INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Effects of Chemical and Physical Perturbants in Aggregation and Nanoscale Assembly of Peptides

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SHORT ABSTRACT

Interactions between proteins in a transient manner are central to many biological processes that happen with high precision in biological systems. Self-assembly of peptides or proteins is a spontaneous process resulting in very stable ordered structures. In biology, the concept of self-assembly was popularized by cross-beta spines of amyloid fibrils. From instigating dementia in Alzheimer's disease (AD) to causing type 2 diabetes (T2D), amyloid diseases are some of the most progressively debilitating malady in human system. Currently, there are no known therapies for averting amyloid diseases, and so far, attempts to discern anti-amyloid cure have been mostly unproductive. Modulating or inhibiting the amyloid aggregation may be a useful therapeutic intervention to overcome the multifaceted pathology allied with amyloid diseases. The cross-β structure of amyloids consists of insoluble fibrous β-sheet aggregates, and is considered thermodynamically to be the most stable biological structure. Developing an effective way to control the organization of these self-assembling fibrils will not only be of great value to the armamentarium of anti-amyloid therapeutics, but will be useful in harnessing the remarkable stability of amyloid fibrils for fabricating application oriented materials at the molecular level.

The work detailed in this dissertation is an attempt to understand the critical aspects of amyloidogenic-assembly of steric-zipper peptides derived from broader segments of proteopathic peptides/proteins. We will discuss the effects of electric and magnetic fields of varying strengths on the assembly of the smallest self-assembling peptide, diphenylalanine. We have synthesized a series of short steric-zipper peptides, to employ them as model systems in our study. We have examined the consequence of electric field-mediated stress on the aggregation kinetics of reported aggregating peptides and tested their efficacy as non-invasive anti-aggregation therapeutic. We have designed and synthesized over 20 peptide-based perturbants, to target the core-hydrophobic motifs of amyloid-β peptide and tau protein, which are hallmarks of AD pathology. The efficacy of the designed molecular perturbants was investigated on the model peptide systems using several biophysical as well as cell-viability assays. We have

also performed a comparative analysis of aggregation kinetics of our model peptides and studied the geometric and energetic rationale for their differential aggregation rates. Further, a prototype design of a futuristic non-invasive therapeutic device based on electric-field mediated modulation of amyloidogenesis has also been proposed. The thesis is divided into six working chapters describing the design and characterization of physical and molecular perturbants of aggregation.