process that leads to the generation of pathogenic aggregates is imperative for therapeutic interventions. For decades, researchers have been in pursuit of identifying novel structural motifs that dictates amyloidogenesis. On the other hand, self-assembled peptide materials have recently sparked the field of biomedicine and their implications may exceed far beyond amyloid disorder.

This thesis first provides a brief introduction to peptide self-assembly and its implications in disease association and functional biomaterials. Chapter I describes the implications of crucial sequence motifs in the self-assembly of amyloidogenic peptides. Chapter II demonstrates the role of GxxxG repeating motif in regulating the self-assembly and neurotoxicity in Amyloid-beta (Aβ) mediated AD pathogenesis. Our results suggest that the $G^{33}xxxG^{37}$ is the primary motif responsible for Aβ neurotoxicity, providing a direct structure-function correlation. Subsequent experimental observations further provide unique insights into the regulatory role of G33 and G37 in membrane-mediated oligomerization of Aβ40. We illustrate how nanodiscs facilitate the formation of relatively stable oligomers, which are conformationally distinct from native Aβ40 and other minor states of free Aβ40 oligomers. Similar SxxxG/GxxxS motif is also present in the C-terminal region of human Islet Polypeptide (hIAPP). By employing different temperatures and sample agitation conditions, we show the significance of the C-terminal hIAPP fragment in generating structurally distinct oligomers. These oligomers could significantly accelerate the hIAPP aggregation, while potentially reducing the overall toxicity. Targeting these motifs, therefore, can be a promising strategy to prevent cell death associated with AD, type II diabetes and other related diseases. Next, we emphasize on how Singular Value Decomposition (SVD) can be employed to reveal hidden patterns and dominant modes of interaction that dictates the complex process of amyloidogenesis. We applied SVD to elucidate the interactions between amyloidogenic peptide and membrane mimic, as well as the complex process of peptide self-assembly, co-assembly, and seeded amyloid growth. Lastly, the unique ability of peptides to self-assemble into diverse nanostructures were investigated for biomedical applications. Three pentapeptide sequences derived from C-terminal of SARS CoV E protein with same amino acid residues but different sequence distributions were investigated. The relationship between peptide sequence arrangement and molecular assembly structure, and how these influence the mechanical properties of the hydrogel were also covered. Moreover, these hydrogels or micellar like supramolecular assemblies with tunable morphology and mechanical properties, are suitable for tissue engineering, injectable delivery, and 3D bio-printing applications.


Dibakar Sarkar 29/02/24

**(Dibakar Sarkar)**

29/2/24

**(Sign of the Supervisor with Seal and Date)**

DR. ANIRBAN BHUNIA
*Professor*
Dept. of Chemical Sciences
BOSE INSTITUTE (GOVT. OF INDIA)
EN 80, Sector-V, Bidhannagar
Kolkata-700091, India